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EDITORIAL

Evolve osteoporosis and other guidelines avoiding cognitive bias

Evolve, the Royal Australasian College of Physicians’ (RACP) equivalent of the American Board of Internal Medicine (ABIM) Foundation’s Choosing Wisely campaign, was launched in 2015. The aim of these campaigns is to demonstrate to the community the profession’s tangible commitment to its social justice principles, which include effecting responsible stewardship of entrusted resources. Unfortunately, early indications are that the RACP programme is taking the same pathway to failure as the initial phases of the ABIM campaign suggesting the need for a reset.

As a percentage of gross domestic product (GDP), inflation-adjusted expenditure for health care in Australia, New Zealand and the United Kingdom has continuously increased for 20 years. In real terms, for the period 2009–2014, the average annual growth in per capita health spending in Australia was 2.0% (down from 2.9% in the preceding 5-year period) while in New Zealand, it was 0.6% (down from 4.1%). As a percentage of GDP, in 2014, Australia, New Zealand and the United Kingdom spent 9.4, 11.0 and 9.1% of their respective GDP on healthcare compared to 20 years earlier when each spent circa 7%. In New Zealand, there was a sharp rise from 8.4% in 2007 to 10.7% in 2008.

The ABIM Foundation launched the Choosing Wisely campaign in 2012 encouraging specialty groups to adopt the ‘Top Five’ list approach. This approach encouraged the identification of five diagnostic tests or treatments that are amongst the most expensive and commonly ordered by members of a specific specialty but which have been shown by currently available evidence to provide no meaningful benefit to significant categories of patients. Over 12 OECD countries have adopted similar programmes. The primary goal is to reduce waste in the healthcare system and avoid risks associated with unnecessary treatment.

At the second RACP sponsored Evolve meeting in Sydney on 7 April 2016, several medical specialty societies adopted the choosing wisely approach and presented their lists of low-value tests or procedures. Several items were duplications of ABIM counterparts.

Choosing wisely: early results and cognitive dissonance

There is much interest in the effectiveness of the ABIM Foundation campaign as it is the longest running. To maintain support, such programmes need to demonstrate both short- and long-term effectiveness. Analysis of the short-term impact on medical and pharmacy claims to one USA health insurer covering 25 million members suggests that the approach of developing and promoting lists of low-value tests and procedures has effected little if any change in physician behaviour.

Within the American College of Rheumatology top five list was a recommendation concerning monitoring bone mineral density (BMD): Do not routinely repeat dual X-ray absorptiometry (DXA) scans more often than once every 2 years.

The level of evidence for this recommendation was given as Grade 1C: a strong recommendation, with low quality or very low-quality evidence. This dissonant grading leaves a reader uncertain. How can a strong recommendation be made despite the acknowledged low or very low-quality evidence? What does the evidence relate to: the frequency of testing or whether testing is of any value at all? While acknowledging the lack of evidence for the recommendation, the attached explanatory note gave a tacit insight into the cognitive biases that may have been operating in developing the item:

The optimal interval for repeat DXA scans, especially in high-risk patients such as those initiating glucocorticoids, is uncertain. Despite this uncertainty, availability of physician office-based DXA scanners and a Medicare policy that reimburses for repeat DXA scans every 2 years likely contributed to higher utilisation of this technology in some groups of patients.

In discussing the item, it was concluded further research is needed on the timing and frequency of DXA testing in patients at risk for osteoporosis and those with known osteoporosis who are receiving treatment.

As in the USA and contrary to original intentions, two characteristic themes are evident amongst many items within the RACP specialty lists.

1. The statements are outward looking.
2. The statements are educational with no significant measurable impact.
For example
do not use antihistamines to treat anaphylaxis
and
do not order ANA testing without symptoms and/or signs suggestive of systemic rheumatic disease.

These are recommendations directed at groups outside the craft group from which they were developed. They are educational statements covered in textbooks, pathology test manuals, test report comments and similar resources. They do not engender ownership in those to whom they are directed and as such, if read at all, are unlikely to have any lasting impact.

**Evolve clinical/practice guidelines**

An approach with potentially greater short- and long-term impact would be to undertake critical appraisal of clinical/practice guidelines. Such guidelines are becoming increasingly embedded in electronic pathways for general practice.7–9 Local medical specialty groups are major contributors to these guidelines, but critical appraisal using standardised instruments is either not done or not acknowledged as being done. In addition, despite their potential impact on consumption of healthcare resources, conflicts of interest of those generating the guidelines are rarely if ever transparently addressed and what if any debiasing strategies are used in development are not apparent.

**A case study of cognitive bias: osteoporosis guidelines**

A recent review of management recommendations for osteoporosis in 78 clinical guidelines lodged at the Agency for Health Research and National Guideline Clearinghouse noted that 90% recommended BMD measurement as a monitoring procedure.10 Local guidelines understandably incorporate the same recommendations.7 It is difficult to determine if these guidelines have been evaluated against either international or national validated and endorsed appraisal instruments such as the Canadian Institutes of Health Research’s Appraisal of Guidelines for Research and Evaluation (AGREE) II11 or the Australian National Health and Medical Research Council standard for clinical guidelines.12

BMD is one of several predictors of fragility fracture risk. Its utility varies in different geographic populations and ethnicities. In New Zealand, a BMD measurement is one criterion amongst others enabling qualification for a public subsidy for bisphosphonate therapy. However, BMD adds only a small percentage to the predictive power of FRAX, a commonly used online Fracture Risk Assessment Tool developed under the auspices of the World Health Organization.13 Take a 65-year-old woman with one previous fragility fracture and no other risk factors except for a femoral neck T-score of −2.5. Her FRAX calculated risk for a major osteoporotic fracture or hip fracture in 10 years is 17 and 3.6%, respectively, whereas if the T-score is not included it is 19 and 4.9%.

In a real world setting, a Canadian study examined the predictive power for fragility fractures of FRAX with and without femoral neck BMD in a cohort of over 35,000 women aged 50 years and over.14 The cohort was divided into those not treated with anti-resorptive therapy, those currently treated and those treated in the past. The aim of the study was to determine how the predictive power of FRAX performed for fragility fracture in these groups. Of relevance to the current discussion was the finding that the addition of BMD to the FRAX score was not additive to the predictive power of FRAX without the inclusion of BMD. Nevertheless, irrespective of the comparatively small weighting BMD gives to predicting fragility fracture, reduced baseline BMD does increase the risk. This observation and the incorporation of BMD monitoring into guidelines has cemented its use into routine medical practice.

**Illusory correlations: association is not causation**

Treatment with bisphosphonates over 3–5 years has been shown in multiple large clinical trials to be associated with an increase in BMD and an absolute risk reduction in fragility fractures in post-menopausal women at significant risk: vertebral fractures 5% reduction, hip fractures 1% reduction and other fractures 2% reduction.15,16 Despite strong objections, this association between increases in BMD density and absolute risk reduction in fracture in mainly post-menopausal osteoporosis has been used to justify the use of BMD as a surrogate end-point for fragility fracture in osteoporosis treatment trials in other groups at risk.

Absolute reduction in fragility fractures from bisphosphonate therapy in those taking corticosteroids is not defined although BMD in these mainly rheumatic disease patient populations is either maintained or increased after 3–5 years of therapy.17 In other meta-analyses of treatment effect in steroid-associated osteoporosis, there was a statistically significant relative risk reduction in combined asymptomatic and symptomatic vertebral fracture but not in hip fractures.18

The optimal duration of bisphosphonate therapy is undefined.19 Reports of bone complications such as the increased risk of ‘atypical’ femoral fractures sounded a
cautionary note to the long-term safety of these agents. Given the mechanism of action of bisphosphonates, this not unexpected complication prompted the recommendation that after 5 years of therapy patients should be reviewed as to the appropriateness of continuing therapy.\textsuperscript{15} What predictors of future fracture risk should be used to guide therapeutic interventions during and at completion of anti-resorptive therapy is unknown but several studies have addressed this question with respect to BMD.

In 2005, Watts \textit{et al.} combined the data of three phase III randomised, double-blind placebo-controlled trials of post-menopausal women with osteoporosis treated for up to 3 years with risedronate ($\pi = 2561$) where fracture was the trial end-point.\textsuperscript{20} They aimed to study the relationship between treatment-related change in BMD and reduction in the incidence of non-vertebral fracture. They concluded that BMD at neither the spine nor the femoral neck as measured by DXA predicted the degree of reduction in non-vertebral fractures.

\begin{table}[h]
\centering
\caption{The Seven Deadly Sins: checklist of seven common and insidious forms of cognitive bias}
\begin{tabular}{|l|l|l|}
\hline
Cognitive bias & Brief description & Explanatory example(s)/statements \\
\hline
1. Overconfidence & The discrepancy between the correctness of the response and the belief in the correctness of the response increases as the respondent becomes more knowledgeable & ‘Experts’ may more often be correct than non-experts, however, the strength of the conviction that they are correct is disproportionately high compared to the probability of them being correct. This bias is closely linked to the ‘halo’ effect: the uncritical acceptance of an opinion from an individual because they have admirable yet unrelated qualities. ‘I don’t have time to look at the evidence on BMD but the expert guidelines recommend it so I do it’ \\
\hline
2. Illusory correlations (magical thinking) & Finding correlation and assigning causation & Confusing diagnostic specificity with positive predictive value. Concluding that because bone mineral density correlates with the risk of osteoporotic fracture, bone mineral density is a marker of causation of osteoporotic fractures. \\
\hline
3. Predictability in hindsight & The conviction that something could have been predicted if the information revealed after an event had been known prior to the event & Having been told the diagnosis the physician then constructs a ‘educational’ scenario from knowledge gained in hindsight to convince himself/herself and others that the diagnosis could have been known earlier if what is now known was known prior. Closely linked to confirmation bias: Emphasising experiences that support the belief that measuring BMD has beneficially influenced medical practice and ignoring instances where no such benefit has accrued. \\
\hline
4. Anchoring & The first off the block with an idea, publication, or claim holds the central ground & Explaining away information that does not fit with a strongly held view. ‘The information presented in this article isn’t really relevant to every day clinical practice. BMD monitoring is part of practice so it is clearly useful’ \\
\hline
5. Ease of representation & What easily comes to mind dominates our thinking & ‘If only that patient with the fracture had had her BMD measured earlier this wouldn’t have happened’. The regret of omission being more powerful than the regret of ‘commission’: ‘I will be pilloried by my colleagues if I don’t measure BMD. The X-ray report recommends it’. Closely related to the availability heuristic: ‘the known is given more weight than the yet to be known or the unknowable’. \\
\hline
6. Probability blindness & Acting as if the correctness of a decision can be graded in terms of certainty rather than grades of uncertainty & Characterising risk to the individual as relative rather than absolute. Corruption of hypothesis testing by referring to research results as having ‘proved a hypothesis’ rather than ‘not having disproved’ a hypothesis. ‘If the evidence is not against the hypothesis it is for it’ \\
\hline
7. Reconsideration under suitable scripts & Conjoining the notions of coherence (creating a consistent and easy to follow story), plausibility (seeming reasonable) and probability (objective likelihood – what do the numbers tell us) & Conjoining: ‘Having less dense bone makes it weaker, having more dense bone makes it stronger therefore monitoring bone mineral density must be a clinically useful measure of bone strength’. Behaving as if there is additive diagnostic weight to separate tests that measure the same pathological process, for example, measuring ESR and CRP. \\
\hline
\end{tabular}
\end{table}

Adapted from Piatelli-Palmarini,\textsuperscript{27} with permission. BMD, bone mineral density.
The Fracture Intervention Trial long-term extension (FLEX) trial examined at-risk post-menopausal women who had received 4–5 years of alendronate therapy. Participants were randomly assigned to either receive placebo or continue alendronate therapy for a further 5 years. The FLEX trial did not show any statistical difference in the absolute risk of hip fracture or other non-vertebral fractures between the placebo and treatment groups. There was a 2% absolute reduction in the number of clinical vertebral fractures in the treatment group.

In another study with a similar extension phase (HORIZON-PFT) but using a different bisphosphonate, there was a 2.5% reduction in morphometric (asymptomatic and radiographic) vertebral fractures and no demonstrable reduction in hip and other fractures. Further analysis of pooled data from these extension trials suggested that there may be no benefit in reducing vertebral fracture risk or reducing non-vertebral fracture risk from continuing bisphosphonate therapy beyond 3–5 years.

The FLEX study also examined the clinical utility of repeat BMD measurements and markers of bone turnover in identifying subjects at risk following alendronate therapy. While BMD showed a moderate decline in those discontinuing alendronate therapy and a gradual rise in biochemical markers of bone turnover neither of these measures was useful in prediction models of bone loss in those continuing alendronate or those switched to placebo.

This poor predictive power of BMD monitoring has been noted for over 10 years. It is difficult to explain why it continues to be recommended as a tool for monitoring fracture risk in treated patients or those stopping therapy without invoking cognitive dissonance: that resistance to act on evidence that runs counter to deeply embedded beliefs that are reinforced by routine practice.

**Guideline development, review and cognitive debiasing**

Our understanding of the influence of cognitive bias in decision-making owes much to the pioneering work of Amos Tversky and Daniel Kahneman. Over 40 years of research has revealed reproducible patterns that are generic to both professional and day-to-day life. No individual, no matter how intelligent, is immune. However, recognising their existence and the scenarios in which they are prone to operate may alert clinicians to enact debiasing strategies in decision-making processes.

For ease of memory, a check list that uses a humorous intuitive classification of the more insidious and dangerous cognitive biases called the Seven Deadly Sins (Table 1) is one tool that may be used at times of critical decision-making. If such a check list or other debiasing strategy is used along with the use of validation tools in the development of or review of osteoporosis and other guidelines a priori, it is likely that recommendations lacking adequate evidence, such as the inclusion of BMD for monitoring treatment effectiveness would not have been included. However, if we take the history of BMD monitoring as a guide, such measures may not be enough to overcome the power of cognitive dissonance. Collaboration with medical jurisdictions and unbiased stakeholders is likely to be required in order to dismantle the dogma of established practice.

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Clinical approach to autonomic dysfunction

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Abstract

Patients with autonomic dysfunction may present with a variety of seemingly unrelated symptoms, both generalised and involving specific systems, including fatigue, difficulty concentrating, orthostatic intolerance, palpitations, constipation or diarrhoea, early satiety, urinary retention or incontinence and erectile dysfunction. Failure to connect the diverse symptoms with a single underlying mechanism may lead to incorrect diagnoses, inappropriate interventions and frustration on the part of both doctors and patients. We describe recent developments in the understanding of the pathophysiology of autonomic dysfunction, including the link between the autonomic and immune systems resulting in the ‘inflammatory reflex’. We then provide a rationale to guide the management of patients exhibiting features of autonomic dysfunction, including postural tachycardia syndrome.

Introduction

Patients with autonomic dysfunction may present with a variety of seemingly unrelated symptoms that may be generalised, including fatigue, difficulty concentrating or involve specific systems. These may include various combinations of cardiac (tachycardia/bradycardia), vasomotor (orthostatic intolerance, peripheral blood pooling), sensory (coat-hanger distribution of pain in the upper back, reflecting fatigue in large postural muscles of the neck and shoulders), gastrointestinal (constipation, diarrhoea or nausea/early satiety secondary to gastroparesis), urogenital (urinary incontinence, frequency, erectile dysfunction), sudomotor (increase or decrease in saliva, tears, sweating – sometimes with heat intolerance) and ophthalmological (impaired accommodation often resulting in intolerance to light and difficulty with vision) symptoms. Failure to connect the diverse symptoms with a single underlying mechanism may lead to incorrect diagnoses and inappropriate interventions.

There is a very active internet-based community of people who identify themselves to be affected by autonomic dysfunction. The aim of this paper is to review some recent developments in the understanding of autonomic dysfunction, which inform the workup and management of patients falling within the continuum of the autonomic dysfunction spectrum.

Causes of autonomic dysfunction: peripheral, ganglionic or central

Degeneration of small peripheral nerve fibres is seen frequently in association with diabetes mellitus. Rarely, peripheral autonomic nerve fibres degenerate due to toxins, a limited peripheral synucleinopathy termed ‘pure autonomic failure’ (PAF), or are infiltrated by amyloid deposits. Pure autonomic failure and amyloidosis are diagnoses entertained in patients with significant and progressive deficits.

Importantly many commonly prescribed pharmaceuti
cals for management of otherwise seemingly unrelated diseases, including depression, hypertension, heart failure, asthma/airways disease, overactive bladder/bladder outlet obstruction, Alzheimer-type dementia and glaucoma, mediate their effect by moderating the peripheral autonomic nervous system and therefore may contribute to, or mask, autonomic dysfunction.

Patients with autoantibodies directed against adrenergic, muscarinic or nicotinic receptors may also present with autonomic dysfunction. Assays for the ganglionic receptor (alpha-7 nicotinic acetylcholine receptor), seen in autoimmune autonomic ganglionopathy, are not readily available in Australia. However, as ‘seronegative’ patients may also respond to immunotherapy,1 the decision to pursue immunomodulatory options (intravenous immunoglobulin, plasmapheresis or pharmacological approaches) has been made in some centres on the basis of the predominance of ‘anti-cholinergic’ symptoms, that is dry mouth and eyes, or severe gastroparesis.

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Hypotension frequently develops following traumatic interruption of autonomic pathways in the spinal cord or paravertebral sympathetic chain.

Spinal cord injuries above the level of T6 are commonly associated with autonomic dysreflexia. Malignant hypertension can develop suddenly in association with an unrecognised stimulus (e.g. blocked urinary catheter, faecal impaction or pressure sores). Recognition and management of the precipitating stimulus are paramount in the management of autonomic dysreflexia. Anti-hypertensives are usually required only short term if at all.

Central autonomic failure can occur in association with neurodegenerative conditions, such as Parkinson disease or multiple system atrophy. Although these patients may describe anhidrosis, a transcutaneous stimulus may stimulate sweating in patients with central autonomic dysfunction as peripheral nerves can still be intact.

Currently, the majority of patients referred to autonomic clinics have symptoms of postural tachycardia syndrome (POTS), with or without chronic fatigue syndrome (CFS).

### Postural tachycardia syndrome

POTS is diagnosed if heart rate (HR) increases by >30 beats per minute (40 beats per minute in adolescents) within 10 min of patients moving from a supine to an erect posture. The increased HR is usually a physiological response to a reduced venous return, accompanied by pooling of blood in the peripheries or splanchnic vasculature. Symptoms usually reflect reduction in capacity to autoregulate cerebral blood flow (lightheadedness, ‘brain fog’) and the metabolic sequelae of persistent tachycardia (fatigue).

At rest, baroreceptors generate action potentials in the afferent limb of the baroreflex arc. The frequency of action potential firing reflects the tension in the walls of the thoracic vessels, adjusting with minute changes to intrathoracic pressure (breathing or Valsalva manoeuvre) or hydrostatic pressure (posture, blood volume). These action potentials travel through the afferent limb of the vagal nerve, communicating in the medulla with both the parasympathetic ‘afferent’ arm of the baroreflex (also travelling through the vagal nerve) and the sympathetic centres. When the baroreflex functions appropriately, standing generates a fall in baroreceptor firing with an immediate increase in HR through both inhibition of vagal tone and increase in sympathetic outflow. Simultaneous upregulation of sympathetic outflow from the medullary baroreflex connections increases vascular tone mediated through the action of noradrenaline on alpha-1 adrenergic receptors in the blood vessels’ smooth muscle cell membranes.

In patients with POTS, the baroreflex-generated sympathetic outflow fails to compensate adequately for the fall in venous return that occurs on standing. This may be due to inadequate alpha-1 receptor activation or due to the presence of a strong vasodilating stimulus (e.g. calcitonin gene-related peptide, neuropeptide Y, substance P, prostaglandins and/or nitric oxide) generated in response to acetylcholine. The latter may be particularly relevant in patients who develop POTS following an infective episode as it is now well recognised that acetylcholine is produced by a subset of T cells expressing choline acetyltransferase following an inflammatory stimulus. Thus, the primary cause for the failure to maintain homeostasis may have multiple different primary drivers.

Attempting to identify the primary driver can be a frustrating exercise. There is an indisputable association of POTS with hereditary hypermobility (including some forms of Ehlers–Danlos syndrome), raising the question of a matrix or connective tissue defect, but it is rarely possible to identify a relevant genetic mutation. Many patients develop POTS after an acute illness in their adolescent years, in association with the appearance of antibodies to Epstein–Barr or influenza viruses. Unfortunately, anti-infective and/or immunological therapies are usually ineffective. Although management of the cardiovascular symptoms does not necessarily address the underlying precipitant, it can substantially improve quality of life for patients with POTS.

### Link between the autonomic and immune systems

Between 2000 and 2003, several landmark papers described the ‘inflammatory reflex’ and ‘cholinergic anti-inflammatory pathway’. The reflex is initiated when inflammatory molecules such as IL-1b and prostaglandins are released by immune cells (tissue dendritic cells) in response to infection (pathogen-associated molecular patterns) or inflammation (damage-associated molecular patterns). IL-1b and prostaglandin receptors on afferent vagal fibres are activated, generating a signal that passes through the vagal afferent fibres to the nucleus tractus solitarius of the medulla. Connections within the brainstem result in downregulation of sympathetic outflow, activation of the hypothalamic–pituitary axis (febrile response and increase in glucocorticoids) and activation of the vagal dorsal motor nucleus in the medulla. From the medulla, the efferent arm of the reflex passes through efferent vagal fibres to nerve fibres in the myenteric plexus, macrophages in the gut wall and through
the celiac ganglion and splenic nerve (sympathetic) connects with T cells within the spleen. The net result of the efferent arm of the reflex is downregulation of the inflammatory response. Vagotomy, splenectomy or beta-blockade significantly reduce this anti-inflammatory effect.6

Thus, control of sympathetic and parasympathetic outflow is dependent not just on baroreceptor activation but also on inflammatory stimuli, including infection, trauma or autoantibodies. Altering vagal tone and/or manipulating acetylcholine signalling pharmacologically can capitalise on this interaction between the immune and autonomic systems.

Intervening in the inflammatory reflex

Electrical stimulation of the vagal nerve

Vagal nerve stimulation (VNS) has been shown to reduce inflammation in animal models of endotoxaemia,7 haemorrhagic shock,8 burn-induced injury,9 colitis10 and postoperative ileus. In animal models, the anti-inflammatory effect can be lost if pharmacological or genetic ‘knock-out’ of nicotinic receptors is performed or a splenectomy or vagotomy precedes the inflammatory stimulus.11

Implantable VNS devices have been tried in patients with heart failure,12–14 with beneficial effects independent of the effect of VNS on HR. A phase-2 trial of implantable devices providing VNS for patients with rheumatoid arthritis is in progress and a phase-1 trial of an implanted VNS device for fibromyalgia showed remarkable responses in a small number of patients.15

Less invasive and less costly approaches to VNS include stimulation of the auricular branch of the vagus nerve16 or transcutaneous stimulation of the cervical vagal trunk. Experiments in animals showed that transcutaneous stimulation was protective in animal models of endotoxaemia and sepsis.7 Non-invasive VNS is already used in the management of intractable seizures, cervical dystonia, migraines and mental health disorders and is likely to become increasingly adopted in inflammatory conditions.17

Reducing inflammation in the gut (microbiome and food intolerances)

It is likely that in the future a personalised recommendation for dietary modification may be possible through study of an individual’s glycaemic and microbiome responses to specific foods; however, at present there is no universally accepted approach. Most patients with POTS and/or CFS go through a phase of exclusion diets and probiotics with variable success. In some centres, recommendations include use of histamine-receptor antagonists (both H1 and H2) and/or use of a diamine oxidase supplement with foods. In the absence of better evidence, we promote a limited trial of dietary and faecal microbiome manipulations while encouraging patients to revert to a healthy balanced diet if the trial fails to improve symptoms.

Suppression of chronic infections

As the inflammatory reflex can be activated by pathogens, reports of individuals in whom chronic infections are ultimately identified as the stimulus for POTS are to be expected. Local epidemiology should be taken into account in selecting relevant investigations for occult infections. It may be worthwhile prescribing antivirals at suppression doses for patients experiencing frequent recurrences of herpes simplex virus.

Acetylcholinesterase inhibitors

Neostigmine and pyridostigmine inhibit acetylcholinesterase enzymes resulting in an increase in acetylcholine at both autonomic and neuromuscular junctions. Neostigmine is often used to reverse neuromuscular blockade at the conclusion of anaesthetics whilst pyridostigmine is primarily used to counter autoantibodies blocking neuromuscular receptors in patients with myasthenia gravis. The increase in acetylcholine at muscarinic receptors limits the tolerability of anticholinesterase inhibitors. In the anaesthetic setting, atropine is usually administered concomitantly with neostigmine to counter these effects. In patients with autonomic dysfunction, the effect of pyridostigmine is unpredictable, with variable activation of the somatic, parasympathetic, sympathetic, immunologic and central nervous systems. Pyridostigmine may be helpful in the management of gastroparesis and orthostatic hypotension, because it appears to improve orthostatic symptoms without increasing supine hypertension, potentially by increasing sympathetic ganglionic transmission. However, stimulation of muscarinic receptors on vascular endothelial cells can increase nitric oxide synthase levels and because nitric oxide is a potent vasodilator, the effect of pyridostigmine can either alleviate or exacerbate orthostatic symptoms.

Domperidone has also been used for patients with gastroparesis. Despite being a dopamine antagonist, it does not readily cross the blood–brain barrier and therefore may not alter transmission in the dopaminergic neurons of the basal ganglia in patients with Parkinson disease.
Management of orthostatic intolerance

Non-pharmaceutical interventions for orthostatic symptoms include use of simple manoeuvres such as crossing the legs while standing/tonic muscle contraction, use of pressure stockings to counteract vascular pooling and avoiding environmental conditions that predispose to vasodilation (e.g. hot showers). Some patients find elevation of the head of the bed by approximately 10 cm helpful, whilst for others, smaller, more frequent meals and maintenance of blood volume with approximately 2.5 L water and approximately 8 g salt each day may moderate symptoms.

Expansion of blood volume through use of fludrocortisone (or occasionally vasopressin) and increasing vascular tone through use of alpha agonists (phenylephrine, midodrine) may be life-changing in patients with severe orthostatic intolerance.

Patients with POTS sometimes improve with HR control, using small doses of propranolol or ibradine off-license.

Droxidopa (L-DOPS) may also have a role to play, although it is not currently registered by the Therapeutic Goods Administration (TGA) and needs to be imported with TGA permission. L-DOPS is a pro-drug, converted to noradrenaline by aromatic amino-acid decarboxylase. Deficiency in dopamine beta-hydroxylase (the enzyme that normally converts dopamine to noradrenaline) is exceedingly uncommon, yet L-DOPS has proved effective in neurally mediated hypotension at doses ranging from 100 to 600 mg three times a day.18 As outlined earlier, pyridostigmine may improve or exacerbate orthostatic symptoms and whilst we have not found it to be particularly helpful in the management of orthostatic intolerance in our patients, there are other centres where it is used relatively often.

Management of supine hypertension

Patients with autonomic dysfunction may become hypertensive when supine due to dysfunction of the baroreflex. It is important to differentiate supine hypertension from sympathetic dysreflexia in which a block to the descending inhibitory signals fails to moderate the vasoconstriction generated when sympathetic nerves are activated by a noxious stimulus (e.g. urinary retention, bowel distension, sacral pressure sores). This scenario is commonly seen in patients with a spinal cord injury. With sympathetic dysreflexia, the raised blood pressure can be acutely lowered using nitrates, but addressing the primary cause (e.g. by unblocking a urinary catheter) is essential if control of BP is to be regained.

In contrast, supine hypertension is managed by providing a 10° head-up bed tilt and, in patients who still have some sympathetic tone, a central alpha-2 agonist (clonidine) reduces sympathetic outflow overnight when given in the late afternoon without exacerbating orthostatic hypotension during the day.

Management of hyperhidrosis

Surgical interruption of the sympathetic chain at the level of T1–T3 is still performed in some centres, but is irreversible and associated with significant adverse effects. Although sweat glands are innervated by post-ganglionic sympathetic fibres, uniquely to the sympathetic system, these fibres use acetylcholine as their neurotransmitter acting on muscarinic receptors. Effective pharmacological approach to hyperhidrosis, therefore, can entail reduction of central sympathetic outflow (clonidine) as well as anti-cholinergic approaches (botulinum toxin, glycopyrrolate). The use of botulinum toxin is usually impractical due to the extent of the area, the need to repeat treatment several times a year and the high cost. A compounded lotion of glycopyrrolate (1–6%) applied to the affected area has been used in our patients with good effect, although a formal randomised controlled trial has not been undertaken. Being a large, highly charged molecule, systemic absorption after administration on the skin is minimal and therefore the anti-cholinergic side-effects seen with oral administration (i.e. drowsiness, reduced saliva and tear production, urinary retention, constipation and tachycardia) tend not to be an issue.

Management of the neurogenic/overactive bladder

Pharmacological management

Bladder contraction is mediated through para-sympathetic (cholinergic) neurons. Thus, the first approach to patients with urinary frequency is often a trial of an anti-cholinergic medication. Darifenacin/solifenacin possibly cross the blood–brain barrier less readily than do oxybutynin, but with all medications in this class, the potential for deterioration in cognitive performance in a susceptible population is concerning. In addition, constipation may be exacerbated (solifenacin > oxybutynin/tolterodine), and QT prolongation may occur (solifenacin at higher doses). Acetylcholinesterase inhibitors prescribed for cognitive impairment may exacerbate urinary frequency.

Local blockade of acetylcholine release through direct injection of botulinum toxin into the muscles of the bladder wall at cystoscopy can be extremely effective for approximately 9 months post-injection. Intermittent or
indwelling urinary catheterisation may be required for a variable time after the procedure.

Active relaxation of muscles in the bladder wall is mediated through beta-3 (noradrenergic) receptors. Mirabegron, a beta-3 agonist, may therefore be helpful on its own or in combination with anti-cholinergics in the management of urinary frequency.

Alpha agonists (e.g. midodrine, phenylephrine) and alpha antagonists (e.g. prazosin) may relieve or precipitate urinary incontinence respectively (and vice versa for retention) through their action on receptors in the bladder outlet. However, these medicines are used for urological symptoms, predictable consequences of stimulating/blocking vascular alpha receptors (hyper-/hypotension) must be borne in mind.

By reducing the volume of urine produced overnight, small doses of vasopressin (anti-diuretic hormone) may play a role in the treatment of nocturia.

**Non-pharmacological management of overactive bladder/nocturia**

Adopting the supine position at night, and thereby reducing hydrostatic pressures in the legs, results in reabsorption of fluid from peripheral tissues into the bloodstream. The ensuing expansion of intravascular volume increases urine production (through both anti-diuretic hormone inhibition and increased glomerular filtration rate), exasperating nocturia. Use of pressure stockings during the day, raising the head of the bed by approximately 10 cm and leg elevation in the hours prior to retiring to bed can help moderate the volume of urine production overnight.

Over-riding neural messages through the use of sacral nerve stimulators may be very effective in some patients, but they are expensive and placement may be difficult for anatomical reasons. Weekly, 30-min sessions of posterior tibial nerve stimulation through a needle inserted adjacent to the posterior tibial nerve (near the ankle joint) is a less invasive and cheaper alternative that may benefit some patients. Long-term benefits are often maintained with less frequent (monthly) sessions after the first 6 weeks of more intensive treatment.

**Autonomic dysfunction: ‘the new black’**

Many patients with chronic disease, particularly neurological conditions and diabetes, will develop autonomic dysfunction.

The point at which autonomic function testing is warranted will depend on whether demonstration of autonomic dysfunction will alter the patient’s management.

Many patients with CFS will have a degree of autonomic dysfunction, reflecting a chronic inflammatory state. There is a thriving online environment providing information to such patients because of which autonomic dysfunction has become better known within this community of people than it is within the mainstream of the medical profession, often leading to miscommunication and frustration on both sides.

In patients with significant postural vascular pooling leading to orthostatic intolerance, pharmacological management may dramatically improve symptoms, but will not address the underlying precipitant, for example presence of autoantibodies, gut dysbiosis, allergen/food intolerance or mitochondrial/cell signalling dysfunction secondary to nutritional deficiencies. Attempts to manipulate the multiple factors impacting on the immune and autonomic systems in these patients remain a great challenge for both patients and their doctors.

**References**


REVIEW

The limitations in implementing and operating a rapid response system

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Abstract

Despite the widespread introduction of rapid response systems (RRS)/medical emergency teams (MET), there is still controversy regarding how effective they are. While there are some observational studies showing improved outcomes with RRS, there are no data from randomised controlled trials to support the effectiveness. Nevertheless, the MET system has become a standard of care in many healthcare organisations. In this review, we present an overview of the limitations in implementing and operating a RRS in modern healthcare.

Introduction

To quote from Reade, ‘Many patients naively believe that when admitted to hospital they will be cared for by
a specialist doctor who is constantly available, supported by, nurses and allied health professionals who are equally committed to nothing but their optimal clinical outcome; working in a system that facilitates communication, oversight, efficiency and continuous improvement. Many junior doctors embark on their hospital career with similar misconceptions.11 Despite the naïve belief of patients and the aspirations of young doctors embarking on their careers, the healthcare system in Australia and indeed in many other countries has moved to an alternative way of escalating inpatient care.

Various response systems such as medical emergency teams (MET),2 rapid response teams (RRT),3 patient at-risk teams4,5 and critical care outreach teams6 have now been described. The MET call system was possibly the first, outlined by Hillman et al. in the early 1990s,2 and has continued to develop and spread around the western world as part of a rapid response system (RRS). The MET call is a hospital-based system designed to alert and call other staff for help when a patient’s vital signs or other factors that have fallen outside set criteria. The ‘response’ generally requires intensive care unit (ICU) medical and nursing staff to attend, meaning that they must move beyond their traditional boundaries of control.

Despite the widespread introduction of RRS, there is still controversy regarding how effective they are. Their introduction was prompted by a few before-and-after single centre studies that showed a reduction in the rate of cardiac arrests.6,7 Although a major multicentre, cluster-randomised, controlled trial (MERIT)8 failed to demonstrate a mortality benefit and a few meta-analyses9 questioned the need, RRS have become the standard of care in many healthcare organisations for managing patients in the general wards of acute care hospitals. However, such teams may be treating the root cause.10 The RRS also represents a political change within the hospital hierarchy, and this political dimension is not commonly discussed in scientific literature.

RRS is not a perfect system and does have limitations. In this review, we highlight these limitations in implementing and operating a RRS in the modern healthcare system.

The doctor–patient relationship

The doctor–patient relationship has been and remains a cornerstone of care.11 The relationship between doctors and their patients has received philosophical, sociological and literary attention since Hippocrates, and is the subject of some 8000 articles, monographs, chapters and books in the modern medical literature. A robust doctor–patient encounter and relationship can guide decision-making in healthcare plans. The medical interview remains the major medium of healthcare. Most medical encounters are spent in discussions between practitioners and their patients. The medical interview comprises gathering information, developing and maintaining a therapeutic relationship and communicating information. These functions inextricably interact.11 For example, a patient who does not trust or like the practitioner will not disclose complete information efficiently. A patient who is anxious will not comprehend information clearly.12 As approximately one-third of MET calls involve end-of-life care decisions,13 the doctor–patient relationship assumes even greater relevance. Sadly, such difficult sensitive discussions are often left to a member of the RRT under circumstances devoid of time and established trust.

Patient-centred care

Patient-centred care requires that clinicians communicate and interact with patients and carers and encourage their participation in shared decision-making. Patient-centredness is becoming a widely used, but poorly understood, concept in medical practice. It may be most commonly understood for what it is not: technology centred, doctor centred, hospital centred and disease centred. A systematic review and synthesis of qualitative studies of older patients’ and relatives’ experiences in acute care settings demonstrated that patients wished for ‘sharing decision-making: include me’.14 Older patients in hospital may feel helpless, fearful or not in control of what happens, especially if they have impaired cognition or communication difficulties. Depending on the hospital setting, a rapid response is provided by a spectrum of healthcare professionals. This paradigm shift of introducing a spectrum of new healthcare workers during a critical time of a patient’s stay is the antithesis of patient-centred care.

The patient experience after activation of a RRS has not been well studied. A PUBMED search using the keywords patient experience/rapid response team/MET team revealed only five results. Apart from one publication that addressed the experience of a single patient with the MET system,15 none of these publications addressed the patient’s experience. Despite the paucity of literature on the patient’s experience during attendance of a RRS, this unprecedented invasion of their privacy may certainly contribute to feelings of fear, anxiety and exclusion in decision-making. From the patients’ perspective the rapid appearance of innumerable unfamiliar, anxious faces accompanied by a flurry of activity and urgency of investigations could not be construed as patient centred.
Afferent limb failure

The RRS system consists of the ‘afferent limb’ that observes patients and identifies instability while the ‘afferent limb’, consists of staff skilled in critical care who should promptly respond and manage deteriorating patients. Afferent limb failure (ALF) is defined as serious events (such as cardiac arrests and unanticipated ICU admissions) that occur as a result of either a delay or non-activation of the RRS in patients with documented calling criteria.

The afferent limb that reports patient instability consists largely of nursing staff and junior doctors. In essence, the process for triggering a RRT review involves someone taking vital signs, documenting them, understanding that there is an issue and then responding to the altered physiology by calling a RRT. There is considerable disparity in RRT use between hospitals and this is related not only to understanding the principles of RRS, but also to the positive perceptions of the RRT. Nurses’ engagement with the RRT has been shown to be influenced by their level of training in its use, their clinical experience and their support both from the RRT and ward teams. Suboptimal MET activation is an important obstacle limiting the efficacy of the RRS. The intervention hospitals of the MERIT study had higher incidence of failed MET activation.

Failed activation has also been observed in mature systems with incidences as high as 42%. Failed activation may be due to ‘failure to monitor’ (especially respiratory rate which traditionally is not accurately documented), ‘failure to recognise’ (triggers used for clinical deterioration not appreciated by ward staff) or ‘failure to escalate’ (not activating RRT despite patient criteria). ALF amplified not only the patient’s morbidity and mortality but also hospital resource utilisation through increased unanticipated ICU admissions. Multiple issues have been identified that potentially impede the RRS activation process. These include poor skill mix, casual and part-time staff, local policies, hierarchical issues and lack of experience and education. More clinical deterioration occurs when nurses have less time to observe patients, such as overnight or during drug rounds or clinical handover. Nursing ratios may also affect the detection of deterioration, but there are conflicting data about this. A recent observational cohort study confirmed that outlier inpatients experience more emergency calls in hospital, implying that RRT activation may be a marker of quality of ward care. If vital signs are not measured frequently enough or not accurately documented (especially respiratory rate), signs of deterioration can be missed. One Australian research program has looked at measurement of postoperative vital signs and concluded that the practice of collecting vital signs postoperatively was based on tradition, not on evidence or clinical needs.

A recent study described that only 63% of junior doctors could confidently identify and escalate care for a clinically deteriorating patient. Furthermore, more than one-third were concerned about waking seniors at night. The study found that many junior doctors would escalate care because of the suboptimal documentation of limitation of medical therapy (LOMT). These data suggest that substantial improvements in-patient care could be achieved with standardised handover procedures and robust communication between senior and junior staff, and within medical teams, potentially decreasing the reliance on RRT.

Efferent limb limitations

Efferent limb failure is much harder to evaluate. Team composition plays a key role in the efferent limb and traditionally, both ICU medical and nursing staffs have led teams in Australia. However, alternative structures have been used elsewhere, including nurse and respiratory technician-led teams. Variation in team makeup and management and infrequent involvement of ICU consultants in the Australian RRT services may impact on the effectiveness of the RRT. Although almost all Australian RRTs were physician-led, in many sites the most senior member would be unlikely to have advanced airway skills. There is little published literature reporting the effectiveness of RRTs and certainly no studies that compared outcomes in nurse-led as opposed with doctor-led RRS.

Interestingly, a retrospective observational study comparing ICU-led and resident-physician-led RRT revealed no difference in the rates of cardiac arrests, ICU admissions or hospital mortality. The common RRT interventions that included administering supplemental oxygen or intravenous fluids, suctioning patients’ upper airways, securing intravenous access and ordering basic investigations (ECG, arterial blood gases, chest X-ray and routine bloods), could potentially be done by the home team ward staff. Certain studies focussed on a tiered response to RRT (i.e. a 2-tier system, where the first tier involves less urgent clinical review criteria, while the second tier involves more serious criteria triggering review by RRT). Not surprisingly, this strategy reduced the cardiac arrest rates but was associated with a progressive and significant increase in both tier responses.

Communication errors and lack of collaborative decision-making between RRT members and ward staff are not uncommon, leading to disjointed care of individual patients.
**Disruption to normal hospital routines**

There is also the added complication that there is limited understanding of what happens to an ICU, when many resident medical staff are deployed outside the unit and not readily caring ICU inpatients. A recent single centre study reported that despite no harm to ICU patients as a result of RRT calls, delayed ward rounds was a common occurrence with significant disruption to normal hospital routines and inconvenience to staff. Not surprisingly, the study concluded that despite these problems occurring frequently they were significantly under-reported using normal hospital reporting systems. The findings do infer that the potential advantages of the RRS for individual patients should be deliberated in the light of potential systemic disruption. The implication of disruption to normal hospital routines on patient flow would be difficult to quantitate and warrants further research in this area.

Different studies have used different criteria for activating RRT. Simple clinical judgement of nurses on the basis of subjective worry or general concern is a common trigger for RRT activation. The generic ‘worry’ significantly increased the RRT activation 35-fold when compared with activation based on vital signs. The number of RRT activations as a result of false positive calls has not been investigated. The trend of patient relatives having the right to initiate the RRT directly may bypass the chain of command and in fact increase the number of RRTs.

**End-of-life care issues**

A retrospective study described that documentation of advance care directives, including LOMT and not-for-resuscitation (NFR) directives at patients’ admission was extremely low (18%). Another study identified that LOMT and NFR directive documentation rates doubled after RRT involvement. One-third of the RRT’s interventions involve end-of-life care issues as reported in a recent review. Interestingly, LOMT discussions were performed more commonly than resuscitation interventions such as endotracheal intubation.

An end-of-life RRT call is probably patient centred, as it avoids inappropriate cardiopulmonary resuscitation or ICU admission, even though the means of achieving this goal is less than ideal. These RRT calls, however, often occur out of hours, when parent teams are not in the hospital. As the patients are acutely unwell, they are often unable to participate in discussions regarding their preferences for active, conservative or palliative care treatment. Accordingly, these taxing and emotionally burdened decisions are typically left up to covering doctors, the RRT and family members and often need to be made expeditiously.

**Inconsistencies in the education of both the RRT members and ward staff**

Many of the deteriorating patient education programmes are now taught at both undergraduate and postgraduate levels. Even though it is a requirement for all hospitals in Australia to educate staff in recognising and responding to clinical deterioration (Standard 9 and National Consensus Statement, Australian Commission on Safety and Quality in Health Care), the training is not homogeneous across all organisations.

There is paucity of evidence regarding the impact of education on actual RRT outcomes. Most of the evidence regarding education comes from survey-based studies measuring residents’ and nurses’ perceptions of patient safety and education. Another single centre web-based survey of junior doctors and nurses recorded contrasting opinions: the ward nurses believed they benefited from RRT calls, but the junior doctors felt that RRTs decreased their opportunities to obtain critical care skills or education. Although regular simulation training of paediatric RRT improves hospital response to deteriorating patients, the same was not observed in an adult population.

Interestingly, there is also currently no agreed model for training medical team leaders in the management of RRT calls. International models for training RRT members may not apply to typical healthcare systems in Australia and New Zealand. The model should also consider the tasks required in managing a deteriorating patient, which includes multiple communication episodes involving RRT members, ward staff, the patients and their relatives.

**De-skilling of ward staff**

De-skilling and loss of autonomy of ward staff is potentially an undesired by-product of RRS. The emergence of ICU and emergency department (ED) as specialties is likely to have a bigger impact in this regard. As RRS consist of an ‘expert’ team to solve any emergency situation, concerns have been raised about the de-skilling of ward staff in evaluating and caring for unstable patients. Even though single centre studies argue that the RRS do not de-skill the floor staff in tertiary hospitals, these studies were conducted by teams that pioneered the setting up of the RRS. This raises issues of not only of bias but also the generalisability of these findings in other institutions. Jones in a recent podcast discussed the issue of de-skilling of ward staff. The factors that may
contribute to de-skilling include shorter working hours, increased administrative tasks, much more risk adverse environments, more complex and sick patients with shorter hospital length of stays.

**Patient safety measures and outcomes**

Mortality is not necessarily a good measure of hospital safety as it depends on various factors that range from patient’s underlying clinical condition to the type of interventions they had. It is difficult to find agreement on the best ways to measure patient safety in hospitals despite enormous resources devoted to improving and studying safety. This patient safety net has possibly caused an over reliance on RRS. This may provoke a decreased sense of responsibility on the part of the hospital ward team. Hospital ward teams may be less likely to provide optimal care knowing that there is a backup system of RRS to identify and treat patients if they worsen, even though evidence suggests that being proactive prevents the development of reactive RRT. The presence of RRS may also inadvertently lead to confusion as to who has primary responsibility for the patient.

**Exploitation of RRT for system failures**

RRT systems have inadvertently been used to safeguard patients from dangers of system failure, exploiting the over-burdened RRS. These system failures include staffing shortages or suboptimal staff-to-patient ratios, inappropriate triage and disposition of emergency patients, premature discharge of unstable patients from critical care areas, bed pressures, inadequately trained junior medical staff and insufficient on-site presence of senior medical staff. The Australian government implemented the national emergency access target in 2010 (‘4-h rule’) aiming for >90% patients’ disposition from ED within 4 h. This has resulted in significant increases in RRT activations within the first 24 h of ward admission (55% of activations happened in patients admitted via ED), and with 12% of these patients requiring ICU admission, resulting in the use of considerable ICU resources. These system failures have occurred on a background of increasingly complex patients, tight budgets, high hospital bed occupancy and greater patient throughput.

**Economics**

The cost-effectiveness of RRT is not well studied. There are some data from a paediatric healthcare setting that RRT reduced clinical deterioration and was thereby cost effective. In adult healthcare services, there are no data to support cost effectiveness. Some authors have attempted to model the cost effectiveness of RRTs. Based on this financial modelling, they claim that RRT implementation may aid in cost saving by reducing length of stay and increasing the flow of patients through the patient care system. However, it remains to be seen if this modelling will translate to cost saving in current clinical practice. It is vital to study the cost effectiveness of this system given the increasing implementation of RRT across healthcare.

**Further research required**

RRT systems remain a fertile ground for further research. Areas of particular interest include: exploring patients’ experience after activation of a RRT, the potential implications of disrupting normal hospital routines, qualitative evaluations of potential de-skilling and standardised models for training medical team leaders in the management of RRT calls. When considering the increasing implementation of RRT across healthcare, studies should also focus on the cost effectiveness of RRS. While there are some observational studies that outcomes are improved with the introduction of RRS, there are no data from randomised control trials to support the effectiveness. Repeating the MERIT study on mature MET systems to demonstrate mortality benefits would likely be practically very difficult, but may be required if the question of effectiveness is ever to be answered.

**Conclusion**

There remains an enthusiastic response by many to embrace RRS with some evidence of benefit on the incidence of in-hospital cardiac arrests and on hospital mortality. It may, however, be appropriate to consider the implications of these disparately trained and structured small teams on patient-centred care, the relationship between patients and their healthcare professionals and the skill mix required of healthcare professionals in acute care hospitals.

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An evidence-based system for health surveillance of occupational divers

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Key words
occupational divers, fitness-to-dive, health surveillance, evidence-based.

Abstract

Background: The value of the commonly required routine annual medical examination of occupational divers has been questioned, and there is a need for a robust, evidence-based system of health surveillance for this group of workers.

Aims: To determine whether the medical examination and investigation component of occupational divers’ routine comprehensive health surveillance adds significantly to the information gained from the questionnaire component in determining fitness for diving.

Methods: An occupational diver database was interrogated to identify divers issued with a ‘limited’ medical clearance or considered ‘unfit’ for diving over a 5-year period. Reasons for the ‘unfit’ or ‘limited’ designation and the source of the critical information, whether the annual health questionnaire or the medical examination or questionnaire component (or both) of the initial or 5-yearly comprehensive medical evaluation, was recorded. For divers completing the 5-yearly repeat comprehensive medical evaluation, the sensitivity and specificity of the questionnaire alone for determining unfitness for diving was compared with that of a nominal ‘gold standard’.

Results: Of 5178 certificates issued to 2187 divers over a 5-year period, 158 (3%) were provisionally designated as either ‘limited’ or ‘unfit’. Of nine divers identified by the examination component of the 5-yearly comprehensive medical evaluation, four were eventually designated ‘fit’, two ‘limited’, and three were lost to follow up. None who had completed subsequent investigations remained ‘unfit’. The sensitivity and specificity of the questionnaire to detect unfit divers compared with the gold standard were 84.6 and 99.3%, respectively, and its accuracy was 98.9%.

Conclusion: The current New Zealand occupational diver medical certification process, comprising annual health questionnaires and 5-yearly full examinations, detects all health issues critical to the determination of fitness to dive.

Introduction

Most occupational divers worldwide are required to undergo an annual comprehensive medical examination. The widely accepted but unproven rationale is that comprehensive health surveillance should reduce occupational morbidity and mortality. Industry standards and guidelines exist to assist examining medical practitioners in the determination of fitness for diving.1–4 These include examples of medical conditions that could render the diver unfit, or fit for diving, but with certain limitations.

One country where the requirement for annual comprehensive medical examination does not apply is New Zealand, where a 2002 analysis of 300 occupational diving medical assessments cast doubt on the value of comprehensive medical evaluations and prompted the institution of a system requiring such evaluations only 5-yearly, with the completion of a health screening questionnaire in the intervening years.5 We previously audited the first 336 divers completing a 5-year cycle under this system and demonstrated that the annual health questionnaire detected all significant health problems arising after the initial comprehensive medical, with the 5-yearly full medical examination adding little value.6

The aim of the current study was to revalidate or refute the latter finding in a larger and more...
contemporary cohort of occupational divers whose health status has been monitored under the New Zealand system.

Methods

This study was approved by the Waitemata District Health Board Human Ethics Committee (reference number RM13088). All divers whose records were accessed had consented to their anonymised occupational medical information being used for research purposes. The New Zealand occupational diver medical database was interrogated to identify all divers issued with a ‘limited or conditional’ medical clearance or considered ‘unfit’ for diving over a 5-year period, from the beginning of 2010 to the end of 2014. When a diver was designated ‘limited’ or ‘unfit’, we recorded the reasons for this designation identified from the divers’ individual records and the source of the information leading to application of those designations, whether from the questionnaire alone or the examination component of the initial or 5-yearly comprehensive medicals or from the annual questionnaires. To be clear, we include any findings from discussions or system reviews in the definition of the ‘examination component’ of the comprehensive medicals.

As the focus of this study is on the adequacy of the health surveillance of occupational divers, we limited our analysis to experienced divers who had previously undergone an initial comprehensive dive medical examination followed by four annual health questionnaires. We therefore defined the ‘gold standard’ for the determination of diving fitness as the combination of the questionnaire plus the ‘subsequent’ medical examination and any investigations that were indicated. The primary outcome measure was a calculation of the sensitivity and specificity of the questionnaire alone in detecting problems leading to a designation of unfit or limited, in comparison with this gold standard. Statistical analysis used a web-based Bayesian calculator for the exact 95% confidence limits of a proportion (or credible interval) to define the sensitivity, specificity and accuracy of the questionnaire compared with the gold standard. The accuracy of the questionnaire in determining ‘unfitness’ or ‘limited fitness’ to dive was calculated by dividing the sum of true positive and true negative outcomes by the total sample number. We defined a ‘positive’ finding as a finding of unfit, limited or lost to follow up. The latter group was included as a conservative assumption for sensitivity calculations only because of the possibility of unfitness. As a secondary outcome, we recorded the source of the critical information and the nature and incidence of various health conditions leading to the provisional ‘limited’ or ‘unfit’ designation.

Results

Within the entire programme (initial comprehensive medicals, annual questionnaires, 5-yearly repeat comprehensive medicals), 5178 certificates were issued over 5 years, representing 2187 active occupational divers, of which about 1000 apply or re-apply each year. The age distribution of these divers is presented in Figure 1. The mean age of all divers was 39 years (range: 18–68). The sources of key information leading to the designation of a diver as unfit or limited are summarised in Figure 2.
and stratified by diagnosis in Table 1. The bottom four lines of Figure 2 represent the gold standard findings. The 158 unfit or limited certifications represented 130 divers (21 were represented more than once), of whom 29 were females, and whose mean age was 37 years (range: 18–65). In 28 of these certifications (17.8%), the critical information leading to a limited or unfit designation was revealed by medical examinations alone, 18 (64%) of which were at the initial compulsory medical examination. In contrast, in 130 of the 158 (82.2%) limited or unfit certifications, critical information was revealed by the questionnaire.

Nine of 663 divers (1.4%) who completed a 4-year cycle in which no important problems were detected by the annual questionnaire were provisionally designated as either limited or unfit based only on the examination component of the subsequent full medical examination. Of these, three were lost to follow up, and four were designated ‘fit’ and two ‘limited’ (none ‘unfit’) after further investigations. The two ‘limited’ had abnormal lung function tests but then passed a saline challenge test and were designated ‘limited’ only because of a requirement for annual saline challenge tests. The three lost to follow up represented four certifications because one of them presented for a full medical examination twice in consecutive years but was lost to follow up both times after failing to complete the recommended investigation. Two were obese and were asked to perform an exercise electrocardiogram, and the other had an abnormal lung function test and was asked to submit to a hypertonic saline challenge test. Even counting these three divers as ‘unfit’, the unfitness detection rate for the examination component of the 5-yearly comprehensive medical was 4 out of 1409 (0.28%) certifications or 3 out of 663 (0.45%) individual divers.

In comparison with the gold standard, the sensitivity and specificity estimates of the questionnaire to detect unfit divers were 84.6% (confidence limit
The estimates of sensitivity and specificity were based on figures for true and false positives and negatives derived from the data shown in Figure 2. The derivation of the values for true positives (33), true negatives (1360), false positives (10) and false negatives (6) is demonstrated in Figure 3. These numbers refer to the number of certifications, not divers. To clarify, using the ‘gold standard’ as defined above and the focus on the subsequent comprehensive medicals, the values in Figure 3 were reached by following the right branch of Figure 2. It is implicit that a finding of unfit by ‘examination only’ means the questionnaire finding was ‘fit’. So, for example, to derive the figure for true positives, we added the gold standard findings where the questionnaire also found divers to be unfit (1 + 4), limited (15 + 9) or lost (2 + 2), giving a total of 33. For the true negatives, we added the 1356 designated ‘fit’ at the first step (of the 5020 found ‘fit’ by both examination and questionnaire) to the four under the ‘examination only’ heading found fit by the gold standard because these were also found fit by the questionnaire, giving a total of 1360.

The most common positive responses to the questionnaire were to the questions on current medication (38%), previous chest X-rays, audiograms, spirometry or hypertonic saline challenge tests (33%), history of asthma (28%) and past hospitalisation (21%).

**Discussion**

Our data demonstrate that important health information relating to fitness for occupational diving are much more likely to be revealed by a screening questionnaire than by examination or investigations conducted as part of a comprehensive medical evaluation. Moreover, the majority of any positive examination/investigation findings are made at the initial compulsory comprehensive medical and a 4-year intervening evaluation. Only 9 of 663 divers who completed an initial comprehensive medical and a 4-year intervening period of negative responses to a screening questionnaire had significant problems detected by a subsequent examination, and none of the six who completed further investigations was eventually found to be unfit. The assumption of a worst case (‘unfit’) designation for the remaining three divers who were lost to follow up resulted in an ‘unfitness’ detection rate of 0.45% (excluding those with ‘limited’ fitness) for the examination component of the 5-yearly comprehensive medical evaluation. This represents the contribution to unfitness detection made from adding the examination and investigations to the questionnaire at the 5-yearly comprehensive medical stage.

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**Table 1** Incidence and source of diagnoses leading to the provisional designation of 130 New Zealand occupational divers as unfit/unfit limited over the 5-year period 2010-2014

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Questionnaire (Q)</th>
<th>Medical examination (M)</th>
<th>Both (Q + M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>18</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Abnormal LFT</td>
<td>13</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Obesity</td>
<td>11</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Chamber</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Hearing deficit</td>
<td>5</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>13</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Blood disorder</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx pneumothorax</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Colostomy</td>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Bronchiectasis</td>
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<td></td>
</tr>
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<td>Ankylosing spondylitis</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hx DVT/PE</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Recent hx DCS</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
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<td></td>
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</tr>
<tr>
<td>Epilepsy</td>
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<td></td>
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</tr>
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</tr>
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<td>Valvular defect</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hx chest pain</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PFO</td>
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</tr>
<tr>
<td>Recent IEBt</td>
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<td></td>
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</tr>
<tr>
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<td>Post-concussion syndrome</td>
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<td>Recent retinal surgery</td>
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<td>Thrombocytopenia/SLE</td>
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<td>Thyrotoxicosis</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Recent head injury</td>
<td></td>
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</tr>
</tbody>
</table>

CAD, coronary artery disease; DCS, decompression sickness; DVT, deep vein thrombosis; Hx, history; IEBT, inner ear barotrauma; LFT, lung function test; PE, pulmonary embolism; PFO, patent foramen ovale; SLE, systemic lupus erythematosus.

(CL) = 70.2–92.7% and 99.3% (CL = 98.7–99.6%) respectively. This could mean that up to two potentially unfit divers per year were missed by the questionnaire. The width of the confidence interval for the sensitivity suggests that this study was underpowered, but the sensitivity estimate is conservative based on the inclusion of two divers who were actually fit to dive but required annual respiratory review and three whose fitness-to-dive is unknown. As mentioned above, none of these divers was definitively unfit. The accuracy of the questionnaire was 98.9% (CL = 98.16–99.30%).
This study corroborates the findings of our previous investigation, which demonstrated that no important medical problems undetected by the annual questionnaire were subsequently detected by the examination component of the 5-year comprehensive medical in 336 divers who completed a 5-year cycle under that system. This study audited all certifications over a 5-year period, whereas the previous study followed a cohort of 336 occupational divers who completed two comprehensive medicals, and the intervening annual questionnaires, over the same time frame. The advantage of auditing all certifications is that it captures the divers who ‘fall at the first hurdle’ and can deduce the health reasons and method of detection.

These results provide an evidence base for challenging the ‘traditional’ insistence on a comprehensive annual medical evaluation for all occupational divers. In particular, there appear strong grounds for claiming that after completion of a comprehensive medical evaluation on entry to the industry, ongoing health surveillance can be adequately achieved by annual completion of a well-designed screening questionnaire, with further comprehensive evaluations at greater than annual intervals (in our case, every 5 years). In our setting, such a system has not resulted in important medical problems being overlooked, and considerable money has been saved by avoidance of expensive comprehensive consultations and repetitive investigations. The reasons for regulating authorities adhering to the tradition of an annual comprehensive medical evaluation in the face of evidence that there is no corresponding health benefit for divers are unknown.

The value of routine, annual, comprehensive physical evaluations in the context of an asymptomatic general population has been questioned, apart from a small number of components (such as blood pressure, weight, Pap smears) whose regular monitoring may result in improved health outcomes. However, such evaluations (the ‘yearly physical’) remain popular with both the general public and with physicians, who cite benefits like reduction of patient anxiety, strengthening of the doctor–patient relationship and the sense of caring and forestalling possible medico-legal complaints. In the context of routine occupational health assessments, it is likely that many employers take legal, rather than evidence-based, medical advice regarding the frequency and comprehensiveness of physical examinations, but they may also be persuaded by these other putative benefits.

Divers, like many other occupational groups, face specific, job-related health risks, and although pre-existing health conditions can contribute, most of the risk is derived from a combination of factors, such as accidents, equipment failure, inexperience or adverse environmental conditions, rather than health status alone. How-ever, if risk mitigation is possible through periodic health assessments, regulating authorities and/or employers are obliged to ensure that the nature and frequency of such assessments are based on evidence.

Studies of questionnaire-based health assessments of recreational divers in Scotland have demonstrated virtually invariable detection of divers whose health required further investigation. A study of recreational diving in Australia challenged these findings by reporting 9 of 632 diver candidates answering in the negative to all questions on a screening questionnaire who subsequently failed a face-to-face medical. The reasons for some of these failures were open to debate (such as failure to meet arbitrary spirometry standards), and it can be argued that such problems are more likely in a more comorbid recreational population whose mean age is considerably higher than the occupation cohort reported here. In the occupational setting, our previous audit of 336 New Zealand occupational divers over a 5-year period and the data presented here support the Scottish findings.
This study has several limitations that must be acknowledged. First, the questionnaire used for the annual health surveys is not the standard document designed for use in comprehensive occupational diver medicals in Australia and New Zealand. It is a more comprehensive questionnaire that focuses on enquiry about symptoms as much as diagnoses, and it went through a substantial development phase in which we adjusted it to improve utility and comprehension during informal trials with divers. Its use would be generalisable, but the fact that it is not a standard questionnaire needs to be acknowledged.

Second, New Zealand has a system of central arbitration in which all returned questionnaires and completed comprehensive evaluations are viewed, and certifications are issued by a primary reviewer supported by a secondary expert panel. This may enhance the efficacy of questionnaires as tools for health surveillance because individual divers become known and can be tracked although they may interact with different doctors in the community. This system also provides consistency in the evaluation of divers’ fitness and mitigates the inconsistency found in the diving fitness decisions of doctors in both New Zealand and Australia. Although we believe a questionnaire system would still work if administered locally by individual doctors, the circumstances of the study do raise a possible limitation of the generalisability of our findings in those jurisdictions where it may not be practicable to develop a diver certification system that includes central evaluation.

Third, the low incidence of ‘unfitness’ in this cohort, likely to be a ‘healthy worker’ effect, resulted in the study appearing to be underpowered. We would expect a higher incidence of unfitness if we included divers attending their initial comprehensive medical, but we focused on the more experienced divers for this study, acknowledging that there is a pre-selection bias. To achieve the same sensitivity (85%) for the questionnaire to detect unfit divers, in comparison with the gold standard, with 95% confidence but narrower confidence limits of say 80–90%, would have required a sample size five times as large as our study cohort. In the New Zealand setting, this would require data collection over 25 years, and this is not currently feasible.

Finally, our results and conclusions could be challenged on the basis of value judgements about whether the cost and logistic savings from not requiring frequent comprehensive medical examinations outweigh the potential harm from a diver being incorrectly certified as healthy. Our response to such criticism would be twofold. First, not a single diver in our study was definitively found to be unfit based on information obtained solely from the examination component of the follow up comprehensive medical. We have assumed that the three divers who did not complete follow up (see above) were unfit for the purposes of analysis, but this is a deliberately conservative assumption. Second, while we acknowledge that insistence on annual comprehensive medicals can only lower the risk of an adverse event, we believe that the principle of not pursuing costly interventions with very low yield just because there is a small chance of benefit is well established in medicine. A detailed cost-benefit analysis of our results is beyond the scope of this study but is a probable topic for future consideration.

Conclusion

After the initial comprehensive medical evaluation, health issues leading to occupational divers being considered ‘unfit’ were discovered almost exclusively from an annual online health questionnaire. A routine 5-yearly comprehensive medical examination provided little or no extra critical information. Apart from their perceived ‘intangible’ benefits, costly annual comprehensive medical examinations are difficult to justify for occupational divers.

Acknowledgement

We thank Mr Murray Polson (CEO, Erudite Software Ltd, Auckland) for developing and maintaining the electronic database for New Zealand occupational divers and retrieving the data required for this study.

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Goserelin toxicities and preferences for ovarian suppression method in pre-menopausal women with breast cancer

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Key words
goserelin, ovarian suppression, pre-menopausal women, breast cancer, preference.

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Abstract

Background: Goserelin, a form of medical ovarian suppression, is an effective treatment for pre-menopausal women with breast cancer (PMBC). Meta-analysis data showed that similar efficacy is achieved with medical ovarian suppression and non-pharmacological ovarian suppression (NPOS) – oophorectomy or ovarian irradiation. The acceptance rate of NPOS remains low.

Aims: This study explored the reported toxicities of PMBC women and their preferred ovarian suppression method whilst on goserelin.

Methods: A postal survey consisting of 22 study-specific questions was sent to PMBC women who received goserelin at the Flinders Medical Centre.

Results: Nineteen women were identified from the database; 12 versus 7 women received goserelin in the adjuvant versus metastatic setting respectively. Thirteen (68.4%) responded to the survey. Women in the adjuvant cohort were more likely to report toxicities. The most common were hot flushes (100% vs 50%, \(P = 0.033\)), myalgia/arthralgia (71.4% vs 16.7%, \(P = 0.048\)) and decreased libido (57.1% vs 16.7%, \(P = 0.135\)). NPOS was recalled to be offered to five (38.5%) women, with acceptance by one BRCA2 carrier. NPOS was declined initially due to fear of procedure, surgical/anaesthetic risk, invasiveness and planned future pregnancies. If given the option, upfront oophorectomy was indicated in seven (53.8%) women due to inconveniences with monthly goserelin.

Conclusion: Half of PMBC women indicated a preference to NPOS, but only a minority recollected NPOS being discussed. Inconvenience with monthly goserelin is the main driver toward a preference of favouring NPOS. Clarification from larger trials that research patients’ decision process and preferences regarding ovarian suppression is needed to validate our findings.

Introduction

Recent reports from large clinical trials have established that tamoxifen or aromatase inhibitor (AI) in combination with ovarian suppression strategies was superior to tamoxifen alone in very young women.1,2 This led to updates in the American Society of Clinical Oncology guidelines, now recommending the combination, especially in young pre-menopausal women.1 Medical ovarian suppression (MOS) with luteinising hormone-releasing hormone analogue (LHRHa), such as goserelin or triptorelin, is equally efficacious to non-pharmacological ovarian suppression (NPOS) methods, which includes surgical oophorectomy and ovarian irradiation.4-7 MOS, however, has far supplanted other NPOS modalities and is the most commonly prescribed among pre-menopausal women with breast cancer (PMBC) women with hormone-positive breast cancer, owing mainly to its non-invasiveness and reversibility.3 Furthermore, recent data from the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) indicated that the superiority of combining AI with goserelin in the cohort of adjuvant PMBC women younger than 35 years may potentially result in an increased utilisation of MOS in the future.1,2 Little is known previously whether women, despite the benefits of MOS, would opt for a change to NPOS during a course of cancer treatment.

Here, we report the self-reported experiences of PMBC women who were prescribed goserelin in the adjuvant...
or metastatic setting. We also report PMBC women’s preference and concerns regarding the various modalities of ovarian suppression in an attempt to identify whether women, after being on MOS, would consider opting for NPOS as their primary method of ovarian suppression.

**Methods**

An initial retrospective chart review was performed to identify eligible women who were pre-menopausal at the time of diagnosis of breast cancer, >18 years of age, had primary breast cancer (early or metastatic) with immunohistochemical staining positive for either oestrogen and/or progesterone receptors of >1% and had received goserelin as part of their breast cancer treatment at the Flinders Medical Centre between 2009 and 2015. The pharmacy dispensary list, iPharmacy database, was utilised to identify eligible PMBC women on goserelin. Data on demographics, clinico-histopathological characteristics, treatment, physician-documented goserelin-related toxicities and survival outcomes until 30 June 2015 were collected. PMBC women who received goserelin for fertility preservation during chemotherapy were excluded.

From this cohort of women identified by the chart review, a 22-item postal survey was mailed out to those who were still alive and contactable as of 30 December 2015. The questions were developed specifically for the survey, with inputs from experienced clinicians to explore PMBC women’s perceived toxicities whilst on goserelin, whether NPOS methods were offered, and whether a change of preference to NPOS modality was considered during their treatment course (see Supporting Information, Appendix S1). The questionnaire was pre-tested for content, wording and time required to complete the survey prior to posting of the survey to study participants. The Southern Adelaide Clinical Human Research Ethics Committee approved the study.

**Statistical analysis**

The cut-off date for data extraction utilised for analysis of the chart review was 30 June, 2015. Descriptive analysis by proportion and mean was utilised to analyse both audit and survey components of the study. A Chi-squared test was applied to compare whether numerical differences between the adjuvant and metastatic cohort were of any significance. A significant P value was considered to be <0.05. The Adjuvant! Online risk assessment tool (accessed at www.adjuvantage.com) was utilised to calculate cancer recurrent risk for only those with early-stage breast cancer. Correlation between factors that predicted preference to NPOS was analysed.

**Results**

**Demographics and disease**

From 1 January 2009 to 30 June 2015, 33 eligible women were identified (Fig. 1); 12 PMBC women received goserelin in the adjuvant setting compared to 21 in the metastatic setting. The later cohort also included four women who commenced goserelin as part of adjuvant treatment but went on to develop systemic recurrence. The mean age of patients for the whole study was 41.3 years. The adjuvant cohort in comparison to the metastatic cohort had a higher number of T1 size tumours (58.3% vs 9.5%, P = 0.003), with median tumour size measuring 24.1 mm versus 43.3 mm respectively. The tumours in the adjuvant cohort were more likely to be of well to moderate differentiation (66.7% vs 19.1%, P = 0.006) with negative axillary lymph node involvement (75.0% vs 9.52%, P = 0.0001). Both cohorts, however, exhibited a similar pattern of oestrogen and progesterone receptor positivity, with the most prevalent receptor characteristics being hormone receptor-positive but human epidermal growth receptor 2-negative breast tumours (Table 1).

**Concurrent treatment**

In the adjuvant cohort, the majority (7/12, 58.3%) of women received endocrine therapy alone, whilst the remainder received additional adjuvant chemotherapy with taxanes ± anthracyclines or trastuzumab. Combined endocrine therapy (goserelin with anti-oestrogens) was similarly utilised in both cohorts of women, with tamoxifen being the most commonly prescribed anti-oestrogen therapy among PMBC women.

**Goserelin use and toxicity**

A median of 18 doses of goserelin were administered to the entire cohort during the study period. The dose ranges for the adjuvant versus metastatic cohort were 3–45 versus 4–96 doses respectively. The most common physician-documented ovarian suppression toxicity was hot flushes (83.3% vs 66.7%) followed by tiredness, myalgia/arthralgia and emotional lability. Similar ovarian suppression toxicities were observed between the two study cohorts except for emotional lability, reported more commonly by women in the adjuvant cohort (33.3% vs 4.8%, P = 0.028). The duration of goserelin
therapy did not impact the frequency with which PMBC women experienced ovarian suppression toxicities.

**Survival outcomes**

The overall median follow-up was 51.5 months (8–163 months). Only 28.6% (6/21) of the metastatic cohort were alive at time of data cut-off, with median overall survival of 2.9 years achieved. All women in the adjuvant cohort in comparison were alive and undergoing routine surveillance as per institutional protocol. Their median predicted risk of breast cancer relapse utilising the Adjuvant! Online Risk Assessment tool over the next 10 years was 35.9%. None of the PMBC women in the adjuvant cohort, however, at the time of manuscript writing has suffered recurrence of their breast cancer.

**Results**

As illustrated in the flow diagram (Fig. 1), 19 surveys were sent out to the subgroup of PMBC women identified still to be alive at the time of survey posting. Survey response rate was 68.4% (7 vs 6 – adjuvant vs metastatic). Half of the respondents from each cohort were still on monthly goserelin. None from the metastatic cohort but three from the adjuvant cohort ceased goserelin prematurely; two changed to adjuvant tamoxifen alone after 14 doses, whilst the remaining one discontinued after 35 doses due to emigration to another country. Majority of the respondents reported a high level of compliance with goserelin. One respondent each from both cohorts of women, however, admitted to having missed five doses of goserelin, whilst the remainder of women claimed full adherence to monthly goserelin.

Similar to results from the chart review, self-reported hot flushes was the most common toxicity in both cohorts but was found to be of greater concern among women in the adjuvant cohort in the survey (100% vs 50%, $P = 0.033$) (Table 2). Myalgia/arthralgia (71.4% vs 16.7%) were the next common toxicity, but dissimilar to what was found in the chart review, decreased libido (57.1% vs 16.7%) was the third most frequently reported toxicity among women in the survey in both cohorts. Half of the women from the two study cohorts found hot flushes to be the most debilitating self-reported toxicity, with its frequency occurring up to 6–8 times a day. Myalgia and arthralgia were of concern only to women in the adjuvant cohort and was the second most intolerable toxicity to PMBC women in the survey.

Five women in total (3 vs 2) recollected that NPOS with either surgical oophorectomy or ovarian irradiation was offered as an alternative to goserelin during the course of cancer treatment. Only one respondent, however, accepted surgical oophorectomy due to being a...
known carrier of the BRCA2 mutation. Reported reasons for not choosing upfront NPOS were fear of surgery/radiation, concerns regarding surgical/anaesthetic risk, invasiveness of the procedure and plans for future pregnancies. Seven (53.8%, 3 vs 4) women from the survey, however, indicated a change of preference to oophorectomy if given the option upfront; two women remained uncertain, while the remaining four still preferred MOS irrespective of alternative options. Main reasons that prompted women to prefer NPOS over MOS were less time consumption, less frequent hospital visits, less injections, concerns over heightened risk of disease recurrence upon cessation of goserelin and fear of ovarian cysts development with long-term MOS use. All respondents

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adjuvant cohort (n = 12)</th>
<th>Metastatic cohort (n = 21)</th>
<th>P value (&lt;0.05)</th>
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<tbody>
<tr>
<td>Age, n (%)</td>
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<tr>
<td>&lt;35 years</td>
<td>0 (0)</td>
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<td>35–39 years</td>
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<td>9 (40.9)</td>
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<td>40–49 years</td>
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<td>≥50 years</td>
<td>0 (0)</td>
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<td>Tumour size, n (%)</td>
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<tr>
<td>T1</td>
<td>7 (58.3)†</td>
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<td>4 (33.3)</td>
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</tr>
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<td>4 (19.1)</td>
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<td>G3</td>
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<td>Lymph node status, n (%)</td>
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<td>ER ‘−/PR ‘+’</td>
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<tr>
<td>Her2 positive, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>10 (83.3)</td>
<td>15 (71.5)</td>
<td>0.443</td>
</tr>
<tr>
<td>Positive</td>
<td>2 (16.7)</td>
<td>6 (28.5)</td>
<td>0.443</td>
</tr>
<tr>
<td>Concurrent endocrine therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2 (16.7)</td>
<td>0 (0)</td>
<td>0.054</td>
</tr>
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<td>Tamoxifen</td>
<td>7 (58.3)</td>
<td>12 (57.1)</td>
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</tr>
<tr>
<td>Tamoxifen, AI</td>
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<td>0.409</td>
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<td>AI</td>
<td>2 (16.7)</td>
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</tr>
<tr>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Exemastane</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Toxicity from MOS, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flushes</td>
<td>10 (83.3)</td>
<td>14 (66.8)</td>
<td>0.301</td>
</tr>
<tr>
<td>Tiredness</td>
<td>4 (33.3)</td>
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<td>Emotional lability</td>
<td>4 (33.3)</td>
<td>1 (4.8)</td>
<td>0.028†</td>
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<td>Decreased libido</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td>0.179</td>
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<td>Headache</td>
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<td>1 (4.8)</td>
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<td>Sleep disturbance</td>
<td>0 (0)</td>
<td>2 (9.5)</td>
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<td>Injection site pain</td>
<td>0 (0)</td>
<td>1 (4.8)</td>
<td>0.443</td>
</tr>
<tr>
<td>None</td>
<td>0 (0)</td>
<td>1 (4.8)</td>
<td>0.443</td>
</tr>
<tr>
<td>Oophorectomy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12 (100.0)</td>
<td>17 (81.0)</td>
<td>0.107</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0)</td>
<td>4 (19.0)</td>
<td>0.107</td>
</tr>
</tbody>
</table>

†Percentages may not sum to 100% for a given characteristic owing to rounding. ‡Symbol indicating significant P value between the groups in terms of characteristics listed in the table. AI, aromatase inhibitor; ER, estrogen receptor; Her2, human epidermal growth factor receptor 2; MOS, medical ovarian suppression; PR, progesterone receptor.
from the survey, irrespective of their age, ethnicity, education level and occupation, shared similar views.

Discussion

This study provided insight into PMBC women’s perception and decision-making process on their preference for MOS or NPOS to practising oncologists. From our study, we identified that only a minority of PMBC women recollected NPOS being discussed during their treatment course, with half of these women preferring a change to NPOS after being on MOS. Our study also demonstrated that contrary to common belief, NPOS may be more readily accepted by PMBC women, with surgical oophorectomy preferred over ovarian irradiation. Such a high rate of change in preference of women towards NPOS found in our study compared to the lower reported rates of 16%–18% found in the SOFT and TEXT trials was certainly intriguing.1,2 No specific breakdown was reported in these large prospective trials of the proportion of PMBC women opting to undergo bilateral oophorectomy or ovarian irradiation when the change to NPOS was chosen. Although triptorelin, and not goserelin like in our study, was used in SOFT/TEXT trials, there was no reason to assume a difference in toxicity profile between triptorelin and goserelin impacting a woman’s decision on ovarian suppression. Dissimilar to SOFT/TEXT trials, where only women in the adjuvant setting were included, our study included both an adjuvant and a metastatic cohort of women. It is possible that those with incurable metastatic disease are more likely to choose permanent methods of ovarian suppression and could perhaps account for the higher rate of NPOS found in our study.

Ovarian irradiation, a common form of NPOS utilised among PMBC women, was shown in the Early Breast Cancer Trialists’ Collaborative Group meta-analysis to result in a mortality reduction of 24% in the absence of chemotherapy.6 The procedure has the benefit of being low risk with minimal complications. Long-term safety data on ovarian irradiation are however, lacking. Reasons for the low uptake of ovarian irradiation among PMBC women mainly pertain to its irreversibility in addition to its variable success rate regarding ovarian ablation. In one institution, for example, after a standard schedule for ovarian irradiation with 20 Gy in 10 daily fractions at 2 Gy/fraction over 2 weeks, successful ovarian ablation was achieved only in 75% of patients.8 This certainly may cause concern in younger pre-menopausal patients, where studies have shown that the rate of effective ovarian ablation being heavily influenced by age was lower, but, in some, the effect of ovarian irradiation may take up to 7–28 months to complete.8–10 This perhaps explained why none of the PMBC women in our study chose to undergo ovarian irradiation or indicated a preference change to upfront ovarian irradiation if given the option.

Surgical oophorectomy, the other form of NPOS, unlike ovarian irradiation, is effective immediately and is expected to be 100% complete. One study further demonstrated that oophorectomy was, in fact, a cost-effective method of ovarian suppression as the incremental cost required for 2 years of goserelin administration exceeded that of a one-time laparoscopic oophorectomy (US dollars: $5072 for 2 years of goserelin vs $3966 with oophorectomy).11 The benefits of oophorectomy in women with BRCA mutation is of even greater significance. This relates to their high lifetime risk of breast cancer at 56%–84% and high ovarian cancer risk at 36%–46% and 10%–27% in BRCA 1 and BRCA 2 mutation carriers.12 Risk-reducing salpingooophorectomy in this setting is likely to be more widely

Table 2 Summary of ovarian suppression toxicities from audit and survey components

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Audit</th>
<th>Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjuvant (%)</td>
<td>Metastatic (%)</td>
</tr>
<tr>
<td></td>
<td>N = 12</td>
<td>N = 21</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>10 (83.3)</td>
<td>14 (66.6)</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>4 (33.3)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>4 (33.3)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>4 (33.3)</td>
<td>8 (38.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0 (0)</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (8.3)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>0 (0)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Cannot remember</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>None</td>
<td>0 (0)</td>
<td>1 (4.8)</td>
</tr>
</tbody>
</table>

†Symbol indicating significant P value between the groups in terms of characteristics listed in the table.
accepted by PMBC women upfront as it produces up to 79% risk reduction in overall mortality by lowering risk of ovarian, fallopian tube, primary peritoneal and second breast cancers.13 This certainly was true in one of our PMBC women in the metastatic cohort who was not only the only patient in our survey cohort to undergo an oophorectomy but has done so shortly after four doses of goserelin. This wider acceptance of prophylactic salpingo-oophorectomy may be further potentiated by the ‘Angelina Jolie’ effect, where the impact of her high profile celebrity status has resulted in an increased public awareness of the elevated lifetime cancer risk in BRCA mutation carriers.14 Accompanying this, a noticeable increase in the number of referrals of at-risk women to familial cancer centres was made, with a subsequent surge of BRCA testing followed by increased enquiries made by at-risk women on risk-reducing salpingo-oophorectomies.15 Thus, despite oophorectomy being invasive, irreversible and having associated surgical/anaesthetic risk, a proportion of women in our study were willing to opt for oophorectomy after being on MOS due to its perceived benefits.

Goserelin, a form of MOS, was traditionally the most widely accepted upfront method of ovarian suppression in PMBC women due to its advantage of being easy to administer, non-invasive and reversible. Despite this, as clearly illustrated in our study, the inconveniences with monthly goserelin in terms of time consumption, frequent visits required and frequent injections were the reasons why some women in our study may not want to continue with MOS. This, coupled with recent published data suggesting gonadotrophin-releasing hormone analogue (GnRHa) may have reduced clinical efficacy in PMBC women, may be of potential concern.16 The data were based upon endocrine studies where GnRHa monotherapy was found to cause recovery of follicle-stimulating hormone after 1 month, with resultant stimulation of estradiol secretion. The addition of concurrent tamoxifen to GnRHa could potentially prevent this phenomenon. On the contrary, the addition of AI to goserelin resulted in an incomplete and highly variable estradiol suppression. Estradiol levels ranging from 8.6 to 56.8 pmol/L in pre-menopausal women were seen for the combination when the postmenopausal levels were only 4.4–5.9 pmol/L.17 This incomplete ovarian suppression was further compounded by AIs, potentially inducing increased estradiol synthesis via its partial agonist properties on the ovaries.16,17 What remains unclear is whether this incomplete ovarian suppression may lead to worse disease-free survival in these women, thereby necessitating the utilisation of other forms of NPOS warrants further clarification from validation studies.

Irrespective of the method of ovarian suppression, whether MOS or NPOS, majority of PMBC women will experience some form of toxicities from ovarian suppression. The two most common goserelin-induced toxicities from our study were hot flushes and myalgia/arthralgia. This was similar to what was reported in SOFT/TEXT trials.2 Interestingly, in our study, women from the metastatic cohort were noted to report less frequent ovarian suppression toxicities compared to their adjuvant cohort (Table 2). It is possible that women in the metastatic cohort may not perceive potential ovarian suppression toxicities as MOS-related due to them more likely to have pre-existing bodily symptoms from their combined higher disease burden and effects from past treatments.18 Equally as interesting was the observation that discrepancy was noted between clinician-recorded ovarian suppression toxicities and what were self-reported by women in the survey. This was certainly true for symptoms like decreased libido and vaginal dryness, where women self-reported concerns regarding these symptoms in the survey as the third most worrying toxicity, but the concerns were not captured in the chart review. Instead, from the chart review, emotional lability and tiredness were more of a concern to PMBC women. Lack of transcribing into case notes or simply due to certain toxicities not enquired by practising clinicians may both be plausible explanations for such a discrepancy.

The main limitation of our study pertained to its small population size, combined adjuvant and metastatic cohorts being studied, together with the heterogeneous concurrent treatment, which prevented the generalisability of the results. Recall bias introduced by potential poor recollection of occurred events by study participants may be another major limitation of this study.

Conclusion

Our study highlighted that while only a minority of women selected NPOS, approximately half of the women were willing to consider NPOS to mitigate the inconveniences associated with the administration of monthly goserelin. Larger-scale studies are warranted to validate further our findings and also to provide further insight into our patients’ decision process regarding preferred modality for ovarian suppression.

Acknowledgements

Our thanks to the members of the medical oncology unit at the Flinders Medical Centre for their support in writing this manuscript.
References


Supporting Information

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

Appendix S1 Survey on Zoladex (goserelin) for the treatment of breast cancer.
Viruses are frequently present as the infecting agent in acute exacerbations of chronic obstructive pulmonary disease in patients presenting to hospital

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Key words
acute exacerbation of COPD, respiratory viruses, C-reactive protein, flu-like symptoms, nasopharyngeal aspirate, PCR.

Abstract
Background: Viral causes of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are well recognised but only recently have rapid tests become available.
Aims: To identify respiratory viruses in the general population and those associated with hospitalisation in AECOPD using polymerase chain reaction (PCR) on nasopharyngeal aspirate (NPA), and the relationship between symptoms, viral detection and inflammatory markers.
Methods: A review of viruses detected in the general population in a health district between August 2014 and July 2015, using multiplex PCR for viruses from NPA samples. In addition, a single hospital, retrospective audit of patients admitted with suspected AECOPD was conducted.
Results: Of the 8811 NPA tested, 5599 (64%) were positive for at least one virus and 2069 of these were obtained from adults. In adults, the most common viruses identified were Influenza A (31%), Rhinovirus (27%) and respiratory syncytial virus A/B (10%). Most patients with AECOPD (102 of 153) had NPA sent for viral PCR testing and 59 (58%) were positive. The most common viruses identified were Influenza A (31%), Rhinovirus (24%) and respiratory syncytial virus A/B (17%) with co-infecting bacteria cultured in 22 sputum samples. Patients with influenza-like symptoms were more likely to have a positive viral PCR than those without symptoms (P < 0.004). The median C-reactive protein on admission was lower in the virus-infected than uninfected AECOPD (28 vs 60 mg/L, P < 0.026).
Conclusion: The spectrum of viruses detected in patients with AECOPD is similar to that of the general population. Viruses are more likely to be identified in patients with AECOPD who present with influenza-like symptoms and a low C-reactive protein.

Introduction
Chronic obstructive pulmonary disease (COPD) constitutes a major health problem in Australia and acute exacerbations of COPD (AECOPD) have considerable impact on morbidity, mortality and quality of life.1 Common triggers for AECOPD include air pollution and infection with viruses and/or bacteria in the tracheobronchial tree. However, in at least one-third of more severe exacerbations a cause is not identified. Antibiotic therapy is widely, and sometimes inappropriately, used in AECOPD resulting in increased risk of adverse effects and increased antibiotic resistance. Antiviral therapy for influenza viruses is available and needs to be commenced soon after the development of symptoms. Antiviral agents for other viruses including anti-rhinoviral agents are in clinical development, and not yet available for routine use.

Previous longitudinal, community-based and hospitalisation studies showed viral infections are common (39–56%) in patients with AECOPD, and are most usually associated with severe presentations,2 and with a longer median symptom recovery compared with non-viral exacerbations.2 The viruses detected in the upper respiratory tract most frequently are picornaviruses such as human rhinovirus or hRV (36%), influenza A (25%) and respiratory syncytial virus (RSV) (22%).3–5

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While viral causes of AECOPD are well recognised, sensitive and rapid tests for common respiratory viruses have only recently been used widely in clinical settings. Comparison of different diagnostic methods for the detection of respiratory viruses including viral culture, antigen detection tests, serology and reverse transcriptase PCR have shown that nucleic acid tests (NAT) such as PCR are more sensitive and at least equally specific. The PCR technique using nasopharyngeal aspirations (NPA) or swabs has a 2.7 times higher diagnostic yield than conventional viral culture and thus has been widely used in the South Eastern Sydney Laboratory Services (SEALS) reference virology laboratories in the Prince of Wales Hospital (POWH) over the past 2 years, as the screening tool for viral respiratory tract infections.

Given the time between NPA sampling, NAT assay and availability of results, alternate sensitive, but potentially less specific markers that differentiate viral and bacterial respiratory infections would be beneficial to guide initial therapy. C-reactive protein (CRP) is an acute phase protein that increases with infectious and inflammatory conditions. CRP levels have been shown to increase in AECOPD but are not well correlated to severity or outcome. Few studies have examined the relationship between microbial aetiology and CRP levels in patients with AECOPD.

Within POWH, a single centre in the Sydney Eastern Suburbs Local Health District (SESLHD), most respiratory patients presenting to the Emergency Department (ED) who are likely to require admission and who have symptoms suggestive of a viral respiratory tract infection during the annual influenza season undergo NPA for viral PCR and isolation until the results are available. In this group of patients, a significant proportion has underlying COPD and these patients are commenced on antimicrobial treatment based on clinical criteria for AECOPD. It would be helpful to have early indicators of viral infection, either by direct identification of viruses or by a surrogate. This would allow appropriate treatment and isolation of such patients. The aim of this study was to assess the respiratory viruses associated with hospitalisation in AECOPD identified by NPA viral PCR testing and the relationship between viral detection, inflammatory markers and co-existent organisms.

Methods

This was a retrospective case study design that was approved by the SESLHD Ethics Committee. Two audits were conducted in this study over the same time period:

1. An audit was performed upon the database of all NPA submitted for viral PCR in the SESLHD to the Department of Virology and Serology (SAVID) SEALS Microbiology between 1 August 2014 and 31 July 2015. The subjects were of all age groups and tests were requested from primary healthcare, outpatient and inpatient settings. The inclusion criteria were: (i) age > 18 years (ii) previous diagnosis of COPD or Spirometry performed on admission revealing FEV1/FVC < 70% and (iii) symptoms of AECOPD as per the GOLD definition (worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication). The GOLD definition of AECOPD refers to an acute change in one or more of the following cardinal symptoms: an increase in cough frequency/severity, an increase in sputum volume/change in character and an increase in dyspnoea.

2. A separate detailed audit was performed of the medical records of all patients admitted with an AECOPD during the period between 1 October 2014 and 31 September 2015 under a respiratory physician at POWH in Sydney, who met the inclusion criteria. Inclusion criteria were: (i) age > 18 years (ii) previous diagnosis of COPD or Spirometry performed on admission revealing FEV1/FVC < 70% and (iii) symptoms of AECOPD as per the GOLD definition (worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication). The GOLD definition of AECOPD refers to an acute change in one or more of the following cardinal symptoms: an increase in cough frequency/severity, an increase in sputum volume/change in character and an increase in dyspnoea.

The severity of COPD was defined by the GOLD criteria, that is, mild: FEV1 ≥ 80% predicted, moderate: FEV1 50–79%, severe 30–49% and very severe FEV1 < 30%.

The audit was based on the definition of influenza-like symptoms on the local guidelines for viral NPA testing followed in the ED: patients presenting with fever > 38°C plus one or more of coryzal symptoms, myalgia or headache.

The electronic pathology database was searched for results of viral NPA PCR, CRP or sputum microscopy and culture specimens requested within the first 24 h of arrival to hospital. Similarly, chest x-ray reports from presentation were reviewed and the presence of parenchymal collapse/consolidation noted. The commencement of empirical antibiotics or antiviral agents in the ED was recorded if documentation confirmed their indication was for the treatment of an AECOPD. Instructions to isolate patients with droplet precautions from admission were recorded if documented by emergency staff.

Results

Patient selection

General population

The SESLHD virology database containing 8811 NPA viral PCR results was interrogated and showed 5599 (64%) positive results in the year between August 2014 and July 2015 (Fig. 1). Of the 5599 positive results, 2069 of these NPA were obtained from adults and were positive for at least one of the viruses graphed in Figure 2.
The most common viruses identified in this adult, all-comer population were Influenza A 31% (642), Rhinovirus 27% (565) and RSV A/B 10% (209) (Fig. 2). The profile of viruses from the 3503 patients less than 18 years of age was significantly different to the adult group.

**Patients with AECOPD**

Medical records from a single centre within the SESLHD, POWH found that 153 patients were admitted with AECOPD in a similar 12-month period. The clinical characteristics of the patients are shown in Table 1. The cohort had a mean age of 72 years (range: 32–98). Prior to the index presentation, COPD was previously recognised in 130 (85%) patients and of those in whom spirometry was initially performed, the majority were classified as having severe COPD. The remaining 23 (15%) patients were found to have obstructive spirometry on presentation consistent with COPD; however, spirometric data to exclude significant bronchial reversibility were not available so that asthma could not be excluded.

**Virus identification**

NPA (n = 102) were sent for viral PCR of which 59 (55%) were positive.

The most common viruses identified were Influenza A 31% (18), Rhinovirus 24% (14) and RSV A/B 17% (10) (Fig. 2). Multiple viruses were identified in three patients with positive viral PCR. These co-infections included Influenza B/Rhinovirus/Coronavirus, RSV/Coronavirus and Rhinovirus/Coronavirus.

In those with a positive NPA, 13 (22%) cultured co-existent bacteria in sputum tested within 24 h of admission. The most common bacteria and fungi cultured included *Pseudomonas aeruginosa* (31%), *Haemophilus influenzae* (23%) and *Aspergillus* species (23%).

**Viruses identified in AECOPD and SESLHD populations**

![Figure 2 Percentage of viruses identified in AECOPD and SESLHD populations.](image-url)
Clinical associations

Symptoms

Influenza-like symptoms (fever plus one or more of oroviral symptoms, myalgia or headache) were reported by 66 (65%) of 102 patients on presentation to the ED who underwent viral NPA PCR testing (Fig. 3).

Those with influenza-like symptoms were statistically more likely to have a positive viral NPA PCR than those without symptoms (P value <0.004, Chi-squared test).

Severity of COPD

The severity of COPD was able to be estimated for 60% of all patients and 83% of those with positive viral PCR. The majority of patients admitted met GOLD criteria for severe and very severe COPD, but this did not relate to the likelihood of viral positivity.

Radiology

The radiology was reviewed and evidence of consolidation was found in 19 of those with a positive viral NPA PCR, and 17 of those which were negative.

Seasonal variation in viral detection

The seasonal trend in positive viral PCR results in the SESLHD database reflected the peak 4 weeks (4 August 2014–31 August 2014) of laboratory notifications of influenza in NSW during the 2014 flu season. Of the 1034 positive influenza PCR results between 1 August 2014 and 31 July 2015, 43% (443) were confirmed in the month of August alone.

Isolation

Based on initial clinical history, examination and radiology findings, 45 (29%) patients with AECOPD were isolated with droplet precautions as per the influenza season protocol in the ED. Of those 45 patients, 33 (73%) were found to have a positive viral PCR.
the group of 108 patients who were not initially isolated, 26 (24%) were found to have a positive viral PCR.

**Empirical antimicrobials**

Of the 151 (99%) patients commenced on empirical antibiotics for AECOPD, 58 (38%) had a positive viral PCR. A minority of patients, (10 (67%) of 15 patients) were commenced on empirical Oseltamivir and had a positive viral PCR.

**Discussion**

This study retrospectively examined the relationship between the presenting symptoms, inflammatory markers and microbiological results of patients presenting to a single centre with AECOPD after the introduction of viral NPA PCR testing. It demonstrates that the detection rate of respiratory viruses was strongly associated with a low CRP level and influenza-like symptoms on presentation.

When comparing the POWH AECOPD data to that of the wider health district (SESLHD) over a similar time period, some interesting observations can be drawn. The microbiological profile of viruses identified between the adults groups was similar, revealing Influenza A to be the most common virus isolated regardless of underlying COPD followed by rhinovirus, RSV and coronaviridae. It would be informative to establish the proportion of patients with COPD in the POWH group that had received the annual influenza vaccination prior to their presentation, but this information was rarely recorded in the medical record. Compared to the general population captured in the SESLHD data, one would expect this at risk group to have more protection against influenza through greater vaccination rates.

Viral and bacterial infections trigger AECOPD in up to 80% of cases. Co-infection with bacteria and viruses, as in 22% of our patients, suggests that both classes of organisms play a role. In studies of asthma exacerbations, it appears likely that respiratory viruses are the principal initiating infections, with initial bacterial infections being of lesser importance. While the reason behind lower rates of viral detection in exacerbations of COPD compared to asthma is unclear, the overall detection rate of 55% in this study is slightly higher than other similar studies. It would appear likely that viral infections disrupt the airway epithelium, reducing the innate immunity and allowing bacterial secondary infection to occur, as has been previously described.

Surrogate markers to discriminate viral and non-viral AECOPD were reviewed in this audit and both symptoms and inflammatory markers were found to be potentially useful indicators. The current guidelines regarding influenza-like symptoms was found to be strongly associated with positive viral results and thus appear to support this clinical assessment as a key aspect of the history obtained on presentation for triage. Further studies associating influenza-like symptoms and rates of droplet precaution isolation with proven viral infection would determine the necessity of an isolation protocol for such patients and be of public health interest to prevent in-hospital spread.

Previous studies of AECOPD have shown that in patients who have increased sputum purulence, the pattern of increase in CRP is similar to that seen in patients with pneumonia. This suggests that CRP may be used as a marker of significant bacterial infection and may have a role in determining whether antimicrobials should be prescribed. CRP levels were significantly lower in patients with viral AECOPD, supporting the contributory role of this serum marker in establishing the aetiology of AECOPD and its potential to guide treatment.

In previous COPD studies, co-infection appears to increase the severity of the exacerbation, and is associated with more symptoms, higher bacterial loads and systemic inflammation. These findings have implications for treatment. While newly acquired viruses may be the initiating agent, one study suggests antibiotics may minimise the interaction of chronic, colonising bacteria with virus that would have resulted in an increase in bacterial load or phenotypic change. However, this argument needs to be weighed against the potential for empirical antibiotics to cause antimicrobial resistance in an already vulnerable population. This audit has found symptoms and markers of inflammation to be informative in identifying a cause of AECOPD.

Owing to the study design, there are limitations in attributing causation of viruses detected to AECOPD. First, viral infection may have been missed in up to one-third of patients who were not tested on presentation, presumably due to lack of influenza-like symptoms. As viral shedding can occur for several weeks after post-infection, routine testing of all subjects may have affected the study’s findings including the associations of symptoms and inflammatory markers. Second, potential selection bias relating to the indication for viral testing exists between the two cohorts limiting the capacity to compare data sets. The AECOPD cohort was a highly selected group of patients, many of whom had symptoms suggestive of a viral infection to prompt testing. In comparison, the indication for testing in the SESLHD cohort is unknown and likely to be variable, including some screening for infection control. In the future, prospective studies could address whether CRP, and perhaps pro-calcitonin, could be used in addition to clinical acumen to guide empirical antimicrobial use in AECOPD. Likewise, large controlled trials of patients randomised to
receive empirical antimicrobials or targeted viral therapy alone in suspected viral AECOPD may further identify subgroups which would benefit most from antimicrobial treatment.

Conclusions
This audit found the spectrum of viruses detected in the upper respiratory tract of patients presenting with AECOPD to be similar to that of a general, adult population. Amongst the AECOPD cohort, viruses appear more likely to be identified in those who present with influenza-like symptoms and a low CRP. These findings support the potential role of symptoms and inflammatory markers in determining the aetiology and guiding empirical management of AECOPD. Given the prevalence of Influenza A in the AECOPD cohort, widespread vaccination may help to protect these patients and prevent hospital admission.

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Burden of atrial fibrillation: a retrospective review of patients presenting to acute medical services

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Key words
ischaemic stroke, atrial fibrillation, anticoagulation, thromboembolism.

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Abstract

Background: Atrial fibrillation (AF) is a major risk factor for stroke and is associated with increased stroke severity and greater morbidity and mortality. Anticoagulation is highly effective for preventing episodes of thromboembolism but remains under-utilised.

Aims: The aim of this review was to estimate the short-term risk of thromboembolic events in patients presenting with an acute medical illness, to assess rates of anticoagulation in eligible patients with AF and to describe physician decisions when prescribing anticoagulation in a hospital setting.

Methods: A retrospective cohort analysis of patients with AF presenting to acute medical services at Wellington Regional Hospital between 1 January 2012 and 31 December 2012 was performed.

Results: A total of 751 patient presentations with AF was identified; 613 unique patient encounters were eligible for analysis, and 38.8% of patients with a CHA2DS2-VASc score ≥2 were discharged after anticoagulation. The mean CHA2DS2-VASc score was 4.03 (SD = 1.94). The CHA2DS2-VASc score was not associated with being started on anticoagulation, odds ratio 1.16 (95% confidence interval = 0.83–1.61), P = 0.38, but age by decade older was associated with a reduced likelihood of being started on anticoagulation, odds ratio 0.61 (95% confidence interval = 0.41–0.89), P = 0.01. In untreated patients with a CHA2DS2-VASc score ≥2, the most frequently documented reasons not to initiate anticoagulation were decision deferred to the primary care physician, 15.6%; fall risk or frailty, 7.2%; and high bleeding risk, 6.6%. However, no reason was documented in 56.9%. The thromboembolic rate in patients discharged without anticoagulation within 3 months of presentation to acute medical services was 7/330 (2.1%).

Conclusion: Anticoagulation for stroke prevention in AF remains under-utilised in eligible patients presenting to acute medical services at a tertiary-level hospital.

Introduction

Atrial fibrillation (AF) is a major risk factor for stroke, and although the increase in risk depends on the presence of other risk factors, this increased risk is substantial.1 Stroke and concurrent AF are also associated with increased stroke severity, increased mortality, longer in-hospital patient stay and lower rate of discharge to a patient’s own home.1 Anticoagulation is an effective treatment that substantially reduces the risk of cardioembolic stroke due to AF. Anticoagulation with vitamin K antagonists, such as warfarin, or novel oral anticoagulants, such as dabigatran, reduces the relative risk of stroke by approximately 65%. Aspirin should not be used for stroke prevention in AF. Aspirin is no safer than warfarin in elderly people,2 but it is substantially less effective and reduces stroke risk by only 20% at the most.3

International guidelines recommend that the stroke and bleeding risk of patients with AF be assessed and appropriate anticoagulation be prescribed.4,5 CHA2DS2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/Transient Ischaemic Attack (TIA), Vascular disease, Age 65–74 years, Gender category) is a validated stroke risk score that performs better than CHADS2 (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/TIA) in predicting patients with non-valvular AF at high risk of thromboembolism and identifying patients with a truly low risk of thromboembolism.6

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Anticoagulation is under-utilised in eligible patients with known AF. A recent audit of New Zealand’s stroke care delivery reports that among patients presenting with an acute ischaemic stroke, the percentage of patients with known AF was 40%; however, only 24% of patients with AF were on anticoagulants. Overestimation of the risk of bleeding is a key barrier to anticoagulation, particularly among elderly patients. Advancing age, risk of falling and ability to comply with medication are also frequently cited as reasons not to prescribe warfarin in the elderly.

Aims

Anticoagulation rates and stroke risk in patients with AF presenting to the hospital with an acute medical illness are not as well characterised. The aims of this study are to estimate the short-term risk of thromboembolic events in patients with AF presenting with an acute medical illness, to assess rates of anticoagulation in eligible patients and, finally, to describe physician decisions when prescribing anticoagulation to eligible patients in a hospital setting.

Methods

This article included a retrospective cohort study of patients with AF, either assessed in the emergency department or admitted under the general medicine service at Wellington Regional Hospital between 1 January 2012 and 31 December 2012. Study patients were identified by an electronic search of discharge diagnosis codes with ‘atrial fibrillation and flutter’ (International Statistical Classification of Diseases and Related Health Problems 10th Revision code I48) listed as a primary or secondary discharge diagnosis. A primary discharge diagnosis of AF was defined as patients who presented with symptoms attributed to AF. Secondary diagnosis of AF was defined as patients who either had a history of AF or had developed AF during admission.

After review of the identified clinical records, the following records were not included: those with no medical record evidence of AF; stage 5 chronic kidney disease defined as an estimated glomerular filtration rate of <15 mm per minute, the presence of active malignancy or those who died during the admission (and so who would not have received outpatient anticoagulation).

Individual discharge summaries were reviewed for details of the admission and anticoagulation status on discharge. A CHA2DS2-VASc stroke risk score was calculated for each patient based on the information available to the treating physicians during the patient’s admission.

The short-term thromboembolic risk in patients with AF presenting to acute medical services was estimated by a review of subsequent presentations, within 3 months of discharge, to Wellington Regional Hospital with a thromboembolic event. Thromboembolic events were defined as ischaemic stroke, TIA or other arterial embolism.

Additional data were incorporated into the retrospective cohort study from a related 3-month retrospective cohort of admissions to the general medical service between 1 July 2012 and 30 September 2012. These electronic and physical medical records were reviewed for documentation of any stroke risk score or bleeding risk score. Prescriptions for anticoagulation therapy at the time of presentation and any subsequent changes were recorded. Patients with a CHA2DS2-VASc score ≥2 were considered eligible for anticoagulation. The records of patients who were not commenced on anticoagulation were reviewed for documentation of the decision not to prescribe anticoagulants.

Comparisons of continuous variables used independent t-tests. Comparisons of proportions used logistic regression and associated relative risk estimations and chi-square contingency table analysis. SPSS Statistics version 23 (SPSS, Chicago, IL, USA) was used for analyses.

Local health and disability ethics committee approval was sought but deemed unnecessary. This study was conducted in accordance with guidelines of the National Ethics Advisory Committee of New Zealand.

Results

Clinical characteristics

A total of 751 presentations with either a primary or secondary diagnosis of AF between 1 January 2012 and 31 December 2012 was identified. The CCDHB electronic records were reviewed for all 751 presentations, and 613 unique patient encounters were eligible for analysis. The patients are described in Table 1. Overall, 538/613
(87.8%) of patients had a CHA2DS2-VASc score of ≥2, and 365/613 (59.5%) had a CHA2DS2-VASc score of at least 2 based on age >75 years alone. The estimated difference in mean CHA2DS2-VASc scores in those anticoagulated compared with those untreated was 0.47 (95% confidence interval (CI) = 0.15–0.79), P = 0.004.

**Clinical outcomes**

Only 209/538 (38.8%) patients with a CHA2DS2-VASc score ≥2 were discharged on anticoagulation. Of the other 330/538 (61.2%) who were not anticoagulated at discharge, only 14/330 (4.3%) had an absolute contraindication to anticoagulation. The distribution of CHA2DS2-VASc scores and proportion of patients anticoagulated are shown in Figure 1.

Univariate logistic regression showed that increasing age was associated with a decreased likelihood of being discharged on anticoagulation, odds ratio (OR) (per decade older) 0.79 (95% CI = 0.67–0.94), P = 0.007. An increased CHA2DS2-VASc score was associated with an increased likelihood of being discharged on anticoagulation, OR (per point higher) 1.27 (95% CI = 1.13–1.42), P < 0.001. Ethnicity was also associated with a difference in the probability of being discharged on anticoagulation, P < 0.001, with NZ Europeans the least likely to be discharged on anticoagulation. As shown in Table 1, 59.2% of other ethnicities were anticoagulated compared to 43.4% of Maori, 35.7% of Pacific Islanders and 31.5% of New Zealand Europeans.

Seven patients presented again within 3 months with a thromboembolic event, six with ischaemic stroke and one with a TIA. None of these patients was discharged on anticoagulation; thus, the thromboembolic rate in those discharged without anticoagulation within 3 months of presentation to acute medical services was 2.1% (7/330). CHA2DS2-VASc scores and reasons for not anticoagulating at the initial presentation are summarised in Table 2.

**Anticoagulation treatment decision**

A total of 226 unique patient encounters with acute medical services between 1 July 2012 and 30 September 2012 who had data about the physician decision-making concerning anticoagulation was identified. AF was the primary discharge diagnosis in 73/226 (32.3%) patients, and 201/226 (88.9%) had a CHA2DS2-VASc score ≥2, of whom 139/226 (61.5%) had a score of at least 2 based on age >75 alone. Overall, 49/226 (21.7%) of patients

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**Table 1** Clinical characteristics of patients with Atrial Fibrillation by anticoagulation or not at discharge

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All, n = 613</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>75.3 (13.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>4.03 (1.94)</td>
<td>0.004*</td>
</tr>
<tr>
<td></td>
<td>n613 (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>305 (49.8)</td>
<td>0.75</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand European</td>
<td>442 (72.1)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Maori</td>
<td>53 (8.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>Pacific</td>
<td>42 (6.9)</td>
<td>0.98</td>
</tr>
<tr>
<td>Other</td>
<td>76 (12.4)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>247 (40.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypertension</td>
<td>419 (68.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes</td>
<td>137 (22.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>153 (24.9)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>198 (32.3)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*P < 0.05. TIA, transient ischaemic attack.
were prescribed anticoagulation before admission. Eleven patients died during the admission and were excluded from further analysis; 28/215 (13.0%) started anticoagulation during the admission, and 8/215 (3.7%) stopped anticoagulation during the admission. Overall, 68/215 (31.6%) were discharged on anticoagulation, 97/215 (45.1%) were discharged on antiplatelet agents, and 50/215 (23.3%) were discharged without any thromboprophylaxis.

Amongst patients who were untreated at the time of presentation, a stroke risk score was documented in 41/167 (24.6%). A stroke risk score was more likely to be documented if AF was the primary discharge diagnosis (24/63) compared to patients presenting with a different complaint (17/104), relative risk 2.33 (95% CI = 1.36–3.99), \( P = 0.002 \). A bleeding risk score was documented in only 3/167 (1.8%) patients.

Clinical- and record-based characteristics associated with an untreated patient being started on anticoagulation were stroke risk score documentation, OR 0.37 (95% CI = 0.15–0.97), \( P = 0.04 \), and age by decade older, OR 0.61 (95% CI = 0.41–0.89), \( P = 0.01 \). A primary discharge diagnosis of AF, OR 2.15 (95% CI = 0.76–6.12), \( P = 0.15 \), and CHA2DS2-VASc score, OR 1.16 (95% CI = 0.83–1.61), \( P = 0.38 \) were not associated with being started on anticoagulation.

In untreated patients with a CHA2DS2-VASc score \( \geq 2 \), the reasons not to initiate anticoagulation are documented in Table 3. The most frequently documented reasons were decision deferred to the primary care physician, 15.6%; fall risk or frailty, 7.2%; and high bleeding risk, 6.6%. However, no reason was documented in 56.9%.

### Discussion

In this study, we found that the rate of anti-coagulation among medically ill patients presenting to a tertiary referral hospital with a known diagnosis of AF is low. The rate of initiation of anti-coagulation at discharge is low both among those with a known diagnosis and a new diagnosis of AF. The reasons not to prescribe anticoagulation in eligible patients are poorly documented or, when documented, not consistent with robust clinical evidence.

Baseline stroke risk based on CHA3DS2-VASc scores was relatively high in this cohort of patients presenting to the medical service, with a mean score of 4.03. In comparison, the stroke risk score based on the CHADS2 value of patients in recent randomised trials using the novel oral anticoagulants ranged between 2.0 and 3.5.11–13 This probably reflects the fact that those patients presenting to acute medical services are more likely to have greater baseline comorbidities when compared to the general population. However, despite the baseline stroke risk being higher than what has already been shown to be of proven benefit in randomised controlled trials, the rate of initiating anticoagulation was low.

Dabigatran, a novel oral anticoagulant, with a predictable anti-coagulation effect, has advantages over warfarin when initiating therapy for both patient and prescriber as there is no need for monitoring or subsequent dose adjustments. Dabigatran became publicly funded in New Zealand on 1 July 2011, 6 months before the beginning of this audit. Despite the availability of dabigatran, anticoagulation rates remain low at 38.8%, which is comparable with previous studies of anticoagulation rates. In a previous systematic review, the majority of studies (21 of 29) reported anticoagulation rates of <60% in patients who suffered from a prior stroke or TIA, and half (15 of 29) reported anticoagulation rates of <50%.7 Studies that defined high-risk patients by CHADS2 score \( \geq 2 \) also had suboptimal treatment rates, with seven of nine studies reporting treatment levels below 70%.7

### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Initial medical diagnosis</th>
<th>CHA2DS2-VASc score</th>
<th>Reason not anticoagulated</th>
<th>Days between admissions</th>
<th>Stroke diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>Congestive heart failure</td>
<td>3</td>
<td>No reason documented</td>
<td>2</td>
<td>Right MCA PACI</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>Atrial fibrillation</td>
<td>3</td>
<td>Deferred to primary care physician</td>
<td>2</td>
<td>Right MCA PACI</td>
</tr>
<tr>
<td>3</td>
<td>86</td>
<td>Atrial flutter</td>
<td>4</td>
<td>Patient declined</td>
<td>17</td>
<td>Left TACI</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>Upper respiratory tract infection</td>
<td>2</td>
<td>Low stroke risk</td>
<td>24</td>
<td>Right TACI</td>
</tr>
<tr>
<td>5</td>
<td>81</td>
<td>Lower respiratory tract infection</td>
<td>5</td>
<td>Patient declined</td>
<td>32</td>
<td>Transient ischaemic attack</td>
</tr>
<tr>
<td>6</td>
<td>79</td>
<td>Hyperthyroidism</td>
<td>4</td>
<td>Deferred to primary care physician</td>
<td>48</td>
<td>Left MCA PACI</td>
</tr>
<tr>
<td>7</td>
<td>83</td>
<td>Congestive heart failure</td>
<td>8</td>
<td>No reason documented</td>
<td>49</td>
<td>Left PCA stroke</td>
</tr>
</tbody>
</table>

MCA, middle cerebral artery; PACI, partial anterior circulation infarct; PCA, posterior cerebral artery; TACI, total anterior circulation infarct.
We found a very limited number of patients with clear absolute contraindications to anticoagulation. When reviewing the reasons for not initiating anticoagulation, the most commonly documented reason was to leave the decision to the primary care physician. Leaving the decision up to the primary care physician may not be the best option as the rates of anticoagulation in the general population remain low, and doctors in the community are often less well equipped to initiate anticoagulation. The second most commonly documented reason not to commence anticoagulation was frailty or fall risk. A high risk of falls is not necessarily a contraindication to anticoagulation. Despite the increased risk of haemorrhage in patients who are prone to fall, patients still benefit from anticoagulant therapy if they have a CHADS2 stroke risk score of ≥2. Similarly, age and frailty are not necessarily contraindications to anticoagulation. Age is such a strong risk factor; older adults are at greater absolute risk of stroke and therefore the most likely to derive the greatest benefit from treatment. Aspirin is often perceived to be a safer alternative to warfarin despite the low risk of serious haemorrhage caused by warfarin in the elderly. The Birmingham Atrial Fibrillation Treatment of the Aged study showed that in patients over 75 years old, warfarin was superior to aspirin, with no significant difference in haemorrhage rates between patients on aspirin and those on warfarin. Aspirin is no safer than warfarin in elderly people, but it is substantially less effective. If patients are not considered too frail to receive medications to treat hypertension and hyperlipidaemia, they should also not be considered too frail to receive anticoagulation in AF as all these treatments are prescribed to prevent future morbidity and mortality.

All of the observed thromboembolic events occurred in untreated patients. Each of the presentations to the medical service before the patient’s thromboembolic event may have been an opportunity to initiate anticoagulation and prevent the patient’s adverse medical event. Each patient encounter provides an opportunity to review the relevance of evidence-based treatment for known or newly diagnosed AF. We propose that just as smoking cessation is considered with every patient encounter in the hospital setting, so too should anticoagulation be discussed and initiated if appropriate in every patient with AF. Anticoagulation in AF is arguably a quality indicator in healthcare performance.

As a result of this review, the neurology service at Wellington Regional Hospital has now initiated an urgent Atrial Fibrillation Anticoagulation Clinic, which will see any patient with AF referred to it from within the hospital within 7 days to discuss anticoagulation and, if necessary, start treatment on the same day. Whether this removes perceived barriers to commencing anticoagulation in this patient group will be audited.

This review has several limitations. Firstly, CHA2DS2-VASc scores were calculated from demographics and co-morbidities recorded in the clinical record by the responsible medical team throughout the patient’s presentation. These CHA2DS2-VASc scores may in fact be an underestimate of the patients true stroke risk score. Secondly, identification of patient presentations with either a primary or secondary diagnosis of AF relied on the accurate coding of the medical admission. This process is dependent on the medical team assigning the correct discharge diagnosis and subsequent correct coding for both the primary diagnosis and other co-morbidities. Finally, within the wider Wellington region, there are three District Health Boards. It is possible we underestimated the number of thromboembolic events because patients may have presented to either one of the other District Health Boards with their subsequent event or may have moved outside of the region during the follow-up time period.

### Conclusion

AF is an important risk factor for stroke and is associated with increased stroke severity and greater morbidity and mortality. Patients presenting to the acute medical service at a tertiary referral centre are likely under-treated, with low rates of anticoagulation initiation. The reasons not to anticoagulate are often not documented or do not follow evidence-based guidelines. Each patient encounter provides an opportunity to discuss and initiate anticoagulation in patients with AF and should be considered alongside other quality metrics used by hospitals to evaluate and improve patient care.

#### Table 3 Reasons for not using anticoagulation

<table>
<thead>
<tr>
<th>Reason</th>
<th>n/167 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reason documented</td>
<td>95 (56.9)</td>
</tr>
<tr>
<td>Deferred to primary care physician</td>
<td>26 (15.6)</td>
</tr>
<tr>
<td>Fall risk or frailty</td>
<td>12 (7.2)</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>11 (6.6)</td>
</tr>
<tr>
<td>Previous bleeding problem</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Current bleeding problem</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Patient choice</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Low stroke risk</td>
<td>4 (2.4)</td>
</tr>
</tbody>
</table>

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References


The epidemiology of in-hospital cardiac arrests in Australia and New Zealand

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Key words
cardiac arrest, in-hospital, mortality, rapid response, defibrillation.

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Abstract

Background: The epidemiology of in-hospital cardiac arrests (IHCA) in Australia and New Zealand (ANZ) has not been systematically assessed.

Aim: To conduct a systematic review of the frequency, characteristics and outcomes of adult IHCA in ANZ.


Results: We screened 934 studies, analysed 50 and included 30. Frequency of IHCA ranged from 1.31 to 6.11 per 1000 admissions in 4 population studies and 0.58 to 4.59 per 1000 in 16 cohort studies. The frequency was 4.11 versus 1.32 per 1000 admissions in hospitals with rapid response system (RRS) compared with those without (odds ratio: 0.32; 95% confidence interval 0.28-0.37; P < 0.001). On aggregate, the initial cardiac rhythm was ventricular tachycardia/ fibrillation in 31.4% (range 19.0–48.8%) in 10 studies reporting such data. On aggregate, IHCA were witnessed in 80.2% cases (three studies) and monitored patients in 53.4% cases (four studies). Details of life support were poorly documented. On aggregate, return of spontaneous circulation occurred in 46.0% of patients. Overall, 74.6% (range 59.4–77.5%) died in-hospital but survival was higher among monitored or younger patients, in those with a shockable rhythm, or during working hours.

Conclusion: IHCA are uncommon in ANZ and three quarters die in-hospital. However, their frequency varies markedly across institutions and may be affected by the presence of RRS. Where reported, the long-term outcomes survivors appear to have acceptable neurological outcomes.

Introduction

In-hospital cardiac arrest (IHCA) is a major problem in modern healthcare. In the United States there are approximately 209 000 IHCA per year with an in-hospital mortality of 60–80%,1 a mortality that has remained unchanged over 40 years.2

Training and education of hospital staff in the recognition and treatment of IHCA requires considerable resources. The major focus of such training is basic life support (BLS) and advanced cardiac life support (ACLS) which emphasises the importance of administration of early and effective chest compressions, as well as early and appropriate cardiac defibrillation. A previous single centre study,3 however, suggested that less than a quarter of IHCA had an initial defibrillation responsive rhythm. The generalisability of this finding to other hospitals in Australia and New Zealand (ANZ) is unknown. While the epidemiology of IHCA has been extensively studied in the United States and Europe,4–11 less is known on the epidemiology of these patients in ANZ.

We undertook a systematic review of studies reporting on the incidence, characteristics and outcomes of IHCA in ANZ to examine the frequency of IHCA. Furthermore, we assessed for an association between rapid response system (RRS) presence and the incidence of IHCA. In addition, we assessed the documentation of pre-morbid patient demographics and co-morbidities, the details of the initial detected rhythm and aspects of BLS and ACLS. Finally, we examined the outcomes of IHCA and associations with such outcomes.
Methods

Search strategy and cross checking of data

We reviewed Medline for studies published between January 1964 and November 2014 to detect all original studies and reviews using the following medical subject heading terms: ‘arrest AND hospital AND Australia’, ‘arrest AND hospital AND New Zealand’, ‘inpatient AND arrest AND Australia’ and ‘inpatient AND arrest AND New Zealand’. Studies were included if they reported on the characteristics and outcomes of cardiac arrests occurring in adult patients (>18 years) on a general hospital ward. We excluded papers that involved exclusively out-of-hospital cardiac arrests or studies that were not conducted in Australia or New Zealand. We excluded studies that examined cardiac arrests within the intensive care unit. A single investigator (GF) screened all abstracts, reviewed all manuscripts and populated the study tables. Two additional investigators (AH and SR) double-checked all abstracts blindly to ascertain if any potential manuscripts were missed.

We assessed and reported separately on population studies and studies presenting detailed patient cohort analysis. Population studies were those from which overall IHCA data were available without investigators being able to extract original (raw) data.

Research questions and data collected

All authors agreed a priori on the major research questions for the study, as well as the final analysis plan. These questions included evaluation of the cohort size, number of IHCA, number of hospital admissions during the study period, the incidence of IHCA per 1000 hospital admissions and whether the study was conducted before or after the introduction of a RRS.

In studies where data were available, we collected information of the demographics of the patients who suffered IHCA, including age and gender, place of residence, functional status, documented co-morbidities and admission diagnoses. In addition, we evaluated studies for the details of initial rhythm (ventricular tachycardia (VT), ventricular fibrillation (VF), pulseless electrical activity (PEA), asystole) or whether the rhythm was ‘shockable’ (VT, VF) or ‘non-shockable’ (asystole, PEA, non-VF/VT). Furthermore, we assessed whether the IHCA was witnessed or monitored, as well as the time of day and day of week that the arrest was detected.

Details of the provision of BLS and ACLS were obtained. In particular, we documented whether there was a return of spontaneous circulation (ROSC) and the time to ROSC. We recorded the outcome of the arrest, including death during the cardiac arrest, death in-hospital, medium term mortality and functional outcome. Finally, we assessed manuscripts for analysis reporting on predictors or associations with in-hospital cardiac mortality, which we classified prospectively as ‘patient factors’, ‘initial rhythm’, ‘aspects of BLS/ACLS’, ‘logistic factors’ and ‘other’.

Results

Details of literature review and included studies

We identified 934 studies, of which 50 were further analysed for suitability for inclusion and 30 were finally included (Fig. 1). Of the 30 studies included, four publications were ‘population studies’ (IHCA presented as aggregate data) and 26 studies were ‘cohort studies’ (IHCA presented as detailed data). The earliest study identified was published in 1987.

Frequency of IHCA

Population studies

Four population studies reported aggregate data on the frequency and outcomes of IHCA, representing the findings from more than 11.5 million hospital admissions (Table 1). The frequency of IHCA in these studies ranged from 1.31 to 6.11 per 1000 admissions.

Cohort studies

Sixteen single centre studies and one multi-centre study reported specific data on the frequency of IHCA, with values ranging from 0.58 to 4.59 per 1000 admissions (Table 2). Of these, 13 studies simultaneously reported data on both hospital admissions and the number of IHCA, a total of 2302 IHCA in 121 262 admissions (aggregate frequency 2.25 IHCA per 1000 admissions).

Presence of RRS

Overall, 15 studies documented information on both IHCA and the presence of a RRS (Table 3A,B). Where there was no RRS, the frequency of IHCA ranged from 2.90 to 5.06 per 1000 admissions (Table 3A) with raw data from three studies reporting an aggregated value of 4.11 IHCA per 1000 admissions. In contrast, in the presence of a RRS, the frequency of IHCA ranged from 0.58 to 3.76 per 1000 admissions (Table 3B) with raw data from nine studies reporting an aggregated value of 1.33 IHCA per 1000 admissions. The respective frequencies reflect an odds ratio...
(OR) of 0.32 for IHCA where a RRS is present (95% confidence interval (CI) 0.28–0.37; \( P < 0.001 \)).

**Demographics of patients suffering IHCA**

Only seven studies reported some demographic details of IHCA (Table 4). In aggregated data from five studies providing information on patient gender, 63.5% were male and in six studies providing information on patient age, the average ranged between 66.5 and 74.9 years. Three studies reported on the type of admission, and when combined, 72.5% of IHCA occurred in non-surgical admissions. Co-morbidities were only reported by Smith et al.\(^{12}\) for 91 IHCA. The Charlson co-morbidity index was 1–4 in 68% and greater than 4 in 7% of patients. No study provided information on initial place of residence or admission diagnosis.

**Initial cardiac rhythm and details of treatment**

The initial rhythm was documented in 10 studies (Table 5). When combined, the initial rhythm was VT or VF in 31.4% of IHCA, with a range of 19.0–48.8%. However, the documentation of whether IHCA were witnessed or monitored was poor with only three studies reporting whether the IHCA was witnessed, and four reporting whether the patient was monitored.

No studies reported on specific details of adherence to BLS or ACLS guidelines. Jones et al.\(^{13}\) reported median times to cardiopulmonary resuscitation (CPR) (0.5 min), to defibrillation (1 min), to adrenaline (4 min) and to intubation (8 min). Two studies reported on time intervals from collapse to ROSC\(^{13,14}\) and one on automated external defibrillator (AED) use.\(^{15}\) The median time
In-hospital cardiac arrests in ANZ

Table 1: Frequency and mortality of IHCA in Australia and New Zealand, derived from four population studies†

<table>
<thead>
<tr>
<th>Study</th>
<th>Hospitals, n (location)</th>
<th>Admissions, n</th>
<th>IHCA frequency, per 1000 (range)</th>
<th>IHCA mortality, per 1000 (range)</th>
<th>IHCA mortality, %</th>
<th>RRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weerasinghe et al., 200220</td>
<td>19 (NSW)</td>
<td>124 510†</td>
<td>2.04 —</td>
<td>—</td>
<td>67.7</td>
<td>Unknown</td>
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<td>Hillman et al., 200523</td>
<td>23 baseline (ANZ)</td>
<td>125 132</td>
<td>— [1.60–2.61]</td>
<td>—</td>
<td>—</td>
<td>No</td>
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<tr>
<td>Hillman et al., 200523</td>
<td>11 control (ANZ)</td>
<td>150 000†</td>
<td>1.64 —</td>
<td>—</td>
<td>—</td>
<td>No</td>
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<tr>
<td>Hillman et al., 200523</td>
<td>12 intervention (ANZ)</td>
<td>190 840†</td>
<td>1.31 —</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>Chen et al., 2014†</td>
<td>82 (NSW)</td>
<td>921 138</td>
<td>— [1.85–3.72]</td>
<td>— (1.26–2.71)</td>
<td>67.7–72.7</td>
<td>Mix</td>
</tr>
<tr>
<td>Chen et al., 201424</td>
<td>4 (NSW)</td>
<td>146 484</td>
<td>— [1.47–6.11]</td>
<td>— (1.18–4.72)</td>
<td>—</td>
<td>Mix</td>
</tr>
<tr>
<td>Chen et al., 201424</td>
<td>1 (NSW)</td>
<td>479 194</td>
<td>— [1.47–2.64]</td>
<td>1.62 (1.18–2.18)</td>
<td>77.5</td>
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</tr>
<tr>
<td>Chen et al., 201424</td>
<td>3 (NSW)</td>
<td>942 368</td>
<td>— [2.98–6.11]</td>
<td>2.72 (1.99–4.72)</td>
<td>68.5</td>
<td>No</td>
</tr>
<tr>
<td>Chen et al., 201424</td>
<td>2 (NSW)</td>
<td>103 049</td>
<td>— [2.47–2.73]</td>
<td>1.84 (1.70–1.94)</td>
<td>70.2</td>
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<tr>
<td>Chen et al., 201424</td>
<td>1 (NSW)</td>
<td>43 074</td>
<td>— [3.25–4.52]</td>
<td>1.93 (1.93–3.20)</td>
<td>59.4</td>
<td>No</td>
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</tbody>
</table>

†These 10 data-sets are derived from 4 population based studies, each data-set comprising different time periods or different institutions. Both papers from Chen et al.17,24 used the same database with some overlap. Admissions were estimated from reported 3722 IHCA, 20 246 IHCA, and 250 IHCA23 respectively. ANZ, Australia and New Zealand; IHCA, in-hospital cardiac arrest; NSW, New South Wales, Australia; RRS, rapid response system.

Table 2: Frequency of IHCA in cohort centre studies in Australia and New Zealand

<table>
<thead>
<tr>
<th>Study</th>
<th>IHCA, n</th>
<th>Admissions, n</th>
<th>IHCA frequency, per 1000 admissions (range)</th>
<th>RRS</th>
</tr>
</thead>
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<tr>
<td>Britlow et al., 200025</td>
<td>234</td>
<td>50 942</td>
<td>4.59</td>
<td>Mixed</td>
</tr>
<tr>
<td>Salamonson et al., 200126</td>
<td>43</td>
<td>—</td>
<td>0.7–0.8</td>
<td>Yes</td>
</tr>
<tr>
<td>Buist et al., 200227</td>
<td>120</td>
<td>53 995</td>
<td>2.22</td>
<td>Mixed</td>
</tr>
<tr>
<td>Weerasinge et al., 2002201</td>
<td>201</td>
<td>57 975</td>
<td>3.47</td>
<td>Unknown</td>
</tr>
<tr>
<td>Jones et al., 20054</td>
<td>279</td>
<td>145 463</td>
<td>1.92</td>
<td>Mixed</td>
</tr>
<tr>
<td>Jacques et al., 200828</td>
<td>5</td>
<td>3160</td>
<td>1.58</td>
<td>Yes</td>
</tr>
<tr>
<td>Buist et al., 200729</td>
<td>271</td>
<td>186 070</td>
<td>1.46</td>
<td>Yes</td>
</tr>
<tr>
<td>Peters et al., 200720</td>
<td>128</td>
<td>36 727</td>
<td>3.49</td>
<td>Unknown</td>
</tr>
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<td>Smith et al., 200921</td>
<td>152</td>
<td>58 098</td>
<td>2.62</td>
<td>Unknown</td>
</tr>
<tr>
<td>Santamaria et al., 201032</td>
<td>—</td>
<td>—</td>
<td>0.58–2.93</td>
<td>Mixed</td>
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<tr>
<td>Vetro et al., 201135</td>
<td>22</td>
<td>16 142</td>
<td>1.36</td>
<td>Yes</td>
</tr>
<tr>
<td>Jones et al., 2011134</td>
<td>415</td>
<td>235 205</td>
<td>1.76</td>
<td>Unknown</td>
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<td>Kansal et al., 201224</td>
<td>—</td>
<td>53 665</td>
<td>0.95–1.30</td>
<td>Yes</td>
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<tr>
<td>Drower et al., 201334</td>
<td>168</td>
<td>44 184</td>
<td>3.80</td>
<td>Unknown</td>
</tr>
<tr>
<td>Smith et al., 201412</td>
<td>91</td>
<td>43 385</td>
<td>2.10</td>
<td>Yes</td>
</tr>
<tr>
<td>Herod et al., 201414</td>
<td>—</td>
<td>—</td>
<td>1.1–1.4</td>
<td>Yes</td>
</tr>
<tr>
<td>Husband et al., 201417</td>
<td>259</td>
<td>143 581</td>
<td>1.80</td>
<td>Yes</td>
</tr>
<tr>
<td>Total</td>
<td>2345</td>
<td>1 074 927</td>
<td>2.25 (23021021262)</td>
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</tr>
</tbody>
</table>

†All were single centre studies, except Weerasinge et al.20. All studies were Australian except Drower et al.26 and Jones et al.13 which were from New Zealand. IHCA, in-hospital cardiac arrest; RRS, rapid response system.

Outcomes

Table 6 shows the reported outcomes of IHCA. ROSC was achieved in 46% of patients. Mortality in population studies ranged from 59.4 to 77.5% (Table 1). In 19 cohort studies, the aggregated in-hospital mortality was 74.6% (Table 6). Mortality was similar in the presence or absence of a RRS (Table 3). In the three studies reporting on IHCA prior to RRS, the aggregated mortality was 75.0%, versus 75.4% in the five studies reporting after RRS implementation (OR = 1.02; 95% CI 0.73–1.41; P = 0.91).

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Cohn et al. report no correlation between survival and major co-morbidities. Two studies provided data on the discharge destination. Among the combined data on the 85 survivors reported by Smith et al. and Jones et al., only 63.5% were discharged home. Only four studies provided data on longer term survival after hospital discharge. All 34 survivors reported by Smith et al. were alive at 90 days. For patients discharged

<table>
<thead>
<tr>
<th>Study</th>
<th>Admissions, n</th>
<th>IHCA, n</th>
<th>IHCA frequency, per 1000 admissions</th>
<th>IHCA mortality, % (n)</th>
<th>IHCA mortality, per 1000 admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-RRS</td>
<td>Rankin, 1998</td>
<td>—</td>
<td>133</td>
<td>—</td>
<td>73.7 (98)</td>
</tr>
<tr>
<td></td>
<td>Bristow et al., 2000</td>
<td>32 604</td>
<td>165</td>
<td>5.06</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Buist et al., 2002</td>
<td>25 194</td>
<td>73</td>
<td>2.90</td>
<td>76.7 (56)</td>
</tr>
<tr>
<td></td>
<td>Jones et al., 2005</td>
<td>16 246</td>
<td>66</td>
<td>4.06</td>
<td>75.8 (50)</td>
</tr>
<tr>
<td></td>
<td>Santamaria et al., 2010</td>
<td>—</td>
<td>—</td>
<td>2.93</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>74 044</td>
<td>437</td>
<td>4.11 (304/74044)</td>
<td>75.0 (204/272)</td>
<td>2.56 (106/41440)</td>
</tr>
<tr>
<td>Post-RRS</td>
<td>Lee et al., 1995</td>
<td>—</td>
<td>148</td>
<td>—</td>
<td>71.0</td>
</tr>
<tr>
<td></td>
<td>Bristow et al., 2000</td>
<td>18 338</td>
<td>69</td>
<td>3.76</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Salamonson et al., 2001</td>
<td>186 070</td>
<td>271</td>
<td>1.46</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Buist et al., 2002</td>
<td>28 801</td>
<td>47</td>
<td>1.63</td>
<td>55.3 (26)</td>
</tr>
<tr>
<td></td>
<td>Jones et al., 2005</td>
<td>25 216</td>
<td>51</td>
<td>2.02</td>
<td>82.4 (42)</td>
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<tr>
<td></td>
<td>Jones et al., 2005</td>
<td>104 001</td>
<td>162</td>
<td>1.56</td>
<td>84.0 (136)</td>
</tr>
<tr>
<td></td>
<td>Jacques et al., 2006</td>
<td>3160</td>
<td>5</td>
<td>1.58</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Buist et al., 2007</td>
<td>—</td>
<td>—</td>
<td>0.7–0.8</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Santamaria et al., 2010</td>
<td>—</td>
<td>—</td>
<td>2.90</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Santamaria et al., 2010</td>
<td>—</td>
<td>—</td>
<td>1.51</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Santamaria et al., 2010</td>
<td>—</td>
<td>—</td>
<td>0.58</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Trinkle et al., 2011</td>
<td>—</td>
<td>31</td>
<td>—</td>
<td>90.3 (28)</td>
</tr>
<tr>
<td></td>
<td>Husband et al., 2014</td>
<td>143 581</td>
<td>259</td>
<td>1.80</td>
<td>63.3 (194)</td>
</tr>
<tr>
<td></td>
<td>Smith et al., 2014</td>
<td>43 385</td>
<td>91</td>
<td>2.10</td>
<td>62.6 (57)</td>
</tr>
<tr>
<td>Total</td>
<td>552 552</td>
<td>955</td>
<td>1.33 (733/552552)</td>
<td>75.4 (483/641)</td>
<td>1.32 (455/344994)</td>
</tr>
</tbody>
</table>

Table 4 Demographics of patients suffering IHCA

<table>
<thead>
<tr>
<th>Study</th>
<th>IHCA, n</th>
<th>Age, years</th>
<th>Male, % (n)</th>
<th>Non-surgical, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twidale et al., 1989</td>
<td>34</td>
<td>—</td>
<td>82.4 (28)</td>
<td>—</td>
</tr>
<tr>
<td>Jones et al., 2003</td>
<td>279</td>
<td>71.3</td>
<td>68.5 (191)</td>
<td>—</td>
</tr>
<tr>
<td>Trinkle et al., 2011</td>
<td>31</td>
<td>74.9 (12.2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Jones et al., 2011</td>
<td>415</td>
<td>66.5 (15.5)</td>
<td>59.3 (246)</td>
<td>—</td>
</tr>
<tr>
<td>Boyde et al., 2013</td>
<td>519</td>
<td>69 (56–78)</td>
<td>63.1 (328)</td>
<td>—</td>
</tr>
<tr>
<td>Smith et al., 2014</td>
<td>91</td>
<td>70 (62–78)</td>
<td>67.0 (61)</td>
<td>60.4 (55)</td>
</tr>
<tr>
<td>Husband et al., 2014</td>
<td>259</td>
<td>71.3 (61–81)</td>
<td>67.2 (174)</td>
<td>81.1 (210)</td>
</tr>
<tr>
<td>Total</td>
<td>1733</td>
<td>—</td>
<td>63.5 (837/1318)</td>
<td>72.5 (456/629)</td>
</tr>
</tbody>
</table>

Table 3 Frequency and mortality of IHCA before and after implementation of RRS

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Fennessy et al.
alive, 1-year survival was high, ranging from 85.7 to 97.0%. The longer term functional status of survivors of IHCA was reported to be good, with 93.3–97.1% having cerebral performance category (CPC) of 1 or 2 at 1 year. Rankin reported that 44% of patients with shockable rhythms were alive at 1 year, and all had CPC of 1, whereas if the rhythm was non-shockable, only 12% were alive at 1 year and only 73% of these had CPC of 1.
Associations with in-hospital mortality following cardiac arrest

Eight studies provided information on the outcome associated with monitoring or the initial cardiac rhythm (Table 7).

Monitored or witnessed arrest

ROSC was higher in monitored arrests (64.3 vs 36.4%, Cohn et al.\textsuperscript{16} \(P = 0.038\) and 66.1 vs 42.8%, Jones et al.\textsuperscript{13} \(P < 0.001\)) and in witnessed or monitored arrests (71.8 vs 21.4%, Boyde et al.\textsuperscript{14} \(P < 0.001\)). Smith et al.\textsuperscript{12} report that patients in monitored areas were more likely to have shockable rhythms (48.3%) than those in non-monitored areas (19.4%, \(P = 0.022\)). This was the only study that showed a survival advantage (58.6 vs 27.4%, \(P = 0.012\)) among patients who had an IHCA during monitoring. Jones et al.\textsuperscript{13} reported that patients in ‘non-cardiac arrest team’ areas were more likely to die (63 vs 39%, \(P < 0.001\)).

Initial cardiac rhythm

An initial shockable rhythm (VT or VF) was associated with greater rates of ROSC in two studies (66.3 vs 24.4%, Smith et al.\textsuperscript{19} \(P < 0.0001\) and 81.5 vs 41.7%, Smith et al.\textsuperscript{19} §). Smith et al.\textsuperscript{19} § showed that patients in monitored areas were more likely to have shockable rhythms (48.3%) than those in non-monitored areas (19.4%, \(P = 0.022\)). This was the only study that showed a survival advantage (58.6 vs 27.4%, \(P = 0.012\)) among patients who had an IHCA during monitoring. Jones et al.\textsuperscript{13} reported that patients in ‘non-cardiac arrest team’ areas were more likely to die (63 vs 39%, \(P < 0.001\)).

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of arrest</th>
<th>Shockable, % (n/N)</th>
<th>ROSC, % (n/N)</th>
<th>Survival to discharge, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twidale et al., 1989\textsuperscript{21}</td>
<td>Monitored</td>
<td>50.0 (11/22)</td>
<td>36.4 (8/22)</td>
<td>13.6 (3/22)</td>
</tr>
<tr>
<td></td>
<td>Unmonitored</td>
<td>35.3 (12/34)</td>
<td>38.2 (13/34)</td>
<td>23.5 (8/34)</td>
</tr>
<tr>
<td>Rankin, 1998\textsuperscript{18}§</td>
<td>Monitored</td>
<td>65.1 (28/43)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Unmonitored</td>
<td>38.9 (35/90)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Shockable</td>
<td>—</td>
<td>—</td>
<td>46.5 (20/43)</td>
</tr>
<tr>
<td></td>
<td>Non-shockable</td>
<td>—</td>
<td>—</td>
<td>16.7 (15/90)</td>
</tr>
<tr>
<td>Cohn et al., 2004\textsuperscript{16}</td>
<td>Witnessed</td>
<td>—</td>
<td>38.0 (19/50)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Unwitnessed</td>
<td>—</td>
<td>49.0 (27/55)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Monitored</td>
<td>—</td>
<td>64.3 (18/28)</td>
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<td></td>
<td>Unmonitored</td>
<td>—</td>
<td>36.4 (28/77)</td>
<td>—</td>
</tr>
<tr>
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<td>Shockable</td>
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<td>65.0 (13/20)</td>
<td>45.0 (9/20)</td>
</tr>
<tr>
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<td>Non-shockable</td>
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<td>38.8 (33/85)</td>
<td>15.3 (13/85)</td>
</tr>
<tr>
<td>Peters et al., 2007\textsuperscript{30}</td>
<td>Witnessed</td>
<td>—</td>
<td>—</td>
<td>37.5 (33/88)</td>
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<td>—</td>
<td>45.0 (18/40)</td>
</tr>
<tr>
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<td>Monitored</td>
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<td>50.0 (23/46)</td>
<td>37.0 (17/46)</td>
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<td>40.1 (33/82)</td>
<td>19.5 (16/82)</td>
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<tr>
<td></td>
<td>Shockable</td>
<td>—</td>
<td>—</td>
<td>57.1 (24/42)</td>
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<td>Non-shockable</td>
<td>—</td>
<td>—</td>
<td>19.8 (17/86)</td>
</tr>
<tr>
<td>Smith et al., 2007\textsuperscript{19}§</td>
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<td>—</td>
<td>66.3 (55/83)</td>
<td>39.8 (33/83)</td>
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<td>24.4 (39/160)</td>
<td>11.3 (18/160)</td>
</tr>
<tr>
<td>Jones et al., 2011\textsuperscript{13}§</td>
<td>Witnessed</td>
<td>—</td>
<td>15.7 (14/89)</td>
<td>—</td>
</tr>
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<td>Unwitnessed</td>
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<td>10.0 (5/49)</td>
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<td>Monitored</td>
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<td>66.1 (183/277)</td>
<td>—</td>
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<td>42.8 (59/138)</td>
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<td>52.7 (78/148)</td>
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<td>—</td>
<td>13.1 (35/267)</td>
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<td>Boyde et al., 2013\textsuperscript{14}</td>
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<td>—</td>
<td>71.8 (242/337)†</td>
<td>—</td>
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<tr>
<td></td>
<td>Not witnessed nor monitored‡</td>
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<td>21.4 (39/182)†</td>
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<td>81.5 (132/162)</td>
<td>57.4 (93/162)†</td>
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<td>—</td>
<td>41.7 (149/359)†</td>
<td>18.2 (65/357)†</td>
</tr>
<tr>
<td>Smith et al., 2014\textsuperscript{12}</td>
<td>Monitored</td>
<td>48.3 (1429)</td>
<td>—</td>
<td>58.6 (1729)</td>
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<td>Unmonitored</td>
<td>19.4 (1216)</td>
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<td>27.4 (1762)</td>
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<td>Total</td>
<td>Monitored</td>
<td>56.4 (53/94)</td>
<td>62.2 (232/373)</td>
<td>38.1 (37/97)</td>
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<td>31.7 (59/186)</td>
<td>40.2 (133/331)</td>
<td>23.0 (41/178)</td>
</tr>
<tr>
<td></td>
<td>Witnessed</td>
<td>—</td>
<td>23.7 (33/139)</td>
<td>37.5 (33/88)</td>
</tr>
<tr>
<td></td>
<td>Unwitnessed</td>
<td>—</td>
<td>30.8 (32/104)</td>
<td>45.0 (18/40)</td>
</tr>
<tr>
<td></td>
<td>Shockable</td>
<td>—</td>
<td>75.5 (200/265)</td>
<td>56.4 (257/456)</td>
</tr>
<tr>
<td></td>
<td>Non-Shockable</td>
<td>—</td>
<td>36.5 (221/604)</td>
<td>15.6 (163/1045)</td>
</tr>
</tbody>
</table>

\(P\text{-value for significance reported in body of text, otherwise differences are not significant.} \)

\(†\)Witnessed or monitored were not differentiated and were reported together. §New Zealand based studies, the rest were from Australia. IHCA, in-hospital cardiac arrest; Non-Shockable, asystole; PEA, non-VF, non-VT; ROSC, return of spontaneous circulation; Shockable, VF or VT.
Boyde et al.,\textsuperscript{14} \(P < 0.001\), and greater survival to discharge (56.4 vs 15.6\%) Jones et al.\textsuperscript{11} reported that survivors had shorter CPR (6.4 vs 20.4 min, \(P < 0.001\)). No asystolic unwitnessed events survived in the study by Cohn et al.\textsuperscript{16}

**Patient age**

Increasing age was associated with an increased mortality in three studies,\textsuperscript{5,19,20} with one\textsuperscript{19} finding that ROSC was reduced by 35\% (\(P = 0.0002\)) and survival to discharge was reduced by 36\% (\(P = 0.0004\)) with each decade of life.

**Time of day**

Four studies found that daytime cardiac arrests were associated with better outcome with two reporting greater ROSC (41.4 vs 17.0\%, \(P = < 0.001\)) and 58.9 vs 41.0\%, \(P = 0.04\))\textsuperscript{11}, and two others\textsuperscript{19,21} reporting higher survival.

**Discussion**

**Summary of major findings**

We conducted a systematic review on the epidemiology of IHCA in ANZ between January 1964 and November 2014. The overall frequency of IHCA was approximately 2 per 1000 admissions, but varied from 1.3 to 6 per 1000. The incidence of IHCA was significantly lower in hospitals with a RRS. Although IHCA were often witnessed, the initial cardiac rhythm was often non-shockable. In addition, ROSC was achieved in a minority of cases and overall survival was uncommon. However, for those surviving to hospital discharge, long-term survival and functional status was generally acceptable.

**Comparison with previous studies**

Multiple international studies\textsuperscript{4–11} have reported on the epidemiology of IHCA. Peberdy et al.\textsuperscript{11} found 0.17 IHCA per bed per year, an average of 54 events per year for a notional 260 bed hospital. In keeping with our findings, several studies outside of ANZ confirm worse patient outcomes with increasing age.\textsuperscript{4–8} IHCA occurring on general wards,\textsuperscript{4} when unwitnessed\textsuperscript{6} and occurring after hours.\textsuperscript{7,8}

Previous international studies provide findings which are consistent with those in our study. Several studies have reported that the initial cardiac rhythm is mostly non-shockable (65–80\%),\textsuperscript{8,9,11} that non-shockable rhythms have worse survival when compared with shockable rhythms\textsuperscript{6–8,11} and that older people with non-shockable rhythms have a particularly low survival.\textsuperscript{5} Other studies report that ROSC occurs in 20.8–54.1\%\textsuperscript{5,7,9,11} that survival is higher if CPR is begun within 1 min\textsuperscript{8} and if the total duration of CPR is shorter.\textsuperscript{5,7} Survival is very low (2.6\%) in older people who had greater than 4 min of CPR.\textsuperscript{5} Only half of patients with ROSC survive to discharge\textsuperscript{5,7} and overall survival is reported to be between 15.2 and 18.7\%.\textsuperscript{5–7,9,11} Peberdy et al.\textsuperscript{11} reported no changes in the overall outcome of IHCA over 40 years.

In keeping with our findings, international studies have reported an overall mortality of 83\% and that nearly 90\% of all people who suffer IHCA are dead at 1 year.\textsuperscript{6,7} In another study,\textsuperscript{11} 51\% of the few immediate survivors returned home, yet 44\% were discharged to a nursing home, other hospital or rehabilitation facility, compared with only 14\% of those who originally resided in these places. In contrast to our findings, at least two international studies reveal that about 10\% of survivors had severe disability (classed as CPC greater than 2) and 44\% of patients had a CPC score less than what they were admitted with,\textsuperscript{7} which was worse if the patient was older than 70 years.\textsuperscript{8} A large number of older patients had reduced functional outcome post discharge.\textsuperscript{3}

**Implications for clinicians and policy makers**

It has previously been argued that suboptimal end of life care, suboptimal detection and recognition of deterioration, and ‘sudden and unexpected’ deterioration may all predispose to IHCA.\textsuperscript{22} The data available in current literature do not permit allocation to these three categories.

However, irrespective of predisposing factors, our findings imply that in ANZ hospitals, IHCA are infrequent. This makes it unlikely that an individual ward staff member will see more than one or two such events per year. Moreover, two thirds of such events have an initial non-shockable rhythm and more than two thirds of patients die. These observations imply that prevention is more logical than intervention in this field and that current approaches to treatment are broadly ineffective.

**Study limitations**

The major limitation of our study relates to the quality of the data contained within the publications. Such data do not report many important details of patient management before, during and after IHCA. However, the key findings are consistent and repeated across populations and cohorts. As many of the studies assessed are small and
Areas for future research

There is a need to understand better the factors leading up to IHCA and what can be done to prevent them by improving end of life care planning and the detection of deteriorating patients. Such research might help identify which patients are most at risk of IHCA, so that prevention can be targeted. In addition, knowledge of the patho-physiological mode of death may be helpful. If progressive cardiogenic shock is a more common mode of death than neurological damage, then extracorporeal membrane oxygenation may improve outcomes for selected cases of IHCA.

Conclusions

IHCA appear to be relatively infrequent in ANZ hospitals and often not amenable to electrical cardioversion. Three quarters of patients die in-hospital, but long-term functional status in hospital survivors appears acceptable. The incidence of IHCA appears to be lower in hospitals with an RRS. Better treatment strategies are needed to improve outcomes of IHCA.

References


What are the similarities and differences in antimicrobial prescribing between Australian public and private hospitals?

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1National Centre for Antimicrobial Stewardship at the Peter Doherty Institute for Infection and Immunity, 2Department of Medicine, The University of Melbourne, and 4Melbourne EpiCentre, Royal Melbourne Hospital, Melbourne, Victoria, and 3School of Pharmacy, The University of Queensland, Brisbane, Queensland, Australia

Key words
antimicrobial stewardship, hospitals, prescribing, guidelines.

Abstract

Background: Identifying themes associated with inappropriate prescribing in Australian public and private hospitals will help target future antimicrobial stewardship initiatives.

Aims: To describe current antimicrobial prescribing practices, identify similarities and differences between hospital sectors and provide target areas for improvement specific to each hospital sector.

Methods: All hospitals included in the study were part of the 2014 national antimicrobial prescribing survey and conducted one of the following: a whole hospital point prevalence survey, serial point prevalence surveys or a sample of randomly selected patients. Data on the types of antibiotics used, their indications for use and the quality of prescription based on compliance with national and local prescribing guidelines were collected.

Results: Two hundred and two hospitals (166 public and 36 private) comprising 10,882 patients and 15,967 antimicrobial prescriptions were included. Public hospitals had higher proportions of prescriptions for treatment (81.5% vs 48.4%) and medical prophylaxis (8.8% and 4.6%), whilst private hospitals had significantly higher surgical prophylaxis use (9.6% vs 46.9%) (P < 0.001). In public hospitals, the main reasons for non-compliance of treatment prescriptions were spectrum being too broad (30.5%) while in private it was incorrect dosing. Prolonged duration was the main reason for non-compliance among surgical prophylaxis prescriptions in both types of hospitals.

Conclusions: Australian hospitals need to target specific areas to improve antimicrobial use. Specifically, unnecessary broad-spectrum therapy should be a priority area in public hospitals, whilst emphasis on curtailing antimicrobial overuse in surgical prophylaxis needs to be urgently addressed across the private hospital sector.

Introduction

Recent data, from Australia and internationally, show that between a third and a half of all hospital inpatients are receiving an antimicrobial at any point in time.1–3 In Australia, much of the information on antimicrobial use has come from major city public hospitals, including surveys of the indications for antimicrobial use,4,5 compliance with prescribing guidelines6 and investigating risk factors for inappropriate use.1 Australian private hospitals are currently under-represented in antimicrobial prescribing survey data, with only one previous point prevalence survey (PPS) conducted in three large private hospitals.2 However, there are approximately 280 acute care private hospitals in Australia, constituting 31% of all inpatient beds.7

Antimicrobial prescribing practices may vary significantly across different hospital types and be influenced by the types of patients admitted and the resources available. A previous Australian study outlined major differences in the available resources and implementation of antimicrobial stewardship (AMS) programmes between public and private hospitals.8 Identifying common themes associated with inappropriate prescribing in different settings will help direct AMS efforts within each hospital sector. The 2014 National Antimicrobial Prescribing Survey (NAPS) data demonstrated that surgical
prophylaxis was the most common indication for antimicrobial prescribing (13%) in participating Australian hospitals and that 40% of these prescriptions were in some way inappropriate. However, it is unclear if antimicrobial-prescribing practices differed between the two types of hospitals and whether there were any specific targets for AMS intervention within each hospital sector.

The aims of this study were to use the 2014 NAPS data to:

1. describe current antimicrobial-prescribing practices in public and private hospitals,
2. identify similarities and differences between the two hospital sectors in terms of indications for antimicrobial use (in particular surgical prophylaxis), compliance with guidelines and reasons for non-compliant therapy,
3. provide specific recommendations to improve antimicrobial use in each hospital sector.

Methods

Antimicrobial prescribing data were obtained from the 2014 NAPS database. The NAPS is a voluntary, nationwide survey conducted annually and is available to all Australian acute healthcare facilities. The data collection tool is standardised and designed to assist auditing of antimicrobial-prescribing practices and facilitate local quality improvement. The 2014 NAPS took place between August 2014 and February 2015. Hospitals conducted snapshot surveys as either a whole hospital PPS, whole hospital serial point prevalence surveys (sPPS) (i.e. conducted a PPS at regular intervals over a period of several weeks, recommended for smaller hospitals with fewer inpatients) or a one off sample of randomly selected patients (for hospitals with fewer available resources). A minimum data set of 30 prescriptions from each hospital was recommended.

Data collection was in accord with the previously reported standardised NAPS method, and included assessments of compliance with antimicrobial prescribing guidelines (see Table 1 for compliance with guidelines assessment criteria).

Ethics

The study was approved by Melbourne Health Human Research Ethics Committee as a quality assurance/negligible risk research initiative (QA2013066).

Statistical analysis

Data were presented descriptively, with the categorical data presented as frequencies and percentages. Chi-squared tests were used to test for differences across groups for categorical data, with the Fisher’s exact test employed when frequencies were small. All tests were two-tailed and a P-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis

<table>
<thead>
<tr>
<th>Compliance with guidelines assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliant with Therapeutic Guidelines [TG:A11,12]</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Compliant with local guidelines</td>
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<tr>
<td></td>
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<tr>
<td>Non-compliant</td>
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<td></td>
</tr>
<tr>
<td>Other</td>
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</tbody>
</table>

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; TG:A, Therapeutic guidelines: antibiotic.
was performed using Stata version 12.1 (StataCorp LP, College Station, TX, USA).

**Results**

A total of 202 hospitals (166 public and 36 private) was included in the data analysis. In terms of hospital location, the surveyed private hospitals were representative of all Australian private hospitals as determined by a comparison of surveyed versus non-surveyed private sites based on Australian Institute of Health and Welfare classification (Table 2). There was a statistically significant difference in the proportion of females (public: 48.1%, private: 52.4%, \( P = 0.002 \)) and age in the patients admitted to public (median 66, interquartile range: 45–80) and private hospitals (median 68, interquartile range: 54–79) \( P < 0.001 \). Compared with the Australia-wide distribution of all public hospitals and based on Australian Institute of Health and Welfare classifications, major city hospitals contributed a greater proportion of surveyed hospitals (47.0% of surveyed public hospitals vs 25.4% of all Australian public hospitals) and a smaller proportion of remote hospitals (7.2% vs 20.6% respectively).

In public hospitals, the majority of surveyors were pharmacists (64%) followed by doctors (19%) and nurses (17%), whereas in private hospitals surveyors were split evenly between nurses (48%) and pharmacists (45%) \( P < 0.001 \). Of note, there were no doctors involved as surveyors in the private hospitals.

A total of 10,882 patients was included in the study, with data collected from 17,175 prescriptions. Seven percent (1,208) of prescriptions were excluded from the analysis due to the indication for these prescriptions being classified as either ‘unknown’ or ‘other’ by surveyors. The remaining 15,967 prescriptions were included in the analysis. Overall, an indication was documented in 74.1% of antimicrobial prescriptions, with documentation substantially higher in public hospitals compared with private hospitals (77.2% vs 51.8%). This was particularly evident for certain surgical units, including gynaecology (76.5% vs 16.2%, \( P < 0.001 \)), general surgery (74.6% vs 26.0%, \( P < 0.001 \)), ear nose and throat surgery (60.9% vs 15.9%, \( P < 0.001 \)) and plastic surgery (73.3% vs 43.7%, \( P < 0.001 \)).

There were significant differences between public and private hospitals in terms of prescriptions indicated for treatment of infection (81.5% and 48.4% respectively), surgical prophylaxis (9.6% and 46.9% respectively) and medical prophylaxis (8.8% and 4.6% respectively) \( P < 0.001 \). Public hospitals had a higher proportion of patients receiving antimicrobials for community-acquired pneumonia compared with private hospitals (13.0% vs 5.9%).

Overall, the most commonly prescribed antimicrobials were cephazolin (11.1%), ceftriaxone (9.1%),

<table>
<thead>
<tr>
<th>Treatment indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ceftriaxone</strong></td>
</tr>
<tr>
<td><strong>Cefuroxime</strong></td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
</tr>
<tr>
<td><strong>Amoxicillin-clavulanic acid</strong></td>
</tr>
<tr>
<td><strong>Metronidazole</strong></td>
</tr>
<tr>
<td><strong>Flucloxacin</strong></td>
</tr>
<tr>
<td><strong>Doxycycline</strong></td>
</tr>
<tr>
<td><strong>Cephalaxin</strong></td>
</tr>
<tr>
<td><strong>Cefuroxime axetil</strong></td>
</tr>
<tr>
<td><strong>Cephalaxin</strong></td>
</tr>
<tr>
<td><strong>Cephalaxin</strong></td>
</tr>
<tr>
<td><strong>Azithromycin</strong></td>
</tr>
<tr>
<td><strong>Penicillin</strong></td>
</tr>
<tr>
<td><strong>Piperacillin-tazobactam</strong></td>
</tr>
<tr>
<td><strong>Amoxicillin-clavulanic acid</strong></td>
</tr>
<tr>
<td><strong>Flucloxacin</strong></td>
</tr>
<tr>
<td><strong>Chloramphenicol</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical prophylaxis indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cefazolin</strong></td>
</tr>
<tr>
<td><strong>Cefazolin</strong></td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
</tr>
<tr>
<td><strong>Gentamicin</strong></td>
</tr>
<tr>
<td><strong>Cefalothin</strong></td>
</tr>
<tr>
<td><strong>Cefalothin</strong></td>
</tr>
<tr>
<td><strong>Cefazolin</strong></td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong></td>
</tr>
<tr>
<td><strong>Metronidazole</strong></td>
</tr>
<tr>
<td><strong>Flucloxacin</strong></td>
</tr>
<tr>
<td><strong>Cefuroxime</strong></td>
</tr>
</tbody>
</table>

Figure 1 Most common antimicrobials for treatment indications (a) and surgical prophylaxis (b) indications, by public and private. (a), Public; (b), private.

<table>
<thead>
<tr>
<th>Table 2 Remoteness and survey methodology of participating hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public, n = 166</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Remoteness</strong></td>
</tr>
<tr>
<td>Major city</td>
</tr>
<tr>
<td>Inner or outer regional</td>
</tr>
<tr>
<td>Remote or very remote</td>
</tr>
<tr>
<td><strong>Survey methodology</strong></td>
</tr>
<tr>
<td>PPS</td>
</tr>
<tr>
<td>sPPS</td>
</tr>
<tr>
<td>Random sample</td>
</tr>
</tbody>
</table>

†There are no remote or very remote private hospitals in Australia.

PPS, whole facility point prevalence survey; sPPS, whole facility serial point prevalence survey.
metronidazole (6.5%), piperacillin–tazobactam (6.1%) and amoxycillin–clavulanic acid (6.0%). For treatment indications, the three most common antimicrobials used in public hospitals were broad-spectrum agents (ceftaxone, piperacillin–tazobactam and amoxycillin–clavulanic acid), whereas in private hospitals there were narrower spectrum agents that featured in the top three (cephazolin, cephalaxin and metronidazole) (see Fig. 1). For surgical prophylaxis, cephalaxin comprised the vast majority of antimicrobial prescriptions across both public (61.3%) and private (58.8%) facilities. Compared with public hospitals, private hospitals had more frequent use of the oral antibiotic cephalaxin (11.4% vs 5.9%, \( P < 0.001 \)).

There were no significant differences in the frequency of prescription of ‘last line’ treatment antibiotics, such as meropenem, linezolid, daptomycin, colistin and tigecycline.

A small percentage of prescriptions was for topical antimicrobials (3.6%), however, this was higher in public hospitals compared with private hospitals (3.9% vs 1.1%). The most common indications for which topical antimicrobials were used were tinea, oral candidiasis and conjunctivitis. There was some use in surgical prophylaxis (40 of 2246 prescriptions), with approximately half of these being for topical chloramphenicol.

Although there were no statistically significant differences in overall rates of compliance with prescribing guidelines, public hospitals had a higher percentage of antimicrobial prescriptions that were compliant with locally endorsed guidelines, rather that the TG:A \(^{11,12} \) compared to private hospitals (Table 3). Figure 2 shows the breakdown of compliance with guidelines between public and private hospitals for both the top five treatment and surgical prophylaxis prescriptions. Indications with higher overall rates of non-compliant prescribing were community-acquired pneumonia, urinary tract infections and surgical prophylaxis, particularly orthopaedic surgery. There was also greater non-compliance with guidelines for prophylaxis in public hospitals compared with private hospitals for the three most common surgical specialties: plastic surgery (73.4% vs 38.0%, \( P < 0.001 \)), general surgery (45.5% vs 18.2%, \( P < 0.001 \)) and orthopaedic surgery (45.0% vs 37.4%, \( P = 0.039 \)).

Reasons for non-compliance with guidelines are given in Table 4. For treatment prescriptions, the main reason for non-compliance in public hospitals was spectrum being too broad (31.2%) whilst the main reason in private hospitals was incorrect dose/frequency (28.5%). Specific examples of the antimicrobial spectrum being too broad included the use of ceftriaxone for surgical prophylaxis and the use of piperacillin–tazobactam for community-acquired pneumonia. Specific examples of incorrect dosing included the use of cephalaxin 1 g for surgical prophylaxis and the use of cephalexin 500 mg 8-hourly for wound infections and urinary tract infections. Prophylaxis greater than 24 h was the main reason for non-compliance of surgical prophylaxis prescriptions for both public (62.5%) and private hospitals (69.7%).

### Table 3 Compliance with prescribing guidelines for treatment, medical and surgical prophylaxis prescriptions

<table>
<thead>
<tr>
<th></th>
<th>Public ( n (%) )</th>
<th>Private ( n (%) )</th>
<th>Combined ( n (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliant with guidelines</td>
<td>11 459 (81.5)</td>
<td>927 (48.4)</td>
<td>12 386 (77.6)</td>
</tr>
<tr>
<td>Therapeutic guidelines: antibiotic</td>
<td>6486 (56.6)</td>
<td>557 (60.1)</td>
<td>7043 (56.9)</td>
</tr>
<tr>
<td>Locally endorsed guidelines</td>
<td>5356 (46.7)</td>
<td>540 (58.3)</td>
<td>5896 (47.6)</td>
</tr>
<tr>
<td>Non-compliant with guidelines</td>
<td>1130 (9.9)*</td>
<td>17 (1.8)*</td>
<td>1147 (9.3)</td>
</tr>
<tr>
<td>Other</td>
<td>2658 (23.2)</td>
<td>144 (15.5)</td>
<td>2802 (22.6)</td>
</tr>
<tr>
<td>Surgical prophylaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliant with guidelines</td>
<td>1348 (9.6)</td>
<td>898 (46.9)</td>
<td>2246 (14.1)</td>
</tr>
<tr>
<td>Therapeutic guidelines: antibiotic</td>
<td>637 (47.3)</td>
<td>525 (58.5)</td>
<td>1162 (51.7)</td>
</tr>
<tr>
<td>Locally endorsed guidelines</td>
<td>401 (29.8)</td>
<td>464 (51.7)</td>
<td>865 (38.5)</td>
</tr>
<tr>
<td>Non-compliant with guidelines</td>
<td>236 (17.5)*</td>
<td>61 (6.8)*</td>
<td>297 (13.2)</td>
</tr>
<tr>
<td>Other</td>
<td>84 (6.2)</td>
<td>33 (3.6)</td>
<td>117 (5.2)</td>
</tr>
<tr>
<td>Medical prophylaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliant with guidelines</td>
<td>1246 (8.8)</td>
<td>89 (4.6)</td>
<td>1335 (8.4)</td>
</tr>
<tr>
<td>Therapeutic guidelines: antibiotic</td>
<td>1031 (82.7)</td>
<td>70 (78.7)</td>
<td>1101 (82.5)</td>
</tr>
<tr>
<td>Locally endorsed guidelines</td>
<td>262 (21.0)</td>
<td>54 (60.7)</td>
<td>316 (23.3)</td>
</tr>
<tr>
<td>Non-compliant with guidelines</td>
<td>769 (61.7)*</td>
<td>16 (18.0)*</td>
<td>785 (58.8)</td>
</tr>
<tr>
<td>Other</td>
<td>67 (5.4)</td>
<td>10 (11.2)</td>
<td>77 (7.0)</td>
</tr>
<tr>
<td>Total</td>
<td>14 053</td>
<td>1914</td>
<td>15 967</td>
</tr>
</tbody>
</table>

\*\( P < 0.001 \).
Discussion

This study represents the largest survey of antimicrobial prescribing in Australian hospitals to date. Based on the latest hospital demographic data, the survey represents 23 and 13% of all acute care public and private hospitals in Australia respectively. There are notable differences between antimicrobial use in public and private hospitals in Australia based on the findings presented.

Reflective of the differences in casemix between the two hospital sectors, it was somewhat predictable that antimicrobial prescriptions for the treatment of infections predominated in public hospitals, whereas surgical prophylaxis prescriptions accounted for nearly half of all antimicrobial use in private hospitals. These data were consistent with recent PPS in Australian public and private hospitals.1,2

Although, as noted above, overall rates of compliance with prescribing guidelines were similar between public and private hospitals for both treatment and surgical prophylaxis, rates of compliance with locally endorsed guidelines, if different from TG:A,11,12 were significantly higher in public hospitals. It is unclear, however, whether these local guidelines were developed on the basis of direct disagreement with TG:A11,12 recommendations, or simply derived from TG:A11,12 but using locally based data, such as antibiograms. The latter may be a viable approach in settings that require local susceptibility data to initiate adequate empirical antimicrobial therapy, such as tertiary referral intensive care units.13

![Figure 2](image-url)

**Figure 2** Level of compliance for common treatment (a) and surgical prophylaxis (b) prescriptions for public and private facilities (the numbers of prescriptions are shown next to each hospital category). ( ), Compliant; ( ), non-compliant; ( ), other.

<table>
<thead>
<tr>
<th>(a) Treatment Prescriptions</th>
<th>Public (1823)</th>
<th>Private (113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia, community</td>
<td>64.2%</td>
<td>31.1%</td>
</tr>
<tr>
<td>Infections</td>
<td>66.4%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>49.9%</td>
<td>25.7%</td>
</tr>
<tr>
<td>Infections</td>
<td>64.4%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Septic</td>
<td>49.5%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Infections</td>
<td>56.8%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Collagen/erythroblastoma</td>
<td>60.8%</td>
<td>28.3%</td>
</tr>
<tr>
<td>Infections</td>
<td>59.2%</td>
<td>19.7%</td>
</tr>
<tr>
<td>COPD, infective exacerbation</td>
<td>49.9%</td>
<td>42.7%</td>
</tr>
<tr>
<td>Infections</td>
<td>52.2%</td>
<td>34.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) Surgical Prophylaxis Prescriptions</th>
<th>Public (376)</th>
<th>Private (340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopaedics</td>
<td>Public (213)</td>
<td>Private (148)</td>
</tr>
<tr>
<td>General surgery</td>
<td>Public (64)</td>
<td>Private (79)</td>
</tr>
<tr>
<td>Plastic</td>
<td>Public (97)</td>
<td>Private (44)</td>
</tr>
<tr>
<td>Obstetrics</td>
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<td>Private (7)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4 Reasons for non-compliance with prescribing guidelines for treatment and surgical prophylaxis prescriptions†</th>
<th>Public n (%)</th>
<th>Private n (%)</th>
<th>Combined n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>2423</td>
<td>117</td>
<td>2540</td>
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<tr>
<td>Incorrect route</td>
<td>140 (5.3)</td>
<td>5 (3.5)</td>
<td>145 (5.2)</td>
</tr>
<tr>
<td>Incorrect dose/frequency</td>
<td>520 (19.6)</td>
<td>41 (28.5)</td>
<td>561 (20.0)</td>
</tr>
<tr>
<td>Incorrect duration‡</td>
<td>211 (7.9)</td>
<td>16 (11.1)</td>
<td>227 (8.1)</td>
</tr>
<tr>
<td>Spectrum too narrow‡</td>
<td>164 (6.2)</td>
<td>10 (6.9)</td>
<td>174 (6.2)</td>
</tr>
<tr>
<td>Spectrum too broad§</td>
<td>828 (31.2)</td>
<td>28 (19.4)</td>
<td>856 (30.5)</td>
</tr>
<tr>
<td>Antimicrobial not indicated</td>
<td>560 (21.1)</td>
<td>17 (11.8)</td>
<td>577 (20.6)</td>
</tr>
<tr>
<td>Surgical prophylaxis</td>
<td>783</td>
<td>394</td>
<td>1177</td>
</tr>
<tr>
<td>Incorrect route</td>
<td>13 (2.1)</td>
<td>23 (6.8)</td>
<td>36 (3.7)</td>
</tr>
<tr>
<td>Incorrect dose/frequency</td>
<td>151 (24.1)</td>
<td>38 (11.2)</td>
<td>189 (19.5)</td>
</tr>
<tr>
<td>Surgical prophylaxis &gt;24 h§</td>
<td>392 (62.5)</td>
<td>237 (69.7)</td>
<td>629 (65.0)</td>
</tr>
<tr>
<td>Spectrum too narrow‡</td>
<td>22 (3.5)</td>
<td>3 (0.9)</td>
<td>25 (2.6)</td>
</tr>
<tr>
<td>Spectrum too broad§</td>
<td>41 (6.5)</td>
<td>26 (7.6)</td>
<td>67 (6.9)</td>
</tr>
<tr>
<td>Antimicrobial not indicated</td>
<td>164 (26.2)</td>
<td>67 (19.7)</td>
<td>231 (23.9)</td>
</tr>
</tbody>
</table>

†All surveyors were required to indicate whether surgical prophylaxis prescriptions was >24 h; however, all other reasons for non-compliance were optional and more than one reason could be selected per prescription. Medical prophylaxis prescriptions were not included as there was a high rate of compliance with guidelines for this indication. §Only for treatment prescriptions. ¶Only for surgical prophylaxis prescriptions.
The fact that no doctors were involved as auditors in private hospitals is reflective of previous data that noted differences between public and private hospital personnel dedicated to undertake AMS activities. A 2012 survey of Victorian hospitals indicated that approximately a third of surveyed metropolitan public hospitals had funding for pharmacists and/or medical staff available to conduct AMS activities, such as regular auditing of antimicrobial prescribing. In contrast, at the time there was no private hospital that reported having dedicated funding for pharmacists or medical staff to oversee AMS activities, such as auditing antimicrobial prescriptions. In private hospitals, it would appear that nurses are being given primary roles in managing AMS programmes, including auditing.

**Specific targets for AMS interventions**

Use of excessively broad-spectrum therapy will be a major area to target for public hospitals, particularly in the treatment of respiratory infections. Prescribing guidelines, such as TG:A, are a useful starting point to help address these issues, but there are concerns that these may not be able to take into account patient specific factors, and so may not be applicable when used in clinical practice. Additional educational interventions, in the form of patient specific post-prescription advice through an antimicrobial management team or use of computerised decision support systems, if not already implemented, may be considerations for hospitals that report non-compliance due to overuse of broad-spectrum antimicrobials.

For private hospitals, improving antimicrobial dosing/frequency should be a priority, as this accounted for nearly a third of non-compliance among treatment prescriptions. These findings, together with previous qualitative work showing that private hospital specialists self-reported a deficiency in up-to-date antimicrobial knowledge, suggest that ongoing educational support is imperative to improve the quality of antimicrobial-prescribing practices in private hospitals. This may be achieved by having increased time for pharmacists to perform AMS duties within private hospitals.

Both hospital sectors will need to address the issue of overuse of antimicrobials for surgical prophylaxis. Not only are antimicrobials being used beyond the recommended cut-off of 24 h post-operatively but also there is a significant proportion of surgical prophylaxis prescriptions that may not be indicated. As previous Australian data also suggest that there is room to improve timing of antimicrobial administration in relation to surgical incision, there is strong argument for surgical prophylaxis to be viewed as a top priority area for quality improvement Australia wide.

Although this study provides the first detailed picture of antimicrobial prescribing in Australian hospitals, there are some limitations to consider. First, the representativeness of the results may be biased as participation in the survey was voluntary, hence participants may have likely been more interested in AMS. Second, although the data may be considered generalisable for most types of hospitals, major city hospitals were more strongly represented, whilst remote hospitals less so. As many of these major city hospitals are tertiary referral centres and often have more complex patients, this may have contributed to the higher broad-spectrum use observed in public hospitals. Third, surveyors from different professions performed the assessment of compliance, potentially affecting comparability of data between hospitals. The difference in assessor background was particularly evident between public and private hospitals, with the former having nursing surveyors as a minority, whilst the latter having these surveyors as the majority but no surveyors who were doctors. Recent Australian data investigating the reliability of assessments of antimicrobial concordance with TG:A made by assessors from different clinical backgrounds confirms that further work is required to improve inter-rater reliability between this heterogeneous mix of surveyors. Data comparability between hospitals could have been further affected given that assessments made earlier in the study period used the previous version of TG:A. Fourth, certain surgical wound classifications (i.e. Class III and Class IV) often require greater than 24 h of antimicrobial use, often as pre-emptive therapy. However, as the NAPS tool did not specifically capture wound classification, the broad recommendation of greater than 24 h post-operatively was reported as a reason for non-compliance.

**Conclusion**

Although overall rates of compliance with prescribing guidelines are similar between public and private hospitals, there are many other aspects of antimicrobial prescribing that vary between the two groups of hospitals. Importantly, findings from this study have provided priority areas for antimicrobial prescribing improvement for each hospital sector to consider. For public hospitals, improvement will have to include promoting, where appropriate, the use of narrower spectrum antimicrobial agents. Private hospitals, on the other hand, have a significant burden of antibiotics being used for surgical prophylaxis, and given the rate of prolonged prophylaxis, it represents a critical area for improvement.
References


Medication appropriateness tool for co-morbid health conditions in dementia: consensus recommendations from a multidisciplinary expert panel

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Key words
dementia, prescribing criteria, older adults, cognitive impairment.

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Abstract

Background: Medication management for people living with dementia is a complex task as it is unclear what constitutes optimal medication management in this population due to the shifting focus of health priorities and the balance between the benefits and harms of medications.

Aim: This study sought expert opinion to create a consensus list to define appropriate medication management of co-morbidities for people with dementia.

Methods: This study used the Delphi technique. We invited multidisciplinary experts in geriatric therapeutics including pharmacists, doctors, nurse practitioners, a patient advocate and a psychologist to participate. Participants were asked to engage into three or more rounds of questioning. Round 1 was a questionnaire comprised of one question defining dementia and seven open-ended questions about appropriate management of co-morbidities in people with dementia. Two investigators qualitatively analysed the responses to questions from Round 1 using thematic analysis. The results of this analysis were provided to participants as statements in the Round 2 survey. The participants were asked to rate their agreement with each statement on a 5-point Likert scale. The median and interquartile range (IQR) were calculated for the responses to each statement. Consensus was pre-specified as an IQR less than or equal to 1. Statements where consensus was not achieved were presented to participants in Round 3. The Round 2 median and IQR values were provided and participants were again asked to rate their agreement with each statement on a 5-point Likert scale. The statements where participants agreed or strongly agreed were included in the Medication Appropriateness Tool for Co-morbid Health conditions in Dementia criteria.

Results: Fifty-seven experts agreed to participate in the study, of whom 58% were pharmacists and 36% were medical practitioners. Fifty-five participants completed the Round 1 (93% response rate). A total of 128 statements was included in the Round 2 survey. Consensus was reached on 93 statements in Round 2 (n = 48 responders, 84% response rate) and on 18 statements in Round 3 (n = 43 responders, 75% response rate). The participants reached consensus on 111 of 128 statements. Of these statements, 67 statements were included in the Medication Appropriateness Tool for Co-morbid Health conditions in Dementia criteria. The statements were in the broad themes of preventative medication, symptom management, disease progression, psychoactive medication, treatment goals, principles of medication use, side-effects and medication reviews.

Discussion: This research provides consensus-based guidance for clinicians who manage co-morbid health conditions in people with dementia.

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Conflict of interest: None.

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Introduction

Dementia is a life-limiting disease with an average survival time of less than 5 years from diagnosis.\(^1\) It is the third leading cause of death and the leading cause of disability burden in adults aged 65 years and over in Australia.\(^3,4\) Co-morbidities and polypharmacy are common in people with dementia, though evidence is scarce for medication safety, tolerability and efficacy in this population.\(^5\)–\(^7\)

People with dementia have as many co-morbidities as their peers (cognitively intact people of a comparable age) and take a mean of five or more medications daily.\(^6\)–\(^14\) However, people with dementia are more likely than their peers to use certain medication classes, such as antihypertensives, laxatives, diuretics, antidepressants and antipsychotics.\(^15\)–\(^16\) This medication use may reflect risk factors for dementia and common co-morbidities such as cardio and renovascular disease.\(^5\)–\(^7\)–\(^17\)–\(^19\)

Age-related pharmacokinetic changes occur in all older people,\(^7\)\(^0\)–\(^22\) and an altered blood-brain permeability in people with dementia means that they may be more sensitive to neurological and cognitive effects of medications than their peers.\(^23\)–\(^26\) These pharmacokinetic changes are additional to drug-disease interactions that occur in dementia.\(^27\) The safety profile and efficacy of many medications in people with dementia are underdetermined due to their active exclusion from 85% of published clinical trials.\(^26\) Furthermore, the tendency for people with dementia to under-report disease-related symptoms means that it is likely they also under-report side-effects.\(^27\)

Research in people with dementia focuses on treatments that prevent or delay dementia onset and/or progression and manage dementia-specific symptoms,\(^28\) such as the neuropsychiatric or behavioural symptoms common in people with dementia.\(^29\)–\(^30\) Evidence for the efficacy of these medications is conflicting.\(^31\)–\(^32\) and the harms of some, such as antipsychotics and benzodiazepines, make them potentially inappropriate in this population.\(^33\)

Despite the frequency of co-morbidities and medication use among people with dementia, appropriate medication management in this life-limiting condition is infrequently studied and poorly understood. Studies of antihypertensives, hypoglycaemics, statins and anti-inflammatory agents mainly assess their ability to delay dementia onset.\(^34\)–\(^36\) After dementia onset, medication appropriateness to manage co-morbidities is complicated by a relative absence of evidence.\(^3\)–\(^7\) Preventive treatments may require a treatment time to benefit that exceeds life expectancy,\(^32\) or may target treatment goals that are not relevant to the individual or their families.\(^33\) This is combined with a shifting focus on the priorities of healthcare in this patient cohort and the balance between the benefits and harms of medicines.\(^34\)

Medication management is subsequently complicated for people with dementia, and careful consideration should be given to initiation and continuation of all medications. Medication management decisions for people with dementia are often based on data collected in younger adults or peers, which may not be generalisable or relevant to this population. The existing explicit prescribing criteria developed for older people do not account for the additional complexities of dementia or its life-limiting nature.\(^35\)–\(^49\) Consensus-based guidance specifically for people with dementia would assist clinicians with decision-making in this population.\(^50\)–\(^51\) This study aimed to elicit opinion and gain consensus on appropriate medication management of co-morbidities in people with dementia. The intended outcome was to create a consensus-based list of statements to define appropriate medication management of co-morbidities in people with dementia named the Medication Appropriateness Tool for Co-morbid Health conditions in Dementia (MATCH-D) criteria.

Methods

The methods for this study have been previously described in detail,\(^52\) and are briefly described here. Ethical approval was granted from the University of Western Australia’s Human Research Ethics Committee (HREC) (reference: RA/4/1/7172).

Expert panel selection

Clinical and research based experts with relevant backgrounds were eligible for inclusion on the multidisciplinary expert panel. Participants were identified using a multipronged approach.\(^52\) Relevant professional associations and networks were approached to distribute an advertisement for recruitment to their membership. Individuals identified as potentially eligible participants through their peer-reviewed publications, participation in relevant conferences or peer-nominated, were sent personalised letters of invitation to participate. Conflicts of interest were declared and assessed.

Data collection

The Delphi technique consisted of three rounds (Fig. 1), which were administered via Qualtrics: Online Survey Software & Insight Platform.\(^53\) A cover sheet that stated the intention of the rounds was included.

Round 1 – survey design

The survey questions were developed by three investigators (AP, CEB and KP). The Round 1 questionnaire...
asked seven open-ended questions with respect to pharma- 
cocerebral management of comorbidities for people 
with dementia. The questionnaire included one 
statement that measured agreement on a 5-point Likert 
scale. This statement was to define dementia. The ques-
tions asked the expert panelists their opinion on the 
approach to medication management of co-morbidities 
for people with dementia (Supporting Information, 
Appendix S1).

Round 1 – survey pilot
The survey was piloted with all the investigators (three 
pharmacists, a general practitioner and a geriatrician/ 
Figure 1 Flow chart to illustrate the process of the three rounds of the Delphi technique.
clinical pharmacologist). Adjustments were made to the questions and format of the survey based on their feedback. The pilot process was repeated with five senior clinical pharmacists in November 2014. The survey was further adjusted based on their feedback.

**Round 1 – survey administration**
The survey was administered to the expert panel in May and June 2015.

**Round 1 – data analyses**
The responses to the open-ended questions collected during Round 1 were analysed thematically. Two researchers independently coded the data using content analysis to organise the data into themes and collaborated to discuss any disagreement to reach a consensus.

The Round 1 analysis was used to develop statements to present to participants in the Round 2 survey. Statements were amalgamated where the researchers agreed that the statements had the same or very similar meaning.

**Rounds 2 and 3**

**Round 2 – survey design**
The Round 2 survey consisted of statements generated in response to the open-ended questions in the Round 1 survey. Participants were asked to state the extent to which they agree with the statements using a 5-point Likert scale from strongly disagree to strongly agree.

Statements with quantitative thresholds were repeated with different sensitivities to clarify agreement where relevant. For example, participants were asked if they agreed with the statements that a medication review (otherwise known as a medicines use review (MUR)) should be triggered by (i) five or more medications, (ii) eight or more medications and (iii) ten or more medications.

Statements were referenced to early, mid and late stages of dementia. The stages were defined for the participants as:

- Early-stage dementia: “mild cognitive impairment with a preserved ability to self-care and undertake activities of daily living.”

- Mid-stage dementia: “moderate cognitive impairment with physical function often preserved. People with mid-stage dementia may be living with support in the community or a low-care residential aged care setting.”

- Late-stage dementia: “severe cognitive impairment and declining function (inability to recognise loved ones, unable to ambulate independently, incontinent of urine or faeces).”

**Round 3 – survey design**
Statements to which agreement was reached in Round 2 were removed from the survey for Round 3. The remaining statements to which the agreement was not reached in Round 2 were resubmitted to the panel in the Round 3 survey.

**Rounds 2 and 3 – survey administration**
The Round 2 survey was administered in September and October 2015, and the Round 3 survey was administered in November 2015.

**Rounds 2 and 3 – data analyses**
The quantitative data (responses to the Likert scales) were entered into SPSS v22 (IBM, Armonk, NY, USA) for Macintosh statistical software for analysis. To undertake the quantitative analysis, the Likert scale responses were coded numerically as: strongly disagree = 1, disagree = 2, neither agree nor disagree = 3, agree = 4 and strongly agree = 5. Descriptive statistics were undertaken on the entire data set to determine the median and interquartile range (IQR) for each statement. Where the median was not a whole number, it was rounded to the nearest whole unit so that it remained consistent with a response of strongly disagree, disagree, neither agree nor disagree, agree or strongly agree.

**Definition of consensus**
Consensus for an individual statement was pre-defined as an IQR less than or equal to 1.

**Statement synthesis for the MATCH-D criteria**
The statements were condensed to produce the final MATCH-D criteria. Statements were included in the MATCH-D criteria for clinical application where the participant consensus was agreed or strongly agreed. Statements were not included in the MATCH-D criteria where the participants reached agreement that they neither agreed nor disagreed, disagreed or strongly disagreed.

Statements where participants agreed that it was relevant for early, mid and late stage dementia were combined to indicate that these remained relevant regardless of dementia stage. These were collated under the heading ‘all stages’. For statements with multiple quantitative thresholds, we reported the lowest of the thresholds where more than one response elicited the same consensus-based response (i.e. agree or strongly agree).
Results
The multidisciplinary expert panel consisted of 57 experts with qualifications and experience in relevant fields (Fig. 2; Table 1).

Definition of people with dementia for the criteria
Experts agreed on the draft definition in Round 1 but suggested modifications in free text comments. They agreed on the refined definition in Round 2. The final consensus definition of dementia for use in the criteria was:

Dementia is a clinical syndrome characterised by a chronic progressive decline in neurocognitive function, specifically affecting memory, cognition, language, behaviour, emotional control, and social functioning beyond the expected effects of physiological ageing and not attributable to an intercurrent illness. The specific signs and symptoms of dementia and the rate of progression vary accordingly to the aetiology and individual. One or more aetiology may be present at the same time; the most common forms of dementia are Alzheimer’s, vascular, Lewy body, and fronto-temporal dementia.

Agreement on the proposed criteria
The panel considered 128 statements in eight domains for the Round 2 survey. Consensus was reached on 93 (73%) of the 128 proposed statements considered by the expert panel in Round 2: disagree (n = 4), neither agree nor disagree (n = 8), agree (n = 45) and strongly agree (n = 36).

The panel considered 36 statements for the Round 3 survey. Consensus was reached on 19 (53%) of the 36 proposed statements that were re-administered in Round 3: disagree (n = 8), neither agree nor disagree (n = 1) and agree (n = 4).

The expert panel reached consensus on 111 statements (Supporting Information, Table S1) and did not reach consensus on 17 statements (Supporting Information, Table S2).

Table 1 Participant characteristics

<table>
<thead>
<tr>
<th>Age/Gender/Qualifications/Health professional or background/Work environment/Years experience in managing pharmacotherapy for people living with dementia</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20–29 years</td>
</tr>
<tr>
<td></td>
<td>30–39 years</td>
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<tr>
<td></td>
<td>40–49 years</td>
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<td>50–59 years</td>
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<td>60–69 years</td>
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<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Qualifications as an expert</td>
<td>Authored one or more papers connected to medicine use in older people in the last 10 years?</td>
</tr>
<tr>
<td></td>
<td>Credentialed in an area related to medicine use in older people (CGP, AACP, Geriatrician etc.)</td>
</tr>
<tr>
<td></td>
<td>Practised in a relevant field for 5 or more years?</td>
</tr>
<tr>
<td></td>
<td>Participated in an invitation only symposium or focus group related to geriatric medicine use</td>
</tr>
<tr>
<td></td>
<td>Received a personally addressed letter inviting you to participate in this study.</td>
</tr>
<tr>
<td>Health profession or background</td>
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</tr>
<tr>
<td></td>
<td>General practicioner</td>
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<tr>
<td></td>
<td>Clinical pharmacologist</td>
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<tr>
<td></td>
<td>Geriatrician</td>
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<tr>
<td></td>
<td>Physician</td>
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<tr>
<td></td>
<td>General medicine physician</td>
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<tr>
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<td>Research psychologist</td>
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<td></td>
<td>Registered nurse</td>
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<td>11–20 years</td>
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<td></td>
<td>21–30 years</td>
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<td>31+ years</td>
</tr>
</tbody>
</table>

Numbers are n (%) AACP, Australian Association of Consultant Pharmacy; GCP, Certified Geriatric Pharmacist.
Statement synthesis for the MATCH-D criteria

The 85 statements on which consensus agreement was achieved were condensed into 67 statements across eight categories to create the MATCH-D criteria (Appendix S2).

The MATCH-D criteria include a one-page addendum to present the condensed statements for the statements where the consensus was to disagree with the statement (Appendix S2, p. 5).

Discussion

This paper reports consensus statements that describe appropriate medication management in people with dementia. We convened a large multidisciplinary panel of experienced clinicians with backgrounds in pharmacy, medicine and nursing for this project. The expert panel generated a list of statements that provide guidance on appropriate treatment goals in people with dementia and important discussion points for patient-centered care. The MATCH-D statements give specific consensus-based advice on symptom management, prescribing to reduce the risk of future events, medications to slow dementia progression, psychoactive medications, the experience of side-effects and the indications for a medication review in people living with dementia.

Medication management for people with dementia has often been focused on improving cognitive function and reducing symptoms of the dementia. Australia released clinical guidelines on the management of dementia in May 2015. These guidelines describe the use of anticholinesterase inhibitors and memantine for dementia progression and pharmacological management of behavioural and psychological symptoms of dementia with antipsychotics, antidepressants, anxiolytics, mood stabilisers and melatonin. They do not provide guidance on the pharmacological management of co-morbidities except where they may affect behavioural and psychological symptoms. Evidence assessing co-morbidities among people with dementia remains focused on prevalence and assessment of quality of care. Our study complements existing dementia guidelines by describing appropriate pharmacological management of co-morbidities as dementia progresses.

One of the strong messages from our expert panel was the importance of a person-centered approach to
pharmacological management in people with dementia. Medication management needs to focus on treatment goals that are relevant to the individual and their families, as older adults vary in their preferences for treatment when they consider the potential risks and benefits of medication management.\(^43,56\) It is important that people with dementia are involved in decisions about their own care,\(^57\) and that the wishes of caregivers or family are also considered in the decision-making process.\(^58,59\)

General prescribing criteria for older adults do not specifically consider the particularities of a progressive, life-limiting nature of dementia.\(^45–47\) We anticipated that this project would generate a list of appropriate and inappropriate medications for managing co-morbidities in dementia, similar to other existing explicit prescribing criteria in older people such as the Beers and STOPP/START criteria.\(^60,61\) However, the expert responses to the Round 1 questions emphasised individualising treatment and the importance of reviewing treatments for co-morbidities as the dementia progresses. The MATCH-D criteria reported here may add value if used alongside other prescribing criteria designed for older adults and provide health professionals with guidance on when it may be appropriate to de-prescribe specific medications for co-morbidities in people with dementia.\(^62\) The MATCH-D criteria also provide guidance on specific issues to discuss with patients and their families when individualising care in dementia.

This study has several strengths. The panel was large with experts from a variety of health professional fields and we had a high response rate to our initial approach (95% participation in Round 1). We used carefully worded open-ended questions in the initial round to avoid biasing or limiting the possible responses. Two investigators independently analysed the Round 1 responses to increase the objectivity of the process. Existing consensus-based criteria for older people have been criticised for a lack of transparency in the methods.\(^63\) A strength of the current study is that the methods were transparent with a pre-specified published protocol.\(^32\) A weakness of this study is that Round 1 did not generate statements on the anticipated list of appropriate and inappropriate medications as specified in the protocol. As such, we did not anticipate the process of condensing a large number of statements in our protocol. However, this demonstrates that the Round 1 questions did not limit possible responses.

**Conclusion**

More work is required to evaluate whether the MATCH-D criteria are useful in clinical practice. In addition, the MATCH-D criteria may need to be refined or amended for clinical application. In the current version of MATCH-D, we have included statements where there was consensus disagreement in their original format as an addendum (e.g. ‘Health professions should conceal medication in food or drink if [a person with dementia] refuses to take medications’ and ‘Regular medicines intended for symptom relief should be continued indefinitely in people who are unable to reliably report symptom recurrence’ and ‘the wishes and needs of family and carers should take priority over those of the person living with dementia’). It is uncertain without further research whether the inverse of these statements would be ratified.

More research is also needed to determine whether applying the MATCH-D criteria in the clinical setting will improve health outcomes and quality of life for people with dementia. However, the strong message from our experts is that medication management in people with dementia should be individualised to match the person’s changing treatment goals as the disease progresses.

**Acknowledgements**

Thank you to the following members of the expert panel who agreed to be acknowledged for their participation: Dr Chris Alderman, Ms Kristen Anderson, Associate Professor Simon Bell, Dr Mandy Callary, Ms Ginny Chin, Mrs Amanda Cross, Mr Phillip Davis, Ms Laura Dean, Ms Cinny Xin Dong, Professor Jenny Doust, Dr Rohan Elliott, Ms Mary Eitty-Leal, Dr Christopher Freeman, Ms Elizabeth Georgeson, Dr DaniJela Gnjidic, Dr Ivanka Hendrix, Ms Anna Hendy, Professor Sarah Hilmer, Dr Jesse Jansen, Associate Professor Kristina Johnell, Ms Stefanie Johnston, Associate Professor Benny Katz, Ms Lisa Kouladijan, Ms Sarita Lo, Dr John Maddison, Professor Jennifer Martin, Ms Anne Moehead, Associate Professor Vasi Naganathan, Dr John Obeid, Ms Yan Ghee Peng, Mrs Barbara Petrie, Dr Lisa Pont, Dr Ranjeev Pulle, Dr Emily Reeve, Dr Patrick Russell, Ms Debbie Rigby, Ms Robyn Saunders, Dr Ian Scott, Dr Andrew Stafford, Ms Lavinia Verduci, Dr Juanita Westbury, Dr Mackenzie Williams, Mr John Woodward, Associate Professor Michael Woodward.

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Supporting Information

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

**Appendix S1** Round one survey.

**Appendix S2** Medication appropriateness tool for comorbid health conditions in dementia (MATCH-D).

**Table S1** Statements on which consensus was achieved.

**Table S2** Statements where consensus was not achieved in Round 3.
Treatment of aplastic anaemia with lower-dose anti-thymocyte globulin produces similar response rates and survival as per standard dose anti-thymocyte globulin schedules

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Key words
aplastic anaemia, bone marrow failure, anti-thymocyte globulin.

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Abstract
Background: Aplastic anaemia (AA) is a rare acquired bone marrow failure syndrome resulting from the immune-mediated destruction of haemopoietic stem cells. For adults in whom first-line haemopoietic progenitor cell transplantation is not feasible, combination anti-thymocyte globulin (ATGAM) plus cyclosporine A is standard therapy; however, there are minimal data available regarding the optimal ATGAM dosage in terms of efficacy and survival.

Aims: Our institutions have historically used different dosing protocols of ATGAM in the treatment of AA. We aimed to review the outcome of AA patients treated with these protocols and compare them to the published literature.

Methods: We conducted a retrospective study of 31 adults who received first-line ATGAM for AA and compared response rates and survival between cohorts who received standard (40 mg/kg/day D1–4) versus lower-dose (15 mg/kg/day D1–5) ATGAM schedules.

Results: There were similar rates of response (64 vs 71%, P = 1.0), relapse (33 vs 33%, P = 1.0), transformation (14 vs 24%, P = 0.66) or infection (43 vs 47%, P = 1.0), respectively, between standard and lower-dose cohorts. At a median follow up of 24 months, there was no statistical difference between standard and lower-dose cohorts in either event-free (42.2 vs 64.7%, P = 0.91) or overall survival (73.1 vs 88.2%, P = 0.75).

Conclusion: Our experience suggests that lower-dose ATGAM at 15 mg/kg/day D1–5 as treatment of AA produces similar responses and outcomes as per standard-dose ATGAM schedules. Prospective trials comparing ATGAM dose schedules in AA are warranted.

Introduction
Aplastic Anaemia (AA) is an acquired bone marrow failure syndrome characterised by pancytopenia in association with a hypocellular bone marrow. AA results from immune-mediated suppression and the destruction of haemopoietic stem cells. For younger patients, sibling allogeneic haemopoietic progenitor cell transplant (HPCT) provides the best chance of cure, with response rates and overall survival in approximately 90% of patients. However, for patients >40 years old, or when a suitable donor is not available, immune suppressive therapy (IST) is recommended. Prospective studies1–6 have established combination horse (equine) anti-thymocyte globulin (ATG) plus cyclosporine A (CsA) and methylprednisolone (MP) as standard of care, producing response rates of 60–70% at several months following treatment. However, relapses post-IST may still occur in up to 30–40% of patients, with a further risk of the development of myelodysplastic syndromes (MDS) and/or other clonal haemopoietic disorders persisting for several years post-completion of IST.

There are limited data regarding the optimal dosage of ATG in AA, with different dosing schedules used for different formulations of equine ATG. Lymphoglobuline (Genzyme Corp, Lyon, France; now withdrawn from manufacture) has been predominantly used in Europe, with a majority of studies using a dose of 15 mg/kg/day for 5 days. ATGAM (Pfizer Inc, New York, NY, USA) has been more widely used outside of Europe, particularly within USA and Australia. Published dosing schedules
for ATGAM have typically utilised higher doses than those published with Lymphoglobuline, most commonly 40 mg/kg/day for 4 days. However, there are (albeit limited) data to suggest that lower-dose schedules of ATG may be as effective in the therapy of AA as higher dose protocols.\textsuperscript{2,4}

Our institutions have historically used different dosing protocols of ATGAM, at either a higher dose schedule of 40 mg/kg/day day 1–4 (institution 1) or a lower dose of 15 mg/kg/day day 1–5 (institution 2), in combination with standard CsA and MP as treatment of AA when allogeneic transplantation is not indicated or available. We aimed to review the outcome of AA patients treated with these protocols to determine if any difference in outcome was associated with the different ATGAM dose schedules.

**Methods**

Consecutive patients treated for newly diagnosed AA between January 2002 and June 2014 were identified from institutional databases. Diagnostic details and clinical outcomes of individual patients were then determined by a retrospective review of individual medical and laboratory records. Patients were eligible for inclusion in this analysis if they met the following criteria: age >16 years, bone marrow diagnosis of AA, normal cytogenetics by karyotyping at diagnosis and not treated with allogeneic HPCT as first-line therapy. AA severity was defined as per the modified Camitta criteria.\textsuperscript{9–11}

**IST protocols**

Institution 1 utilised ATGAM at a ‘standard dose’ of 40 mg/kg/day D1–4 (total dose 160 mg/kg), while institution 2 used a ‘lower dose’ ATGAM at 15 mg/kg/day D1–5 (total dose 75 mg/kg) in combination with CsA and MP as IST for newly diagnosed patients with AA. ATGAM was administered similarly at each institution, as a slow intravenous infusion over 12 h through a peripherally inserted central catheter. CsA dosing (5 mg/kg/day BD from D1, continued for at least 12 weeks, with dose adjustments to maintain a trough level of 150–300 µg/L) and MP schedules for prevention of ATGAM-related serum sickness (2 mg/kg/day D1–4, weaning by D14) were identical between institutions.

Supportive care strategies were identical between institutions. All patients received prophylaxis against opportunistic infection, including *Pneumocystis jirovecii* (trimethoprim-sulfamethoxazole 800 mg/160 mg twice weekly), varicella zoster (valaciclovir 500 mg daily) and yeast (fluconazole 200 mg). Febrile neutropenia was managed using identical protocols involving serial blood cultures and the empiric use of piperacillin-tazobactam 4.5 g qid with stat doses of gentamicin, and then directed by microbiology results. Granulocyte colony stimulating factor was not routinely used at the beginning of therapy but was included at physician discretion for short-term use in the event of significant neutropenic sepsis. Transfusion support used only irradiated products, with routine transfusion given below a threshold of haemoglobin <80 g/L or platelets <10 × 10\textsuperscript{9}/L (or platelets <20 × 10\textsuperscript{9}/L if infection or bleeding was present). Erythropoietin stimulating agents were not used.

Follow up included physical review and full blood count (FBC) 1–2 times per week for at least 12 weeks, and then tapered based upon response.

**Definitions**

Clinical outcomes of patients who underwent first-line treatment with IST using standard versus lower-dose ATGAM schedules were compared. These outcomes included disease response, relapse, transformation to MDS or acute myeloid leukaemia (AML), infection and survival. Disease response was defined as per EBMT criteria.\textsuperscript{9–11} Complete response (CR) required normalisation of all blood counts, whereas a partial response (PR) required transfusion independence and a haematological improvement in at least one cell line. No response was defined as the failure to achieve a CR or PR, without evidence of transformation. Diagnosis of relapse or transformation to MDS or AML required repeat bone marrow examination. In the event of a recurrent hypoplastic marrow, the development of new and typical cytogenetic abnormalities was used to define transformation to hypoplastic MDS rather than relapsed AA. Episodes of infection were defined primarily by microbiologically proven clinical infections within 120 days of ATGAM administration, but data were also collected for any other culture-negative febrile episodes requiring admission to hospital that occurred up to 120 days after the first day of ATGAM administration.

**Statistical analyses**

Categorical factors were compared by Fisher’s exact test. Survival analyses were calculated by the Kaplan–Meier method and compared using the log-rank test. Time to best response was defined from the first date of ATGAM administration to the first date of the best response ever achieved. Duration of best response was defined from the date of best response until the date of relapse, transformation, death or last follow up. Event-free survival (EFS) and overall survival (OS) analyses were calculated from the first day of ATGAM treatment. EFS was defined

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as time to relapse, transformation or death. For initial non-responders to IST, EFS was defined as date of second-line therapy (if undertaken), transformation or death. Date of death or last follow up was used for the calculation of OS.

Results

Patient characteristics

In total, 31 consecutive patients were treated with ATGAM for newly diagnosed AA during the time period under review, including 14 patients (45%) treated with the standard-dose ATGAM and 17 (55%) with the low-dose schedule. Baseline characteristics are summarised in Table 1. A majority of patients in each group suffered severe AA (SAA). Cytogenetic analysis either failed to grow metaphases or showed a normal karyotype in all patients.

Response to first-line immunosuppression

The clinical outcomes of patients treated with standard versus lower-dose ATGAM are summarised in Table 2. Overall, 21 patients (68%) achieved a PR or CR. There was no statistically significant difference in rates of response, time to response or duration of response between standard- and low-dose ATGAM groups.

The overall rate of relapse or transformation into MDS/AML was similar between groups (Table 2). In total, seven patients suffered relapse of their AA post-initial response to IST, and six patients (19%) suffered a transformation to MDS/AML. Median time to relapse or transformation was not different between standard- versus low-dose ATGAM groups (Table 2). Rate of transformation was no different in responders versus non-responders to initial IST (5/21, 24%; vs 1/10, 10%, respectively; \( P = 0.63 \)). Of the six cases of transformation, five developed MDS (two cases of refractory cytopenias with multilineage dysplasia, two cases of hypoplastic MDS and one case of Refractory Anaemia with Excess Blasts type 1); in each case, transformation into MDS was associated with the development of a new cytogenetic abnormality (three patients with deletion 5q, one case with monosomy 7 and one case with deletion 6p). One patient transformed into AML (with normal cytogenetics). Transformation occurred following an initial response to IST in five of the six cases (83%). No patient developed paroxysmal nocturnal haemoglobinuria (PNH) and/or PNH clones during follow up to date.

The incidence of infective episodes occurring within 120 days of ATGAM administration was not significantly different between patients receiving standard- versus low-dose ATGAM schedules (43 vs 47%; \( P = 1.0 \)).

Second-line therapy

The second-line therapies utilised included IST (using rabbit ATG, alemtuzumab or repeat ATGAM), eltrombopag or allogeneic HPCT. HPCT was undertaken in patients who had either failed to achieve at least a PR or who demonstrated progression to MDS/AML. There was no difference in outcome and/or response to second-line therapies between standard- versus low-dose ATGAM groups.

Of the 10 total patients who failed to achieve at least a PR to initial IST, 7 went on to receive second-line treatment. Therapies included IST (rabbit ATG, \( n = 1 \), eltrombopag \( n = 1 \) and unrelated donor allogeneic HPCT \( n = 5 \)). Responses were only observed following HPCT (40% alive in CR at a median of 12 months post-BMT, range: 6–100 months). The remaining patients either received a third-line HPCT \( (n = 1) \), died \( (n = 2) \) or remain transfusion-dependent \( (n = 2) \) at a median of 20 months (range 14–70 months).

Relapse of AA occurred in seven patients at a median of 5 months following initial response to IST (range: 1–22 months). Of these, six received second-line treatment, all of which were IST (rabbit ATG \( n = 4 \); ATGAM \( n = 1 \); alemtuzumab \( n = 1 \)). Only one patient (16%) achieved a partial response; this patient and one other non-responder subsequently underwent third-line unrelated donor HPCT and remain in CR at a median of 20 months follow up (range: 17–26 months). The

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics at diagnosis</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Number</td>
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<tr>
<td>Median age (years)</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Karyotype</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Failed metaphases</td>
</tr>
<tr>
<td>PNH clone at diagnosis</td>
</tr>
<tr>
<td>Absolute lymphocyte count &lt;1.0</td>
</tr>
<tr>
<td>Reticulocytes &lt;30 ( \times 10^9 )L</td>
</tr>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>Non-severe (NSAA)</td>
</tr>
<tr>
<td>Severe (SAA)</td>
</tr>
<tr>
<td>Very severe (VSAA)</td>
</tr>
<tr>
<td>Median time to treatment (days)</td>
</tr>
</tbody>
</table>

NSAA, Non-severe aplastic anaemia; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.
remaining five patients have either died (n = 2) or
remain transfusion-dependent (n = 3) at a median
follow up of 47 months (range: 9–77 months).

Of the six patients who suffered transformation to
MDS/AML following initial IST, four underwent second-
line therapy, which in all cases was unrelated donor
HPCT. At a median follow up of 89 months (range:
7–123 months), three (75%) of the transplanted patients
remained alive and in CR. The remaining two patients
who did not receive second-line therapy died at a median
of 38 months (range: 8–67 months) post-initial IST.

Survival

At a median follow up of 24 months (range: 6–123 months)
post-IST, survival analyses for the entire cohort demon-
strated EFS 53% (range: 3–103 months; median EFS
62 months) and OS 81% (range: 6–68 months). The
median OS for the entire cohort was not reached (Figs 1,2).

As shown in Figures 3 and 4, respectively, there was
no demonstrable difference in 2-year EFS (42.2% vs
64.7%; P = 0.91) or OS (73.1 vs 88.2%; P = 0.75)
between standard- versus lower-dose ATGAM groups
respectively.

Discussion

Multiple large randomised controlled trials have estab-
lished IST, comprising the combination of equine ATG
(ATGAM) and CsA, as the standard of care in adults
>40 years with newly diagnosed AA.1–6 However, the
evidence for varying the dose and formulation of equine
ATG is limited by a lack of dose-finding studies and the

Table 2 Outcomes post-ATGAM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard dose (n = 14)</th>
<th>Lower dose (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>9 (64%)</td>
<td>12 (71%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (7%)</td>
<td>5 (29%)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>8 (57%)</td>
<td>7 (42%)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>5 (36%)</td>
<td>5 (29%)</td>
<td></td>
</tr>
<tr>
<td>Median time to best response (days)</td>
<td>81 (50–164)</td>
<td>89 (48–2133)</td>
<td>0.43</td>
</tr>
<tr>
<td>Relapse (in responders)</td>
<td>3/39 (33%)</td>
<td>4/12 (33%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Median time to relapse (months)</td>
<td>11 (4–22)</td>
<td>5 (1–6)</td>
<td>0.88</td>
</tr>
<tr>
<td>Transformation to AML/MDS</td>
<td>2 (14%)</td>
<td>4 (24%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Median time to transformation (months)</td>
<td>45 (19–71)</td>
<td>31 (3–81)</td>
<td>0.52</td>
</tr>
<tr>
<td>Infection (any admission to hospital)</td>
<td>6 (43%)</td>
<td>8 (473)</td>
<td>1.0</td>
</tr>
<tr>
<td>Microbiologically proven</td>
<td>0 (0%)</td>
<td>4 (24%)</td>
<td>0.13</td>
</tr>
<tr>
<td>2-year EFS</td>
<td>42.2%</td>
<td>64.7%</td>
<td>0.91</td>
</tr>
<tr>
<td>2-year OS</td>
<td>73.1%</td>
<td>88.2%</td>
<td>0.75</td>
</tr>
</tbody>
</table>

† One patient achieved PR at 60 days post-ATGAM and did not receive any further therapy; CR was eventually achieved at 2133 days post-ATGAM.

AML, acute myeloid leukaemia; ATGAM, anti-thymocyte globulin; CR, complete response; EFS, event-free survival; MDS, myelodysplastic syndrome; OS, overall survival; PR, partial response.

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heterogeneous nature of the drugs themselves. Given the significant adverse effects of IST protocols, such as infection and secondary malignancy,\textsuperscript{2} there is renewed interest in exploring the optimal dosing regimen.

ATG and the now withdrawn anti-lymphocyte globulin (ALG) are inherently heterogeneous compounds; they are polyclonal agents with a broad antigen specificity, created by inoculating different animals with human cells (such as thymocytes or thoracic duct lymphocytes), and their composition differs between manufacturers. To date, there are no published dose-finding studies of ATGAM, particularly in AA, nor are there published prospective studies comparing different equine ATG in AA.

Mathe \textit{et al} published the original studies of IST in AA in the 1970s.\textsuperscript{12} This group evaluated two different ALG formulations at either 40 mg/kg D1–4 (with subsequent HPCT) or 15 mg/kg D1–5, presumably as recommended by the respective manufacturers. Since then, numerous single-agent studies have evaluated different horse ATG or ALG preparations, using schedules that vary from 15 mg/kg D1–10,\textsuperscript{13,14} 15 mg/kg D1–28,\textsuperscript{14} 20 mg/kg D1–8,\textsuperscript{13} and 40 mg/kg D1–4,\textsuperscript{1–4,16} producing similar response rates of 30–70%.

Our study compared 14 patients receiving standard-dose ATGAM at 40 mg/kg/D1–4 (160 mg/kg) to 17 patients receiving lower-dose ATGAM at 15 mg/kg D1–5 (75 mg/kg). We found similar rates of response (64 vs 71%, respectively, $P = 1.0$), relapse (33 vs 33%; $P = 1.0$), transformation to MDS and/or AML (14 vs 24%; $P = 0.66$) and infection (43 vs 47%; $P = 1.0$). Importantly, our outcomes in both dosing schedules appear to correlate with those of the major clinical trials, which demonstrates overall response rates of 60–80% and 5-year overall and EFS rates of approximately 75% and 35–50% respectively.\textsuperscript{1–6}

There is limited evidence regarding the use of ‘lower-dose’ horse ATG in AA. A recent retrospective study suggested inferior response rates when comparing ATGAM at 100 mg/kg compared with 160 mg/kg (PR or better in 51 vs 69%, respectively; $P = 0.023$).\textsuperscript{17} Other literature exists but relates to alternative preparations of horse ATG. One case series used prospective lymphoglobuline at 5 mg/kg/D1–5 in older patients, with response rates less than 10%.\textsuperscript{7} An Indian group retrospectively compared ATGAM 25 mg/kg/D1–4 with a locally made horse ATG (Thymogam), showing 6-month response rates approaching 70%.\textsuperscript{8}

The major limitation of our study is that it contains small numbers and retrospective data, which is not dissimilar to several other published studies in this field. Telomere length, which may predict relapse,\textsuperscript{18} was not routinely measured. A centre effect bias is felt not to be present as all aspects of care, other than ATGAM dosing (including patient selection, CsA/MP dosing and tapering and supportive care), were similar.

\textbf{Conclusion}

In summary, our data suggest that the use of lower-dose ATGAM schedules in the first-line treatment of AA provides non-inferior rates of response, relapse and survival when compared to the standard ATGAM protocol. Given that a significant proportion of newly diagnosed patients will be ineligible for first-line transplantation, further prospective research is warranted to confirm these results.

\textbf{Acknowledgement}

This project received appropriate institutional approval.
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Lower dose ATGAM in aplastic anaemia

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Corrected QT interval anomalies are associated with worse prognosis among patients suffering from sepsis

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Key words
QT interval, corrected QT, sepsis, prognosis, internal medicine, mortality.

Abstract

Background: Patients suffering from sepsis experience organ failure and metabolic derangements, with a negative impact on their prognosis and survival. Objective markers for dismal prognosis in this group of patients are sought.

Aims: To assess the potential role of corrected QT interval anomalies as surrogates for metabolic derangements leading to increased short and medium-term mortality in patients suffering from sepsis.

Methods: This study utilised a historic-cohort analysis of 257 septic patients admitted to internal medicine departments. Personal data, vital signs, laboratory results and electrocardiograms were collected. Patients were grouped according to QTc duration, weather mid-range (395–490 ms) or non-mid-range, and further defined as shorter (<395 ms) or longer (>490 ms).

Results: Mortality rates differed significantly between the mid-range QTc group and the non-mid-range groups at 14 days (23.7 vs 38.2%, respectively; P = 0.014) and at 3 months (38.5 vs 59.6%, respectively; P = 0.001). In a three-group analysis, the 14-day mortality was the highest in the longer QTc group and the lowest in the mid-range group compared with the shorter QTc group (44.4, 23.7 and 35.5%, respectively; P = 0.034), and this difference also remained at 3 months (74.1, 38.5 and 53.2%, respectively; P = 0.001). All differences remained statistically significant in a multivariate Cox regression analysis.

Conclusions: QTc duration anomalies are associated with worse short- and medium-term prognosis and may act as a marker for more severe clinical sequelae.

Introduction

The current toll of death among septic patients in hospitals worldwide is significantly higher than acceptable.1 Therefore, major efforts are made to determine which background data and biomarkers on admission could stratify septic patients according to their risk of short-term mortality.1–3 However, many such biomarkers did not demonstrate superiority over currently used severity scores, applied mainly in the intensive care units (ICU).4 In accordance with the aforementioned facts, there is a growing need for more simple and available tools that allow early rapid recognition of patients who are at a higher risk of mortality in the clinical setting of sepsis.

It was previously shown that electrocardiographic measurement of the corrected QT interval (QTc) is an independent predictor of sudden cardiac death in the general population,5 an independent predictor of mortality in patients suffering from moderate to severe left ventricular (LV) dysfunction6 and a prognosis predictor among patients with acute pulmonary embolism (PE).7 Since QTc duration is affected by a myriad of metabolic factors, which may shift during the course of sepsis and cause either shortening or prolongation of the QTc segment, it is possible that these deranged values may be associated with an increase in short-term mortality.

Methods

Study population

We conducted a retrospective cohort analysis of 257 consecutive patients, for which there was adequate clinical, laboratory and electrocardiographic information within the electronic medical record (EMR), hospitalised in internal medicine departments in a single tertiary hospital from January 2012 to December 2013.
Blood samples were obtained on admission, and the first result was considered. Laboratory measurements were performed in the same central laboratory, and all of the electrocardiograms (ECG) were acquired using the General Electric MAC 5000 device. All patients had been initially diagnosed as suffering from an acute infectious disease with a recognised source, and which were either septic upon admission or developed sepsis during the acute phase of that infection. The EMR data used for data collection is a clinical database, which held the whole relevant clinical and laboratory data. Data mining was done by four of the researchers listed above, while inclusion and exclusion of patients according to the study criteria and adequacy of information were conducted by the whole study group and the principal investigators.

Inclusion criteria were¹ male and female patients over the age of 18 years, admitted to internal medicine departments;² admission diagnosis of an infectious disease of any specified origin, which either presented in sepsis or developed sepsis during the course of acute illness;³ and source of infection recognised upon clinical radiographic or laboratory evaluation. Exclusion criteria were¹ patients’ second or more visits during the recruitment period;² patients admitted with a non-infectious diagnosis who developed an acute infection and/or sepsis later during hospitalisation;⁷ and patients with a presumed infectious disease with no evidence of a source of infection recognised upon clinical radiographic or laboratory evaluation. Exclusion criteria were¹ patients receiving long-term anti-arrhythmic agents known to prolong the QT interval;⁵ patients with no ECG data available in the first 24 h of admission;⁶ patients admitted with a non-infectious diagnosis who developed an acute infection and/or sepsis later during hospitalisation;⁷ and patients with a presumed infectious disease with no evidence of a source of infection.

The QT interval measurement used was the value recorded by the device. All charts were screened manually to rule out technical artefacts that may interfere with the device’s measurements. Our decision to use automated measurement as the basis for our analysis is based on the 2007 AHA/ACC/HRS recommendations⁶ regarding the use of simultaneously aligned superimposed leads in order to measure both the first distinguishable sign of ventricular depolarisation and the last sign of repolarisation, regardless of the lead. QTc calculation was performed using Bazett’s formula when the heart rate was below 100/min, and the Framingham formula for values was above 100/min.⁸

Ethics approval

Prior to data collection, the study was approved by the ethics committee in the Chaim Sheba Medical Center in Tel HaShomer (headed by Prof Dror Haraz) in November 2014, number SMC-14-1698.

Study outcome measures

The primary outcome measure was all-cause mortality within 14 days of admission. Secondary outcomes were length of stay and 3-month survival. In-hospital mortality was determined according to the EMR data, while post-discharge mortality data were obtained from the national Israeli population registry on 1 April 2015.

Statistical analysis

All variables were described according to their properties. Categorical variables are reported in frequencies and percentages, and significance was assessed using the Chi-square test or Fischer’s exact test. Continuous variables were explored using the Shapiro–Wilk test. Variables with a normal distribution were reported as mean and standard deviation values, and significance was assessed using the t-test and ANOVA methods. Continuous variables that did not have a normal distribution were reported as median and interquartile range (IQR, 25–75th percentiles) values, and significance was assessed using nonparametric Mann–Whitney and Kruskal–Wallis tests.

A Classification and Regression Tree analysis was performed, and five distinctive subgroups of patients were initially recognised at the 14-day survival mark, classified by their QTc interval duration on admission. We further combined these groups and eventually composed three groups of patients who had either a QTc duration below 395, 395–490 ms or above 490 ms. Several variables were analysed to distinguish between patients who either died during the first 14 days of admission or survived, using parametric and nonparametric testing according to the variables’ nature in this cohort. We used variables that were significantly different between 14-day survivors/demised in a multivariate Cox regression model. A Kaplan–Meier survival estimation was also calculated. All analyses were performed according to two types of grouping¹: three groups of QTc duration stated above: shorter than 395, 395–490 ms and longer than 490 ms;² and a 2-tier system of mid-range QTc duration (395–490 ms) versus non-mid-range QTc values (either longer than 490 ms or shorter than 395 ms).

The Kaplan–Meier method was used to describe cumulative survival from admission onwards through the follow-up period, both according to two and three QTc subgroups as previously detailed, with between-group comparisons of cumulative event rates calculated by means of the log-rank test.
Multivariate Cox proportional hazards regression analyses were used to evaluate the effect of QTc duration at the end point of 14-day survival through the follow-up period. The Cox model was adjusted for relevant clinical covariates with the use of best-subset regression modelling (including age, gender, heart rate and serum haemoglobin and urea and potassium levels). In order to evaluate the independent effect QTc duration had on the primary end point, we carried out interaction term regression analysis, introducing the QTc grouping product into above-described Cox proportional hazard regression model. All statistical tests were two-sided, and a P value of <0.05 was considered statistically significant. The P values for interaction are reported. Analyses were carried out with the use of spss software, version 23 (IBM Inc., Armonk, NY, USA).

**Results**

We scanned the EMR system of a single tertiary medical centre for patients admitted to internal medicine departments during the years 2012–2013, who had been diagnosed on admission as having sepsis; 972 cases were initially recognised. We further reviewed these cases and excluded patients who either had no available ECG, an uninterpretable ECG or a non-sinus or an otherwise notably irregular rhythm. Patients receiving long-term anti-arrhythmic agents were also excluded from our analysis. Of the 257 patients included in our final analysis, 168 patients (65.4%) had mid-range QTc duration, 62 patients (24.1%) had QTc duration shorter than 395 ms and 27 patients (10.5%) had a QTc duration longer than 490 ms; the distribution of the corrected QT interval in the entire study population is shown in Figure 1. The median QT duration was 426 ms (IQR 396–460 ms).

Patient characteristics, according to QTc classification, are shown in Table 1. Heart rate was significantly higher in the shorter QTc group and lower in the long QTc group compared to the mid-range QTc duration group, 120.0 (±14), 84.8 (±13) and 92.1 (±18) respectively (P < 0.001). Heart rate was also significantly different in a two-group analysis between mid-range and non-mid-range corrected QT duration (P < 0.001). None of the personal medical history variables described was found to be significantly different between these groups.

Fourteen-day mortality rates were the highest in the longer QTc group and the lowest in the mid-range group compared with the shorter QTc group, 44.4, 23.7 and 35.5%, respectively (P = 0.034), and this difference also remained at the 3-month mark, 74.1, 38.5 and 53.2% respectively (P = 0.001) (Fig. 2). In a two-group analysis, 14-day mortality was significantly lower in the mid-range QTc group, 23.7 versus 38.2% (P = 0.014), and this difference remained at the 3-month mark, 38.5 versus 59.6%, (P = 0.001), (Fig. 3). Length of stay did not differ between the groups in both two- and three-group analysis.

Overall 14-day mortality was 28.4% (n = 73). Patient characteristics according to 14-day mortality are described in Table 2. Patients who died within 14 days were older (median age 83 vs 76, P < 0.001), had higher serum urea concentration (median 96.0 vs 57.5 mg/dL, P < 0.001), lower serum albumin concentration (median 2.7 vs 3.1 mg/dL, P = 0.001), higher serum potassium concentration (median 4.5 vs 4.3 mg/dL, P = 0.044), higher serum lactate concentration (median 28 vs 21 mg/dL, P = 0.003) and lower serum haemoglobin concentration (mean 10.66 vs 11.23 G/dL, P = 0.048). No other factors were found to be significantly different at the 14-day mark.

The significant difference in mortality rates between the QTc groups remained significant at both the 14-day and 3-month marks, after using a multivariate Cox proportional hazards regression analysis, adjusting for age, gender and serum haemoglobin, urea, albumin, potassium and lactate (Tables 3,4). At the 14-day mark, patients in the longer QTc group had an adjusted hazard ratio of 3.745 (95% CI 1.795–7.812, P < 0.001), and those with a QTc shorter than 395 ms had an adjusted hazard ratio of 2.405 (95% CI 1.105–5.235, P = 0.027) when compared to the mid-range group. At the 3-month mark, mortality risk in the longer QTc group remained significantly higher, with a hazard ratio of 3.911 (95% CI 2.177–7.026, P < 0.001), yet there was only a trend towards significance seen in the shorter QTc duration group, with a hazard ratio of 1.815 (95% CI 0.959–3.435, P = 0.067). In a binary system analysis, the non-mid-range group had a significantly higher risk of
mortality at the 14-day mark, with a hazard ratio of 2.990 (95% CI 1.616–5.535, P < 0.001), as well as at the 3-month mark, with a hazard ratio of 2.616 (95% CI 1.602–4.274, P < 0.001). In all models, age and serum urea and lactate also remained significant contributors to the models after adjustment.

**Discussion**

QTc duration is influenced by several metabolic and metabolism-dependent conduction derangements.\(^9\)–\(^11\) Many such derangements, like hyperglycaemia,\(^12\) hypokalaemia and liver function anomalies,\(^13\) impact the length of the QTc interval, reflecting their complex effects on the period of electrical repolarisation of the cardiac conduction system. Our analysis has shown that among patients suffering from sepsis, QTc duration correlates independently with short-term mortality, suggesting that QTc duration may serve as an electrocardiographic marker of poor prognosis in these patients. In our cohort, both shorter and longer QTc durations, measured in septic patients, were independently associated with poor prognosis, most probably in correlation with various metabolic derangements seen in these patients.

We have also demonstrated that deranged QTc duration correlates with an increase in medium-term mortality. This may further point QTc duration out as a marker for an acute illness, potentially leading to future debilitation and morbidity.
It is established that QTc prolongation is associated with both systolic\textsuperscript{14,15} and diastolic\textsuperscript{16,17} LV dysfunction. This appears to have special significance in septic patients, who may suffer from myocardial dysfunction even with preserved total cardiac output and arterial blood pressure\textsuperscript{18–20} and, as such, are at increased risk of mortality.\textsuperscript{21} Our findings suggest that QTc monitoring may help clinicians define patients at high cardiac risk, even in the absence of overt pump failure.

Short QTc duration is usually discussed in the context of inherited channelopathies and has an ill-defined cut-off value ranging from 320 to 390 ms.\textsuperscript{8,22–24} Short QTc duration has not been shown to have a significant prognostic effect in low-risk patients, even under the more strict definition of the Seattle criteria\textsuperscript{25} or in a large paediatric, adolescent or young adult cohort.\textsuperscript{26} It is, however, associated with impaired myocardial contraction,\textsuperscript{27} which prompts the question whether similar effects are induced by the metabolic derangements seen in severe sepsis.

The cut-off values we suggest in order to define the different QTc duration groups differ from previous values offered by the American Heart Association,\textsuperscript{8} the European Society of Cardiology\textsuperscript{23} and the Heart Rhythm Society.\textsuperscript{22} These historic and long-debated cut-off values are classically associated with the risk of ventricular tachyarrhythmia, specifically of polymorphic ventricular tachycardia, which is not commonly observed as part of the sequelae of sepsis. This allows room for discussion of other cut-off values for stratification of different outcome risks. It should be noted that our cut-off values, which as noted are higher than traditional values, may also reflect the method of data acquisition, that is, the use of multi-lead simultaneous device measurements visually confirmed over mono- or bi-lead manual measurement.

**Conclusions**

We herein suggest that the QTc duration is somewhat of a ‘metabolic vector’ in which the value derangement, in either direction, may act as a risk marker in the septic patient. This may add a useful, simple and accessible tool to be used in risk stratification and clinical decision-making upon early assessment and admission of septic patients.
Table 2  Patient admission data according to 14-day survival

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 257)</th>
<th>14-day survivors (n = 184)</th>
<th>14-day mortality (n = 73)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td></td>
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<tr>
<td>IHD</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
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<tr>
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<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
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<tr>
<td>Atrial fibrillation/flutter</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td></td>
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<tr>
<td>Heart failure</td>
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<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td></td>
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<tr>
<td>Cerebral VD</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Peripheral VD</td>
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<td>CKD</td>
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<tr>
<td>Anaemia</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Corrected QT interval (ms)</td>
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<tr>
<td>&lt;395</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td></td>
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<tr>
<td>490&lt;</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td>257 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
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</tr>
<tr>
<td>Heart rate</td>
<td></td>
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<td></td>
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<tr>
<td>Serum haemoglobin (G/dL)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Serum urea (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Serum albumin (mg/dL)</td>
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<td></td>
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<tr>
<td>Serum potassium (meq/L)</td>
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<td></td>
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<tr>
<td>Corrected serum calcium (mg/dL)</td>
<td></td>
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<tr>
<td>Serum TSH (mIU/L)</td>
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<tr>
<td>Serum pH</td>
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<td></td>
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<tr>
<td>Serum lactate (mg/dL)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; IQR, interquartile range; SD, standard deviation; VD, vascular disease.

Table 3  Multivariate Cox regression model, three groups of corrected QT interval duration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>14-day mortality (n = 257)</th>
<th>3-month mortality (n = 257)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P</td>
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<tr>
<td>Corrected QT interval (ms)</td>
<td>2.405 (1.105–5.235)</td>
<td>0.027</td>
</tr>
<tr>
<td>&lt;395</td>
<td>3.745 (1.795–7.812)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.032 (1.001–1.063)</td>
<td>0.044</td>
</tr>
<tr>
<td>Female</td>
<td>1.117 (0.624–1.999)</td>
<td>0.710</td>
</tr>
<tr>
<td>Serum haemoglobin (G/dL)</td>
<td>0.966 (0.823–1.133)</td>
<td>0.667</td>
</tr>
<tr>
<td>Serum urea (mg/dL)</td>
<td>1.005 (1.001–1.008)</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum albumin (G/dL)</td>
<td>0.714 (0.457–1.116)</td>
<td>0.140</td>
</tr>
<tr>
<td>Serum potassium (meq/L)</td>
<td>0.977 (0.692–1.379)</td>
<td>0.894</td>
</tr>
<tr>
<td>Serum lactate (mg/dL)</td>
<td>1.022 (1.004–1.040)</td>
<td>0.015</td>
</tr>
</tbody>
</table>
References

14 Davey P. QT interval lengthening in cardiac disease relates more to left


Fulminant type 1 diabetes in pregnancy
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Key words fulminant type 1 diabetes, pregnancy, DKA.

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Abstract
We report two cases of fulminant type 1 diabetes in previously well migrants from South East Asia. This entity, which is rare outside East or South-East Asia, has a high perinatal mortality. The clinical presentation differs markedly from that of typical newly recognised type 1 diabetes in pregnancy. In both our cases, the neonates required intensive care but survived.

Fulminant-onset type 1 diabetes was described first in Japan in 1987,1 but has since been reported from other parts of East or South-East Asia.2,3 It typically presents with a short prodrome of a few days (fever, influenza-like and gastrointestinal symptoms) and the extremely rapid onset of hyperglycaemia and diabetic ketoacidosis (DKA), with complete loss of β-cell function and severe insulin deficiency. Titres of islet cell-associated autoantibodies are negative or low and a transient elevation of pancreatic enzymes is often observed.4 The pathophysiology is poorly understood but both environmental (viral) and genetic susceptibility have been suggested. The Class II human leukocyte antigen (HLA)-risk haplotypes differ from those usually associated with immune-mediated type 1 diabetes.4

A characteristic of fulminant type 1 diabetes is its predilection for pregnancy with the onset of diabetes typically in the third trimester or immediately after delivery. In a nationwide study from Japan, 21% of cases occurred in pregnant women – at a rate 14 times greater than that of typical type 1 diabetes.5 We report two cases of fulminant type 1 diabetes presenting in late pregnancy in migrants to New Zealand from South-East Asia. In both, screening for gestational diabetes had been normal a few weeks before presentation. Maternal and neonatal clinical data are presented in Table 1.

Case 1: A 36-year-old woman from Laos, with an otherwise unremarkable pregnancy, presented acutely at 36 weeks’ gestation following spontaneous rupture of membranes and a rapid vaginal delivery at home. Screening for gestational diabetes at 28 weeks’ with a 50 g glucose challenge test had been normal (1 h glucose 7.3 mmol/L). On arrival, the infant was severely hyperglycaemic, hypoxic with a respiratory acidosis and required ventilation. His blood glucose returned to normal, without insulin treatment, after 6 h. He spent a total of 4 days in neonatal intensive care.

His mother did not appear unwell on admission to the postnatal ward that evening, but during the following morning she was noted by staff to be drowsy, with ‘sighing’ respiration. She gave a history of thirst for a day and shortness of breath for a few hours. On examination she was dehydrated and had respiratory rate of 20/min with ketotic breath. Her plasma glucose was 43.4 mmol/L, and she had a metabolic acidosis with strongly positive serum acetoacetate. DKA was diagnosed and fluids and insulin were initiated. She improved over several hours without complications. At the time of diagnosis, her HbA1c was 48 mmol/mol and autoimmune diabetes-associated antibodies were negative. She has continued to be insulin dependent.

Case 2: A 42-year-old Filipina woman presented acutely at 37 weeks’ gestation with thirst, lower abdominal pain and decreased foetal movements. She had a normal 75 g oral glucose tolerance test at 32 weeks’ gestation (fasting glucose 4.1, 2 h glucose 7.4 mmol/L). Foetal cardiotocography was abnormal at presentation, and an emergency Caesarean section was undertaken. The neonate had low Apgar scores, severe

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hyperglycaemia and metabolic acidosis. His blood sugar glucose returned to normal, without insulin treatment, after 4 h. The infant stayed 3 weeks in neonatal intensive care.

His mother was not noted to be unwell at presentation, but developed increasing thirst and became drowsy the following day. Her plasma glucose was very high (33 mmol/L) and she had a metabolic acidosis with an elevated \( \beta \)-hydroxybutarate. DKA was diagnosed and treated with intravenous insulin and fluids. Additional tests showed undetectable serum C-peptide and a mildly increased serum lipase, which remained elevated 2 months later. Her HbA1c was 44 mmol/mol at diagnosis (compared with 33 mmol/mol at 26 weeks' gestation) and she had a low titre of anti-glutamic acid decarboxylase antibodies. Lipids were not measured and an ultrasound of the abdomen was not performed. She has continued to be insulin dependent.

**Discussion**

The development or recognition of new-onset autoimmune type 1 diabetes in pregnancy is not uncommon and may exceed the rate outside pregnancy, but it rarely presents as DKA. Of all women newly identified in pregnancy as having diabetes in our practice, about 3% have type 1 diabetes. Table 2 details the 18 women with type 1 diabetes diagnosed during pregnancy, at our clinic, between 1985 and 2014. Of the 16 women with typical autoimmune type 1 diabetes, most were diagnosed in the second or early third trimester following abnormal screening tests for gestational diabetes (median gestational age at diagnosis, 26 weeks), but some were diagnosed earlier because glycosuria had been noted. None of the 16 presented with DKA, and indeed only two had symptoms of hyperglycaemia. Tests for autoimmune diabetes-associated antibodies were positive in most cases.

During pregnancy DKA tends to occur at lower glucose values and may progress more rapidly than in the non-gravid state. There has been a handful of case reports of DKA with normal or mild elevation in glucose values (normo- or euglycaemic ketoacidosis). The mechanism remains uncertain, but these cases occurred in the context of starvation associated with vomiting or intercurrent illness rather than in pure insulin deficiency.

Both the patients we described had clear evidence of DKA and fulfilled the diagnostic criteria for fulminant type 1 diabetes proposed by Hanfusa and Imagawa: the occurrence of DKA <7 days after the onset of hyperglycaemic symptoms; elevation of urinary and/or serum

### Table 1 Maternal and neonatal data

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Origin</strong></td>
<td>Laos</td>
<td>Philippines</td>
<td>—</td>
</tr>
<tr>
<td><strong>Age at migration to Aotearoa (years)</strong></td>
<td>19</td>
<td>38</td>
<td>—</td>
</tr>
<tr>
<td><strong>Age at presentation (years)</strong></td>
<td>36</td>
<td>42</td>
<td>—</td>
</tr>
<tr>
<td><strong>Parity (n)</strong></td>
<td>4</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td><strong>Gestational age at negative screening for diabetes (weeks)</strong></td>
<td>28</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td><strong>Gestational age at presentation (weeks)</strong></td>
<td>36</td>
<td>37</td>
<td>—</td>
</tr>
<tr>
<td><strong>Maternal findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>49</td>
<td>44</td>
<td>≤60</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>44</td>
<td>33</td>
<td>&lt;7</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>6.99</td>
<td>7.00</td>
<td>7.35–7.45</td>
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<tr>
<td>Lipase (U/L)</td>
<td>89</td>
<td>16–67</td>
<td>370–1470</td>
</tr>
<tr>
<td>C-peptide (pmol/L)</td>
<td>&lt;30</td>
<td>16–67</td>
<td></td>
</tr>
<tr>
<td>Islet cell autoimmunity – GAD/IA-2 antibodies (U/mL)</td>
<td>Negative/negative</td>
<td>27/negative</td>
<td>≤10 U/mL</td>
</tr>
<tr>
<td>HLA haplotypes</td>
<td>DRB1<em>04:05-DQB1</em>04:01†</td>
<td>DRB1<em>14-DQB1</em>05 and DRB1<em>15-DQB1</em>05</td>
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<tr>
<td><strong>Neonatal findings</strong></td>
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<td></td>
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<tr>
<td>Birth weight (kg)/gender</td>
<td>2.28/male</td>
<td>3.21/male</td>
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<tr>
<td>Birth weight (percentile)</td>
<td>3rd, 31%</td>
<td>3rd, 31%</td>
<td>10th–90th</td>
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<tr>
<td>Apgar scores (1, 5 min)</td>
<td>≤3, ≤3</td>
<td>2, 2</td>
<td>&gt;7</td>
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<tr>
<td>Plasma glucose (mmol/L)</td>
<td>30</td>
<td>23.4</td>
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<tr>
<td>Arterial pH</td>
<td>7.27</td>
<td>6.94</td>
<td>7.35–7.45</td>
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<tr>
<td>Intensive care admission (days)</td>
<td>4</td>
<td>21</td>
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</table>

†HLA DRB1*04:05-DQB1*04:01 and DRB1*09:01-DQB1*03:03 haplotypes have been detected more frequently in patients with fulminant type 1 diabetes.‡ Infant was delivered at home – Apgar score estimated from description by ambulance staff. GAD, glutamic acid decarboxylase; IA-2, islet antigen 2.
ketone bodies; plasma glucose level ≥16.0 mmol/L, and glycated haemoglobin level <69 mmol/mol at first visit, with very low serum or urinary C-peptide.

It is not known why fulminant type 1 diabetes is associated with pregnancy. As in our two cases, it typically occurs in the third trimester or immediately postpartum, with no prior evidence of gestational diabetes. Given the rapid destruction of β-cells resulting in severe hyperglycaemia and metabolic acidosis (which in turn may precipitate premature labour), the prognosis for the neonate is often poor with the reported perinatal mortality ranging from 9 to 35%. In both our cases, the neonates were initially critically unwell and required intensive care support. The neonatal hyperglycaemia was thought to be secondary to maternal hyperglycaemia. It seems likely that the acute nature and severity of hyperglycaemia overwhelmed the foetal pancreas, which was unable to mount an adequate insulin response. This is supported by the fact that postpartum the hyperglycaemia settled after a short period of time (4–6 h), without requirement for insulin. To date, neither of the offspring has developed diabetes.

The pathogenesis of fulminant type 1 diabetes is uncertain. The titres of antibodies directed towards β-cells are typically low or absent. There is marked destruction of both β- and α-cells in the pancreas. Insulitis (infiltration of lymphocytes in or around the pancreatic islet, which is a feature of autoimmune type 1 diabetes) is not a common feature on biopsy but has been reported in post-mortem cases. The marked elevation of pancreatic enzymes (lipase and amylase) reported in cases is consistent with T-cell infiltration of the exocrine pancreas seen on biopsy, which may not only represent autoimmunity but also an immune response. It should be noted that elevation in pancreatic enzymes may also be seen in DKA, and may be non-specific or the result of pancreatic inflammation. Pre-existing hypertriglyceridaemia and gallstones are risk factors for acute pancreatitis in pregnancy; hence, careful clinical workup with relevant biochemistry and imaging may be needed to exclude this diagnosis. However, in fulminant type 1 diabetes, the pancreatic oedema, necrosis or bleeding that characterise acute pancreatitis, is not a feature. These findings along with the characteristic fever and flu-like symptoms have led to speculation about an underlying viral aetiology. Those implicated include enteroviruses (coxsackie and echo viruses) and herpes virus. A case of fulminant type 1 diabetes has been reported following reactivation of herpes (HHV-6) infection in the context of a drug hypersensitivity reaction and high IgA titres to enterovirus infections have been found in a small cohort of patients, suggesting susceptibility to recurrent infections as a possible pathogenic trigger.

As with autoimmune type 1 diabetes, in which certain HLA haplotypes may confer susceptibility to the disease, small studies have identified particular Class II HLA-DRB1 and DQB1 haplotypes in patients with fulminant type 1 diabetes. Of note, the first patient most likely had the previously reported susceptibility haplotype DR4-DQ4 (most likely encoded by DRB1*04:05-DQB1*04:01). DQB1 DNA sequencing was not available at the time of writing. It has been suggested that the higher population frequency of the HLA-DR4-DQ4 haplotype in the Japanese (and other East Asian populations) might explain the higher incidence of fulminant-onset type 1 diabetes in these countries. The condition may therefore result from a combination of genetic susceptibility and environmental exposure to certain viruses. The role of autoimmunity remains uncertain.

In conclusion, fulminant diabetes should be considered in patients presenting acutely with rapid-onset hyperglycaemia and DKA, particularly in pregnant women of East or South-East Asian origin. This condition is associated

<table>
<thead>
<tr>
<th>Gestation at diagnosis (weeks)</th>
<th>HbA1c at diagnosis (mmol/mol)</th>
<th>Autoimmune diabetes-associated antibodies</th>
<th>Ethnicity</th>
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<tr>
<td>37</td>
<td>49</td>
<td>GAD &lt;10/IA-2 &lt;15</td>
<td>Lao</td>
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<td>—</td>
<td>European</td>
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<td>31</td>
<td>41</td>
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<td>30</td>
<td>130</td>
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<td>28</td>
<td>57</td>
<td>GAD &gt;250/IA-2 &lt;15</td>
<td>European</td>
</tr>
<tr>
<td>27</td>
<td>—</td>
<td>—</td>
<td>European</td>
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<tr>
<td>27</td>
<td>60</td>
<td>GAD ‘positive’‡</td>
<td>European</td>
</tr>
<tr>
<td>27</td>
<td>39</td>
<td>GAD ‘strongly positive’‡</td>
<td>European</td>
</tr>
<tr>
<td>26</td>
<td>—</td>
<td>Islet cell antibodies ‘positive’</td>
<td>Māori</td>
</tr>
<tr>
<td>26</td>
<td>46</td>
<td>GAD 108/IA-2 &lt;15</td>
<td>European</td>
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<tr>
<td>26</td>
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<td>GAD 490/IA-2 &lt;15</td>
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<td>European</td>
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<tr>
<td>24</td>
<td>36</td>
<td>GAD 88/IA-2 260</td>
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<td>22</td>
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<td>GAD &gt;250/IA-2 &lt;15</td>
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<tr>
<td>22</td>
<td>56</td>
<td>GAD 44—</td>
<td>North</td>
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<tr>
<td>14</td>
<td>40</td>
<td>GAD 57/IA-2 &lt;10</td>
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</tr>
<tr>
<td>13</td>
<td>101</td>
<td>GAD 22A/2-11</td>
<td>European</td>
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</tbody>
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The two fulminant-onset cases are presented first. Note the late gestation and low or absent titres of autoimmune diabetes-associated antibodies. Results are missing in four cases seen before HbA1c, and antibody testing became routinely available. Titres not available. GAD, glutamic acid decarboxylase (normal value: GAD <10 U/mL); IA-2, islet antigen 2 (normal value: IA2 <15 U/mL).
with a high risk of neonatal mortality. To our knowledge, these are the first cases reported in pregnancy in Australia, but with increasing migration from East and South-East Asia, clinicians should be aware of this dramatic presentation and its potentially serious outcomes.

Acknowledgement

We thank Dr Heather Dunckley (Clinical Scientist, New Zealand Blood Service) for assistance with HLA interpretation.

References

Selecting haematological malignancy patients for intravenous immunoglobulin

L. Paxton, C. Hawkins and P. Crispin

Abstract

Prior randomised studies of immunoglobulin replacement therapy have studied mixed populations with or without a history of infections. Immunoglobulin therapy is expensive and in limited supply suggesting that optimising patient selection is of value. In this retrospective study, infection history identified high-risk groups benefiting from treatment. A group of patients without any infection history had a low risk of infection without immunoglobulin.

Intravenous immunoglobulin (IVIg) reduces the risk of infections in patients with hypogammaglobulinaemia secondary to haematological malignancies. The randomised studies demonstrating benefit of IVIg have included patients with hypogammaglobulinaemia with and without a history of infection. It is however in limited supply, with Australia unable to produce enough domestic IVIg despite a policy of blood product self-sufficiency. It is also expensive to manufacture. Criteria for the supply of IVIg in Australia limit its provision in patients with haematological malignancies to those with a low IgG and a history of severe or recurrent bacterial infections or IgG levels <4 g/L. It is uncertain whether selecting patients to receive or not receive IVIg on the basis of prior infections rather than IgG levels alone is a safe strategy.

We conducted a retrospective study of hypogammaglobulinaemic haematological malignancy patients to determine the safety of withholding IVIg in the absence of a history of recurrent or severe infections and the efficacy in patients selected to receive it under the same criteria. The rate of serious infections, defined as those requiring hospital admission was determined before and during IVIg therapy and also in patients never receiving IVIg.

All haematological malignancy patients receiving at least two doses of immunoglobulin within the Australian Capital Territory (ACT) with follow-up records available at Canberra Hospital to prevent infections between 2009 and 2013 were included. The rate of hospitalisation for infection was compared in 24 months before and after the initiation of IVIg, and with a group of untreated hypogammaglobulinaemic haematology patients during the same period. The untreated group had at least one total IgG level below the lower limit of normal, haematological malignancy and never received IVIg. Up to two untreated patients were selected for each treated patient, stratified by IgG level more or less than 4 g/L, diagnosis, age and sex. Patients were excluded if they received IVIg for indications other than infection prophylaxis. Characteristics of the groups were compared using Fisher’s exact test for categorical variables or Student’s t-tests and event rates expressed as rate ratios with estimated variance to determine 95% confidence limits. Ethics approval was received from the ACT Health Human Research Ethics Committee, and the study conducted in accordance with the Declaration of Helsinki.

During the study period, there were 251 hypogammaglobulinaemic haematology patients. Of these, 67 had IVIg issued and 35 met all inclusion criteria. They were treated for 1194 person-months and 776 person-months of observations available prior to starting treatment. There were 57 untreated low IgG patients identified, with the total observational period being 2587 months. Antibiotic prophylaxis routine practice for hypogammaglobulinaemia, but co-trimoxazole and

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Conflict of interest: P. Crispin serves on intravenous immunoglobulin consultation committees of the National Blood Authority and has consulted for CSL Australia.

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flucconazole are given with chemotherapy involving high-dose steroids, purine analogues or transplantation. Penicillin prophylaxis was used in the one patient following allogeneic transplant.

The untreated group had fewer cases with severe hypogammaglobulinaemia (51 vs 77%, $P < 0.01$), but were otherwise similarly matched for diagnosis, age and sex (Table 1). The treated group showed a rate of hospitalisation for infection of 0.43 (0.29–0.63) per person-year prior to treatment, reducing to 0.14 (0.08–0.23) during immunoglobulin replacement, giving a relative risk 3.1 (1.6–5.9) for infection prior to treatment. The risk of hospitalisation due to infection in patients prior to treatment was significantly greater than the rate of 0.08 (0.05–0.13) per person-year in those never treated, with a relative risk of 5.5 (3.0–10) for those who subsequently went on to immunoglobulin therapy. The risk of infection in IVIg patients prior to starting treatment was 0.51 (0.27–0.90) per person-year in patients with an IgG of <4 g/L and 0.40 (0.25–0.59) per person-year in patients with an IgG of >4 g/L ($P > 0.05$). In patients who were never treated with immunoglobulin, the risk of infection was 0.07 (0.03–0.13) for IgG <4 g/L, significantly lower than patients prior to IVIg ($P < 0.001$), but not different to untreated patients with IgG >4 g/L where the rate was 0.08 (0.04–0.15, $P > 0.05$).

This study demonstrates a population of hypogammaglobulinaemic patients who did not develop infections. The evidence to date suggests that hypogammaglobulinaemia alone is an indication for prophylaxis, rather than requiring demonstrated infection. However, hypogammaglobulinaemia is not always associated with recurrent infections and this study shows a population of hypogammaglobulinaemic patients who had a low risk of infection despite not having prophylaxis. These data support an approach to withholding IVIg unless there is an infection history. We also showed an improvement in the number of hospitalisations due to infection after commencing immunoglobulin therapy. As it is retrospective, the study design precludes definitive conclusions on efficacy, although the findings are consistent with prior randomised trials.

Severe hypogammaglobulinaemia was defined in this study as an IgG of <4 g/L and did not appear to be a major risk factor for infection. IgG levels <4 g/L did not predict infection rates compared with IgG levels >4 g/L in either the untreated group or the treated group prior to the commencement of IVIg. The higher infection rate even in the IVIg-treated group suggests that there are likely alternate risk factors for infection within this group.

Randomised studies of IVIg prophylaxis in myeloma, chronic lymphocytic leukaemia and non-Hodgkin lymphoma have included patients with and without a history of serious or recurrent infections with varying inclusion criteria. In the majority of studies, a history of infection was a potential reason for inclusion, but was not required. When the number of infections prior to randomisation was stated, a majority of patients did not have a significant history of recent infection. Two studies did not indicate the infection history in participants. Only the study by Boughton et al. required all participants to have a history of infection.$^4$

The broad inclusion criteria in prior randomised studies raise concerns about withholding immunoglobulin therapy in hypogammaglobulinaemic patients without a recent infection history. While none of the randomised found infection history to be a predictor of benefit from IVIg, this was specifically examined in only one study. The Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukaemia randomised 81 patients with either an IgG level less than half of the lower limit of normal and/or a history of serious

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
<th>IVIg patients</th>
<th>Untreated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median months observed without IVIG (range)</td>
<td>24 (1–24)</td>
<td>39 (4–133)</td>
</tr>
<tr>
<td>Median months observed with IVIG (range)</td>
<td>26 (3–79)</td>
<td>NA</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic lymphocytic leukaemia</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>B-non-Hodgkin lymphoma</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Other haematological malignancies</td>
<td>3 (AML, post allogeic transplant, amyloidosis and T-NHL)</td>
<td>2 (T-NHL)</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>57</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>68.2 (12)</td>
<td>66.7 (11)</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>IgG level mean (SD)</td>
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<td></td>
</tr>
<tr>
<td>IgG &lt; 4.0 g/L</td>
<td>2.8 g/L (1.6)</td>
<td>4.0 g/L (1.6)</td>
</tr>
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<td>IgG ≥ 4.0 g/L</td>
<td>27</td>
<td>29</td>
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<tr>
<td>P = 0.02</td>
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<td></td>
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<tr>
<td>P = 0.01</td>
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</table>

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infections to immunoglobulin replacement or placebo.\textsuperscript{3} Only 29 patients in the study had a history of severe (requiring intravenous antibiotics or hospital admission within two years) infections, with a further 41 having ‘occasional’ (<3 in the last 24 months) infections. Linear regression to identify risk factors for infection did not identify prior infection history as a risk. The study by Chapel and colleagues in myeloma patients found that patients with thrombocytopenia or anaemia were less likely to benefit from immunoglobulin replacement, presumably due to failure to correct the concurrent infection risk associated with marrow failure.\textsuperscript{2} Conversely, patients who demonstrated a good response to pneumococcal vaccination prior to therapy were also unlikely to show a benefit, presumably as the humoral immune response was better preserved. Pneumococcal antibody responses were not examined in this study.

As a retrospective study, there was no standard definition of infection used to initiate IVIg in our cohorts. There may have been selection bias accounting for the differences. The retrospective design is also subject to missing admission events, although a significant number of admissions at other institutions was included. Assessing the endpoint to hospitalisations aimed to detect the effect on severe infections, although not all severe infections may have required admission. The number of untreated patients with severe hypogammaglobulinaemia was low. Further studies examining the rates of infections in similar cohorts are warranted, in particular examining potential concurrent risk factors on the rate of infection and efficacy of IVIg.

Although there is a reduced risk of serious infections with IVIg prophylaxis, the benefit needs to be considered in light of the costs of therapy. These include patient time and discomfort, potential side effects of IVIg, the institutional costs of infusions as well as costs of the product itself. Although now dated, a cost effectiveness analysis of IVIg prophylaxis in chronic lymphocytic leukaemia based on randomised trial data found it to be of marginal benefit\textsuperscript{7} and when the inconvenience of administration is taken into account, there was no benefit on quality of life. Even excluding patient inconvenience, the costs were well beyond accepted funding standards.

IVIg is manufactured from donor derived human plasma. Adverse effects on patients’ quality of life, limitations on supply, high cost and an ethical obligation to maximise the value of the donated gift of blood require that IVIg is given to patients most likely to benefit from its use. This study demonstrates that selection of patients for immunoglobulin therapy with secondary hypogammaglobulinaemia with a significant history of infection identifies a group most likely to benefit. Conversely, a population of patients with hypogammaglobulinaemia, which may even be severe, with a low risk of infection can safely have IVIg withheld. Further research to identify concurrent risk factors for infection and their impact on the efficacy of IVIg may enable better targeting of IVIg therapy.

References
A 73-year-old man presented with a 6-month history of exertional headaches. Exercise tolerance test demonstrated progressive ischaemic changes concomitant with worsening headache. Cardiac cephalgia was diagnosed and his symptoms resolved after coronary artery bypass surgery. Cardiac cephalgia may occasionally present as exertional headache without chest symptoms.

A 73-year-old Caucasian man was admitted acutely to our department following referral by his general practitioner with a 6-month history of exertional headaches. The headaches were generalised, dull in nature and incapacitating. They were predictably triggered by moderate exertion (e.g. mowing the lawn) and on exposure to cold air. The headaches usually resolved quickly in response to rest, within 5 min. They were not precipitated by cough or straining and were not migrainous in nature. Six weeks prior to admission the headaches became more frequent and occurred in response to lower levels of activity (e.g. walking around the house). Over the same period, he developed chest pain on exertion, but it was the headaches that limited his activity. He had a history of diabetes mellitus type II for 10 years (recent glycosylated haemoglobin 53 mmol/mol) without peripheral neuropathy or retinopathy and only mild renal impairment (eGFR 50 mL/min/1.73 m²). Six years previously he had a traumatic subdural haemorrhage requiring evacuation, and 2 years later he suffered a right posterior circulatory stroke (confirmed by magnetic resonance). Neither episode was complicated by chronic headaches or residual neurological deficit. Doppler ultrasound demonstrated 50% bilateral internal carotid arteries stenosis. He was treated with aspirin, enalapril and simvastatin.

On examination, he was afebrile and anxious but otherwise well. Computerised tomography of the head was normal. His resting electrocardiogram (ECG) was also normal. The short duration and predictability of his headaches was impressive, so in view of his age and risk factors, he was investigated for coronary artery disease (CAD). The standard Bruce protocol exercise test was terminated at 5 min by his typical exertional headache. As the headache worsened, he developed progressive horizontal ST depression in the inferior-lateral leads of the ECG. When he stopped walking, his ECG showed 3 mm horizontal inferior-lateral ST depression that resolved quickly with his headache during recovery (Fig. 1). Coronary angiography demonstrated proximal three-vessel disease, and left ventricular systolic function was normal (Fig. 2). The diagnosis of cardiac cephalgia was made and he subsequently suffered an acute ST elevation myocardial infarction, which was associated with headache. He underwent coronary artery bypass graft surgery (6 months ago) and has been free of headaches since.

Discussion

CAD is a very common condition and remains one of the leading causes of mortality in the Western population. Angina pectoris is the usual presentation. This case reminds us that cardiac cephalgia, by definition caused by underlying CAD, may occasionally present as exertional headache without any chest symptoms. He meets the diagnostic criteria for cardiac cephalgia, defined by the International Headache Society as severe headache associated with acute myocardial infarction or exertion-related ischaemia, which resolves after medical or surgical
treatment of CAD. Review of the literature suggests that cardiac cephalgia is rare and that patients usually complain of associated angina symptoms at presentation.\(^3,4\) When chest symptoms are absent, the diagnosis may be delayed as demonstrated in our patient.

The term ‘cardiac cephalgia’ was coined by Lipton et al. in 1997.\(^5\) They described two male patients who presented with exertional headache as their only symptom. In both patients, the headache was reproduced during exercise ECG testing and associated with acute transient ST changes. Coronary angiograms demonstrated three-vessel CAD and symptoms resolved following appropriate coronary procedures.

Recently, Wei et al. and Bini et al. have separately reviewed all the reported cases (\(n = 32\)) of cardiac cephalgia (which date back to 1978) and in doing so have summarised most of our knowledge of this condition.\(^3,4\) The majority of the patients were men (63%) and the mean age was 63 ± 12 years. The 5 year mortality was up to 13%, which is much higher than the figure quoted for patients presenting with classical angina pectoris (5%).\(^3\) This may be because most cases of the cardiac cephalgia had multi-vessel CAD and took longer to diagnose. The incidence of cardiac cephalgia cannot be calculated from this data but is likely to be very low. Fortunately, a lot of these patients have angina pectoris as well as cephalgia and so are investigated appropriately, but what about patients who present without chest pain? After carefully reviewing all of the 32 original reports, we found 6 other patients (20%) who initially presented without chest symptoms some months before diagnosis.\(^5–10\) A larger group without chest (30%) pain presented more acutely during or preceding an acute myocardial infarction.\(^3,11–13\) The remaining 50% presented with headache and classical angina symptoms. Therefore the scenario we are reporting is extremely unusual and may well be under-diagnosed.\(^3,4\) This is consistent with data from unselected patients presenting for investigation of CAD in whom headache was reported in only 6% and no patient had headache as the only symptom.\(^14\)

The underlying mechanism for cardiac cephalgia is unknown. The most likely explanation is that it is referred pain from the myocardium carried by autonomic afferent nerve fibres to the brainstem converging on other sympathetic afferents or somatic sensory fibres supplying the head.\(^15\) Other possibilities, including sudden release of vasodilators from ischaemic myocardium and cerebral venous congestion secondary to acute heart failure are less likely and have not been demonstrated. Cerebral vasospasm has been demonstrated following...
exertional headache but not during myocardial ischaemia. Cardiac cephalgia may be difficult to diagnose, especially when it is unaccompanied by chest pain. The nature, distribution and duration of the pain, is a variable between patients and may mimic benign headaches related to exertion, tension, migraine and even orgasm. Clues to the diagnosis include age of the patient, recent onset of headache, cardiac risk factors and close relationship between headache and exercise or stress. Its mechanism is uncertain but probably involves false localisation of angina to the head mediated by the converging of autonomic and somatic sensory afferents in the brainstem. Early diagnosis is important because this condition appears to have a preference for men with three-vessel CAD who carry a high mortality risk.

Acknowledgements

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References

12 Martinez HR, Rangel-Guerra RA, Cantu-Martinez L, Garza-Gomez J.
Pregnancy screening prior to chemotherapy administration


Flinders Centre for Innovation in Cancer, Flinders Medical Centre/Flinders University, Adelaide, South Australia, Australia

Key words
pregnancy, chemotherapy, HCG.

Abstract
A retrospective case notes review was performed to determine compliance with screening for undetected pregnancy prior to commencement of chemotherapy at Flinders Medical Centre. All female patients aged 18–55 who commenced chemotherapy between January and December 2014 were included. During the first 12 months, for women identified as having childbearing potential, pre-chemotherapy pregnancy screening was performed only in 40% of patients under 40 years and in 20.5% of the entire age range.

Cancer occurring during pregnancy is uncommon. As almost half of all pregnancies are unplanned, it is possible that women may not be aware that they are pregnant at the time of diagnosis of cancer. Management of cancers during pregnancy is challenging and poses risks to both mother and foetus. Both chemotherapy and radiotherapy can potentially cause teratogenicity and miscarriages when administered to women during pregnancy due to foetal exposure. The risk associated with cytotoxic chemotherapy is higher in the first trimester; this is especially important as the patient may not yet be aware of being pregnant. Several anti-cancer drugs are contraindicated during pregnancy, while selected drugs are recommended to be used only in the second and third trimester to avoid pregnancy-related complications and foetal harm. As many patients with cancer are sexually active as part of their lives, contraception must be used during treatment and for at least 6 months after its completion. Use of one or more highly effective contraceptive methods is often recommended during chemotherapy and thalidomide-like drug treatment to prevent pregnancy and foetal exposure. Barrier contraceptive methods are commonly recommended. Among other methods of contraception, intrauterine contraceptive devices are preferred over hormonal contraception especially for those with hormonally mediated cancers. Several international guidelines recommend routine clinical pregnancy risk assessment and contraceptive planning prior to commencement of chemotherapy.

Women of childbearing potential are often screened for pregnancy prior to enrolment onto clinical trials with experimental drugs. However, in clinical practice, such screening for pregnancy is not routinely performed prior to chemotherapy initiation. The Australian guidelines for the safe prescribing, dispensing and administration of cancer chemotherapy do not explicitly recommend screening for pregnancy.

After a sentinel event in 2013, a policy was introduced at the Flinders Centre for Innovation in Cancer, Flinders Medical Centre, South Australia, Australia, to screen all women of childbearing potential for pregnancy using serum beta-human chorionic gonadotropin (β-HCG) levels in addition to counselling about the risks and the need for contraception prior to chemotherapy administration. The policy outlines the steps necessary to prevent the inadvertent administration of chemotherapy to pregnant women.

This study was performed to evaluate adherence to the policy in routine clinical practice. The main aim of the study was to identify the proportion of women of childbearing potential who underwent pregnancy screening prior to chemotherapy administration. The fertility status and any documented reasons for not screening were also taken into consideration.

This was a retrospective study of case notes and the electronic records of all female patients who commenced chemotherapy between January and December 2014 in the age range of 18–55 years at the start of the first cycle of chemotherapy. When multiple lines of treatment were administered to the same patient within the year, only the first instance was included. Details on demographic

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Conflict of interest: None.
data (age, chemotherapy cycle commencement date), cancer specific data, gynaecological history (surgeries, contraception methods, menopausal status, reproductive hormone levels) and whether β-HCG was tested before the start of chemotherapy, were extracted and summarised. Any reasons for not performing the β-HCG tests, if documented, were also collected. The audit was approved by the local human research ethics committee prior to the commencement of data collection.

A total of 702 patients started a cycle of chemotherapy treatment during 2014. Of these, 109 were females aged between 18 and 55 years when chemotherapy commenced. Their mean age was 47 years. Breast cancer was their most common primary cancer, affecting 65 of the 109 patients (60%), followed by colorectal (14%), lung (10%), ovarian (6%) and upper gastrointestinal (5%) cancers. The rest were cancers of the pancreas, brain, uterus and melanoma.

After collecting information on history of gynaecological procedures (e.g. tubal ligation, oophorectomy, hysterectomy), and reproductive hormone levels, when available, each individual patient’s fertility status was determined. Of the total 109 patients, 31 (28%) were identified as not having any childbearing potential. The remaining 78 (72%) were thus considered to have the potential to be pregnant prior to commencing chemotherapy. Sixty of these women were chemotherapy naïve, and 18 were scheduled to receive second-line therapy. Of the 78 fertile women, only 16 were screened with serum β-HCG, making the adherence rate 20.5% (Table 2). The remainder (62 women) had no record of β-HCG testing. The pregnancy screening rate was higher in women under 40 years of age (40.7%). One of the screened patients had positive results with confirmed pregnancy and received chemotherapy during her second trimester after extensive counselling. No reasons for non-compliance were identified in the medical records.

### Discussion

Screening for pregnancy prior to the initiation of chemotherapy is not uniformly performed in clinical practice except for those enrolled into clinical trials. A thorough literature search failed to identify any prior publication on this issue of pregnancy screening in a cancer clinic. This study is the first to report on pregnancy screening prior to chemotherapy initiation in a cancer centre.

Despite having an institutional policy to screen for pregnancy prior to chemotherapy, it has been shown that adherence to the policy was poor at 20.5% for the whole cohort and 40.7% for those under 40 years of age. There was one patient whose pregnancy was confirmed when screening β-HCG was performed; thereby precautions were taken to avoid chemotherapy during the first trimester. Reasons for not performing the pregnancy screening were also explored. However, none was documented in the medical records. Although the causes cannot be discerned from the notes, the potential reasons for non-adherence are lack of knowledge of the existing policy, presumed low chance of pregnancy among older women, prejudice against screening unwell women with cancer, poor documentation of the discussion regarding potential for pregnancy/contraception or β-HCG tests were performed in a private laboratory and could not be traced.

Use of β-HCG testing to screen for pregnancy is complicated by cancer-associated elevations in serum levels from cancers such as trophoblastic cancers, biliary/pancreatic cancers and other cancers, as well as false-positive results, leading to additional investigations to confirm pregnancy. The presence of various isoforms of β-HCG, differences in the calibration and sensitivity of the assays, and variations in defining the upper reference limit to identify non-pregnant women may all contribute to uncertainty in the optimal use of such screening.8

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of patients</th>
<th>Number of patients screened</th>
<th>Compliance rate (%)</th>
</tr>
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<tr>
<td>18-40</td>
<td>27</td>
<td>11</td>
<td>40.7</td>
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<td>41-50</td>
<td>33</td>
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<td>12.1</td>
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<tr>
<td>51-55</td>
<td>18</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>18-55 (all patients)</td>
<td>78</td>
<td>16</td>
<td>20.5</td>
</tr>
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</table>
The main limitation of this retrospective study is poor documentation in medical records. Determining the women’s fertility status was challenging because of the fragmented documentation of their menopausal and sexual history and past gynaecological procedures in the case notes and patient summaries. A systematic recording of data was not commonly carried out by the health professionals. Incorporating sexual history in a standardised medical record as well as a pre-chemotherapy checklist may potentially improve documentation by the clinicians. Moreover, the study focused only on pregnancy screening prior to chemotherapy and not for those receiving radiotherapy, the other teratogenic treatment often used as part of cancer therapy. We have not evaluated the current practices on pregnancy screening prior to radiotherapy.

Efforts to improve adherence to pregnancy screening are currently being directed towards improving clinician education by periodic prompts and reminders, use of checklists and additional checks by pharmacists and nurses prior to the start of chemotherapy. Education of healthcare professionals on the importance of sexual history and reproductive needs and development of standard templates to document these issues being discussed with their patients is being planned. A repeat audit is planned in future to identify any improvement in compliance with pregnancy screening protocol.

Pregnancy screening prior to chemotherapy initiation is not commonly performed despite having an institutional policy. Further research into adherence to screening in other centres and potential barriers to implementation of the policy is warranted. We also suggest the addition of pregnancy screening (when applicable) into the Australian guidelines for the safe prescribing, dispensing and administration of cancer chemotherapy.

References

Pyrexia of unknown origin associated with rosuvastatin

A 61-year-old Caucasian man was admitted with fever, dizziness, unsteady gait and slurred speech of 3 days duration in the context of self-medication on carbamazepine up to 900 mg/day, which was prescribed for trigeminal neuralgia 3 weeks previously. He has a history of hypertension, controlled on felodipine 10 mg and enalapril 20 mg daily for 5 years, gout on allopurinol 100 mg daily for 10 years, depression and diet-controlled diabetes. Rosuvastatin 10 mg daily was started 6 months previously for dyslipidaemia. Over the preceding 12 months, he was treated for left facial pain with non-steroidal anti-inflammatory medications and oxycodone. He was subsequently trialled on carbamazepine 100 mg TDS. On presentation, his temperature was between 38.1 and 39.9°C. He had horizontal nystagmus, incoordination and a maculopapular rash on the trunk. Investigations revealed mild anaemia (Hb 112 L g/L), mild lymphopenia (0.56 × 10^9/L), high C-reactive protein (CRP) (100 mg/L) and lipase (450 IU/L), and deranged liver functions (ALP 163 IU/L; GGT 384 IU/L; ALT 48 IU/L). Sepsis, autoimmune disease and viral hepatitis were excluded.

Discontinuation of carbamazepine resulted in resolution of neurological symptoms and signs over 2 days, but he remained febrile (Fig. 1). On further questioning, he admitted having intermittent fever for 6 months and had received several empirical courses of antibiotics (amoxycillin + clavulanate and clindamycin). Investigations prior to presentation were remarkable for mild anaemia and fluctuating CRP. Rosuvastatin was ceased on day 7 with resolution of fever within a day (Fig. 1). His haemoglobin, CRP and liver functions normalised over the subsequent months. Persistence of trigeminal neuralgia required reinstution of carbamazepine on day 8, but he remained afebrile. Subsequently, he was diagnosed with multiple sclerosis as the cause of his trigeminal neuralgia. As hyperlipidaemia was modest he was not considered for alternative lipid lowering therapy.

Drug fever is a diagnosis of exclusion with fever coinciding with the administration of the drug and disappearing after its discontinuation. The presence of skin rash or eosinophilia aids the diagnosis, although present in only 20% of cases.

Rosuvastatin is well tolerated and less than 4% of patients have treatment withdrawal due to side effects.

Fever associated with rosuvastatin is extremely uncommon. To date, two cases of drug reaction with eosinophilia and systemic symptoms (DRESS) have been described with statins – a case each with atorvastatin and pravastatin. Although eosinophilia was absent in our patient, the constellation of fever, lymphopenia, abnormal liver and pancreatic functions, and skin rash make DRESS probable based on the RegiSCAR, the DRESS validation tool. Carbamazepine is a well-recognised cause of DRESS and the risk has been shown to increase significantly in those with HLA-A3101 and HLA-B1502 alleles. However, the latter is associated mostly with severe skin hypersensitivity reactions and occurs almost exclusively in patients with Asian ancestry. In any case, carbamazepine-induced DRESS appears less likely in this case as its rechallenge was free of any clinical sequelae. Furthermore, the overall clinical picture particularly features of neurotoxicity in the setting of the patient self-medicating on carbamazepine, favours toxicity more than hypersensitivity, although serum drug concentrations were not available.

In addition to hypersensitivity reactions, it is important to consider the role of pharmacokinetic drug interactions in the patient’s clinical presentation. Drug interactions

![Figure 1](image-url)
between HMG-CoA reductase inhibitors and medications that either induce or inhibit, or are metabolised by the cytochrome P450 system are well known. However, as rosuvastatin is mostly cleared by the kidneys unchanged and only less than 10% is metabolised by CYP2C9 and CYP2C19, drug interactions due to CYP system would appear less likely in this case. Furthermore, as carbamazepine is an inducer of CYP2C9 and CYP2C19, one would expect a reduction in the serum concentrations of rosuvastatin. However, an increase in serum rosuvastatin concentration due to genetic polymorphism in OATP1B1 and BCRP transporter proteins cannot be ruled out.8

The Naranjo scale,9 a validated tool for assessing the probability of adverse drug reaction, estimated the association of rosuvastatin with fever in this case as ‘probable’ rather than ‘certain’, with a score of 7. However, the Naranjo scale probably underestimated this association because of weightings for variables, such as previous reporting of similar events and serum drug concentrations, which are not applicable to rosuvastatin. The temporal association of fever with rosuvastatin, both the onset and resolution, and the uneventful clinical course post cessation of rosuvastatin strengthens the likely aetiological association of rosuvastatin with fever. The rechallenge of carbamazepine further validates this association by excluding carbamazepine as a potential cause of fever. Although the clinical and laboratory features suggest a probable diagnosis of rosuvastatin induced DRESS, the intercurrent use of carbamazepine confounds the clinical picture, and thus makes elucidation of the pathophysiology of fever challenging – DRESS versus isolated drug fever.

References


Fatal outcome of an Epstein–Barr virus positive mucocutaneous ulcer secondary to methotrexate

A 67-year-old man presented with throat pain and significant weight loss over several months. He was known to have rheumatoid arthritis with associated anaemia of chronic disease and was being treated with weekly oral methotrexate 20 mg, for over 20 years. His other medical history was significant for ischaemic heart disease for which he had undergone percutaneous intervention with coronary artery stent insertion and was on secondary thromboprophylaxis, chronic obstructive airway disease from previous smoking and peptic ulcer disease secondary to Helicobacter pylori infection, treated appropriately. He tested negative for human immunodeficiency virus.

The initial clinical suspicion was of carcinoma of the oropharynx (tonsil). He underwent diagnostic computed tomography and magnetic resonance imaging (Fig. 1). This demonstrated a locally advanced, centrally necrotic, right tonsillar mass, with extension into the laryngopharynx and soft palate. The likely diagnosis was a palatine tonsil carcinoma and endoscopy with biopsy were organised. The initial biopsy was inconclusive and so management proceeded to a radical tonsillectomy.
On the third post-operative day, the patient became neutropenic (0.7 × 10^9/L, reference range: 2–7 × 10^9/L) and was referred to haematology services. This was due to methotrexate-related marrow toxicity, confirmed by a bone marrow aspirate and trephine biopsy which showed myeloid maturation delay with otherwise preserved trilineage haemopoiesis and no evidence of a malignant infiltrate. After withdrawal of the methotrexate, the cytopenias improved over the next 4 days of inpatient stay.

The histopathology of the tonsil showed a well-defined ulcer of the surface mucosa. The underlying granulation tissue contained an atypical lymphoid infiltrate comprising large immunoblast-like cells and Reed–Sternberg-like cells rimmed by small lymphocytes. These large cells were CD 20, CD 30 and CD45 positive. On further analysis, Epstein–Barr virus in situ hybridisation and LMP1 immunohistochemistry highlighted these cells as well as a significant number of the smaller lymphocytes. This confirmed the process to be an Epstein–Barr virus positive mucocutaneous ulcer. On the 11th day postoperatively, the patient had a catastrophic haemorrhage from the ulcerated tonsillar fossa. The patient had a cardiopulmonary arrest and could not be resuscitated.

A post-mortem examination was undertaken. There was a 30-mm ulcer involving the right tonsillar bed. Dissection revealed a 3-mm artery terminating in the ulcer floor. Microscopy showed that the ulcer was lined by necroinflammatory slough. There was fibrinoid necrosis of the wall of the artery within the base of the ulcer with an unexpected finding of fungal hyphae and spores within the arterial wall (Fig. 2). No residual pseudo lymphomatous infiltrate was evident within the base of the ulcer. The entire bronchial tree was filled with soft blood clot and the cause of death was considered to be due to hypoxic cardiac arrest, secondary to aspiration of blood arising from the bleeding artery in the tonsillar bed.

Methotrexate is a first-line agent in the treatment of rheumatoid arthritis, a debilitating illness that affects over 2 million Australians.1–3 Epstein–Barr virus mucocutaneous ulcer is a little known entity complicating chronic methotrexate therapy that has only recently been recognised by haematopathologists.4 Case reports of these Epstein–Barr virus positive, ulcerative lesions of the oropharyngeal mucosa, skin and gastrointestinal tract have previously been reported internationally in association with azathioprine, cyclosporin-A and methotrexate.5 The distinct histological features include a polymorphous infiltrate of small lymphocytes, histiocytes and plasma cells with frequently distributed atypical large B-cell blasts, often resembling Reed–Sternberg cell-like morphology, and intermediate-sized lymphoid cells, often associated with vasculitic changes.6,7 The distinction between this and lymphoproliferative disorders can therefore be challenging. Immunohistochemically, however, they are characterised by variable CD20 expression but are positive for CD 30, MUM1, CD79a and EBV-LMP-1.4,6 Identified risk factors include immune suppression and age greater than 60 years old.5,6 All previous reported cases have achieved complete remission after withdrawal of immunosuppressive therapy or conservative management in the case of age-related immunosenescence.7,8

Figure 1 Magnetic resonance imaging of right tonsillar mass.

Figure 2 Silver methenamine stain (×400) highlights the fungal hyphae in the vessel wall (>).
The rare post-operative complication of necrotising vasculitis, experienced by this patient, was found to be due to localised fungal infection, with evidence of hyphae and spores within the arterial wall at the base of the ulcer. The post-mortem findings did not reveal evidence of systemic fungal infection or systemic vasculitis. Candida is the most common fungi to cause this pathology, either by direct invasion of the vascular wall, as observed in this case, or mycotic emboli. The long-term use of methotrexate in our patient was thought to contribute to his susceptibility for fungal infection, compounded by suboptimal oral hygiene in the peri-operative phase.

Epstein–Barr virus positive mucocutaneous ulceration is a diagnostic challenge. The ulcers can mimic a typical carcinoma of this area. Histopathological diagnosis also remains challenging in the differentiation between lymphoproliferative disorders. The diagnostic possibility should be borne in mind in any patient on long-term methotrexate therapy, to ensure prompt withdrawal of the drug until the ulcer has resolved.

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A rare case of coeliac disease in an African teenager

Coeliac disease (CD) is an autoimmune inflammatory disorder of the small bowel that generally affects patients of European (Celtic) descent. It is deemed rare in sub-Saharan African people with only few isolated case reports. We report a case of CD in a female Somali teenager and highlight the importance of vigilance in assessing differential diagnoses in ethnic minorities especially in a setting of increasingly diverse immigration to New Zealand.

A 15-year-old Somali female was referred to the gastroenterology clinic with a 3-month history of intermittent abdominal pain, nausea, vomiting, diarrhoea and weight loss of 8 kg. She consumed a mixed western and traditional Somali diet and noted that vomiting was particularly worse after having wheat-based cereals.

She had a background history of well-controlled asthma and hay fever. She had no known allergies. She had been in New Zealand since the age of 1 with no recent travels. There was no family history of CD or other related conditions. Examination was normal.

Blood tests showed normal full blood count, renal profile, liver profile, C-reactive protein and thyroid function tests. Her ferritin was low at 11 μg/L (20–200). Coeliac antibodies tests revealed anti-TTG IgA >150 units (0–20) and positive endomysial antibodies. Her HLA testing was positive for DQ 2.2 and 2.5. Faeces samples were negative for pathogens.

Gastroscopy was performed and showed decreased folds in the second part of the duodenum with scalloping appearance suggestive of CD. Histology showed villous atrophy, crypt hyperplasia and intraepithelial lymphocytes (Fig. 1) consistent with CD.

References

She was therefore diagnosed with CD, and a gluten-free diet was introduced. This resolved her symptoms and improved histology (near normal villi) and serological results (TTG IgA 3.4) on repeat investigations a year later.

CD is a chronic autoimmune condition due to sensitivity to gluten in genetically susceptible patients with variable small bowel changes and symptoms.

The prevalence of CD has been easier to assess with the aid of blood tests including tissue transglutaminase and endomysial antibodies. In general, CD has been most correlated with a Celtic/European ethnic background history and it is deemed to be rare in sub-Saharan Africa, a region where staple cereals are mostly naturally gluten free.

In 2000, we reported a 1.2% prevalence (1:82) of CD in the Canterbury population with the majority being latent at the time. No report of patients’ ethnicity was recorded at that stage, but Caucasian ethnicity remains predominant in this region. The prevalence of CD is between 0.7 and 2% in most populations. Our case is unique, as to our knowledge, it is the first patient from sub-Saharan Africa to be diagnosed and reported with CD in New Zealand.

The ethnic mix of New Zealand is continually evolving. Reviewing the census data between 2006 and 2013, we note an increase in many ethnic groups (other than Caucasian and Maori) including Middle-eastern, Latin American and African.

Therefore, in conclusion, awareness that CD is not restricted to individuals of Northern European descent is important when considering differential diagnoses in other ethnic groups.

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FIGURE 1 Duodenal biopsies showing villous atrophy and intraepithelial lymphocytes (left) followed by near normal appearance post-gluten-free diet (right).
General Correspondence

Too much or not enough? A comment on discrepancies in published estimates of opioid use in Australia

The paper by Islam and colleagues entitled ‘Prescription opioid analgesics for pain management in Australia: 20 years of dispensing’ and our recently published manuscript in the British Journal of Clinical Pharmacology used similar methodology but resulted in remarkably different estimates for some parameters that warrant explanation.

The majority of the estimates of opioid use presented by Islam et al. was obtained using the database maintained by the Drug Utilisation Sub-Committee (DUSC); this data source was also used in our study. We note marked discrepancies between the results presented in the online (uncorrected) accepted version of the Islam et al. manuscript and those presented in our paper and another publically available source. Specifically, we note a 10-fold inflation of prescription volume in table 2 and overestimation of use according to defined daily dose (DDD)/1000 persons/day in table 2 and figure 3. The authors have acknowledged this in their corrigendum, but many of the errors appear to have been corrected in the published paper in the August 2016 issue of the Journal.

However, some estimates presented in the corrected, published version of the Islam et al. paper remain hard to reconcile. Islam and his colleagues do not detail the medicines included in their analysis in the methods section of their paper, making verification of their results challenging. However, based on the medicines listed in table 1 of Islam et al., we would expect good concordance between estimates of opioid use in their analysis and ours. We note that the yearly prescription volumes detailed in Islam’s table 2 are relatively consistent with those derived from our dataset (data not presented in our paper; see Table 1 for comparisons). However, their data on total opioid use by year according to DDD/1000 persons/day are lower than our estimates, which is unexpected given the comparability of prescription volume estimates. Notably, in 2011, we estimated total opioid use at 17.96 DDD/1000 pop/day, which exceeds the 14.46 DDD/1000 people/day in Islam et al.’s table 2 by almost a quarter.

Moreover, the DDD/1000 persons/day estimates reported in figure 3 of Islam et al. overestimate dextropropoxyphene use by 35% and underestimate codeine use by approximately 40%. For example, in 2011, codeine utilisation is reported as 4.4 DDD/1000 persons/day in the Islam et al. paper compared with 7.4 DDD/1000 pop/day in our paper. We acknowledge that there appear to be small differences in the codeine preparations included in our respective analyses (based on the footnote to figure 3 and the medicines listed in table 1 of Islam et al.), hence, we would not expect our estimates to align perfectly. However, given the similarity in our estimates of codeine (and dextropropoxyphene) prescription volumes, we would expect closer concordance between our respective estimates of DDD/1000 persons/day. Our numbers are within a percentage point of those in the publically available Australian Statistics on Medicines.

The DDD/1000 pop/day metric can be used to obtain an approximate estimate of the proportion and size of the population treated daily with opioids. Extrapolating from our 2011 estimate of total opioid use (17.96 DDD/1000 pop/day), 1.8% of the Australian population (approximately 402 000 people) were treated with opioids daily that year. This exceeds the corresponding estimate from Islam et al. by 0.35% of the population or 78 000 people. Similarly, our study suggests that approximately 165 000 Australians were treated daily with prescription codeine in 2011 (extrapolated from 7.4 DDD/1000 pop/day).

Table 1 Comparison of discrepancies between Islam et al. and Karanges et al. in 2011 opioid use according to DDD/1000 persons/day, with percentage difference relative to Karanges et al. estimates

<table>
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<tbody>
<tr>
<td>Total opioid use</td>
<td>12 436 148†</td>
<td>12 250 000‡</td>
<td>−1.50</td>
<td>17.96‡</td>
<td>14.46§</td>
</tr>
<tr>
<td>Codeine use</td>
<td>3 957 724†</td>
<td>3 893 000§</td>
<td>−1.64</td>
<td>7.37¶</td>
<td>4.36††</td>
</tr>
<tr>
<td>Dextropropoxyphene use</td>
<td>456 079†</td>
<td>456 000¶</td>
<td>−0.02</td>
<td>0.17¶</td>
<td>0.23††</td>
</tr>
</tbody>
</table>

Note the comparative similarity in results according to number of prescriptions dispensed. Small discrepancies in use are expected due to differences between studies in medicine inclusion. †Unpublished additional analyses from Karanges et al. ‡Text of results section from Islam et al. §Table 2 Islam et al. Table 3 and figure 1 Karanges et al. ¶Figure 3 Islam et al. ¶Australian Statistics on Medicines 2012 (data for 2011); † total opioid use: 18.01 DDD/1000 pop/day; codeine: 7.44 DDD/1000 pop/day; dextropropoxyphene: 0.17 DDD/1000 pop/day.
compared with 98,000 from Islam et al., a discrepancy of 67,000 people. However, there are some important considerations when using DDD/1000 pop/day to extrapolate to population estimates. As noted in our manuscript and the Islam et al. paper, the DDDs for many strong opioids were assigned when the medicines were initially listed for use in cancer pain, while the DDD of codeine was based on the lower doses used in cough suppression. As such, absolute population estimates derived from DDD/1000 pop/day are likely to underestimate the true utilisation of strong opioids, particularly morphine, buprenorphine and fentanyl, and overestimate the true utilisation of codeine.

We did not undertake an analysis of opioid use by state/territory in our paper and, given our uncertainty about the medicines and item codes included in the Islam et al. paper, we did not attempt to verify the DDD/1000 people/day estimates presented in figures 5 and 6. We are therefore unable to comment on the accuracy of these estimates.

There are other considerations worth noting when interpreting the results of the state/territory analysis. The paper uses two distinct data sources: that maintained by DUSC, described in detail in the methods, and publicly available Medicare Australia Pharmaceutical Benefits Scheme (PBS) item reports. The latter is used for the state/territory analysis. Unlike the DUSC database, which records dispensing based on the date the medicine is supplied to the patient by the pharmacy, the PBS item reports record dispensing based on the date that the dispensing pharmacy’s claim for reimbursement is processed by the Department of Human Services. Data based on date of processing are less likely to reflect medicine access patterns at particular time points, as delays in the processing of claims followed by periods of bulk processing can produce troughs and peaks in estimates. The state/territory analysis is also affected by changes in medicine reimbursement across different states and territories due to the Public Hospital Pharmaceutical Reforms. The Reforms, which allow public hospitals to provide PBS-subsidised medicines to outpatients and discharging inpatients, were introduced gradually across most states and territories of Australia from 2001. It is unlikely that the Reforms account for all the differences in opioid use between the states and territories but they should be acknowledged when comparing use by jurisdiction.

There are clearly many challenges associated with the use of routinely collected dispensing data to estimate medicine use, and each dataset has its own idiosyncrasies and limitations that impact analysis and interpretation. The Department of Health has recently released a dataset containing linkable Medicare Benefits Schedule and PBS data for a random 10% sample of Australians. With approximately 1 billion lines of data on medicine and healthcare use publically available, this dataset is a powerful resource for pharmacoepidemiological studies, but also carries a substantial risk of error for the uninitiated. Small errors or failure to recognise the limitations of the data may have large implications on estimates. We encourage those contemplating use of this or other data sources to investigate the nuances of the data, and where possible, triangulate their results against other publically available datasets or published literature.

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Is it possible to distinguish between glycogenic hepatopathy and non-alcoholic fatty liver disease without liver biopsy?

I read with interest the paper by Irani et al. regarding a subject with glycogenic hepatopathy (GH). It is generally regarded that a final distinction between GH and non-alcoholic fatty liver disease (NAFLD) can only be made with liver biopsy. Subjects with GH are usually children, and it would be desirable if the diagnosis could be reliably made using non-invasive means. It would be interesting to know if serum lactate was measured in the subject of Irani et al. Brouwers et al. recently reported four cases of biopsy proven GH in whom lactate and lactate-to-pyruvate levels were elevated. None of the subjects had signs of a systemic mitochondrial defect, there was not maternal inheritance of disease, the onset of diabetes was much younger than that commonly observed with mitochondrial diabetes, testing for mitochondrial mutation was negative in one subject, and serum lactate normalised in one subject with improved diabetic control. Similarly, dramatic elevation of serum lactate was reported in half of a series of 31 young people with GH. Magnetic resonance spectroscopy (MRS) may be useful to differentiate GH and NAFLD non-invasively. Several authors have demonstrated elevated hepatic glycogen concentrations using $^{13}$C MRS in natural abundance in subjects with glycogenesis types I and IIIa. Hwang et al. reviewed the use of $^{13}$C MRS in determining glycogen breakdown and synthesis rates during exercise or nutrient ingestion in metabolic studies. MRS has the advantage of assessing the entire liver potentially reducing the risk of sampling error with a liver biopsy. Murata et al. reported the potential use of gradient-dual-echo magnetic resonance imaging sequence of the liver in distinguishing GH from NAFLD in a subject with type 1 diabetes mellitus. Fitzpatrick et al. reported fibrosis on liver biopsy in 73% of 19 subjects with GH. The degree of fibrosis was generally mild although there was bridging fibrosis in two specimens. There may be a role for magnetic resonance elastography in evaluating the degree of fibrosis with GH.

In summary, further studies evaluating the reliability of serum lactate and MRS in differentiating GH from NAFLD in subjects with type 1 diabetes mellitus would be worthwhile.

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Reproducibility and research misconduct: time for radical reform

We know now that much health and medical research which is published in peer-reviewed journals is wrong, and consequently much is unable to be replicated. This is due in part to poor research practice, biases in publication, and simply a pressure to publish in order to ‘survive’. Cognitive biases that unreasonably wed to our hypotheses and results are to blame. Strongly embedded in our culture of health and medical research is the natural selection of poor science practice driven by the dependence for survival on high rates of publication in academic life. It is a classic form of cultural evolution along Darwinian lines. Do not think that even publications in the most illustrious medical journal are immune from these problems: the COMPare project reveals that more than 85% of large randomised controlled trials deviate seriously from their plan when the trial was registered prior to its execution.
start. An average of more than five new outcome measures was secretly added to the publication and a similar number of nominated outcomes were silently omitted. It is hardly far-fetched to propose that this drive to publish is contributing to the growth in the number of papers retracted from the literature for dubious conduct along with the increasing number of cases of research misconduct.

The timely article by Breen covers many of the historical and current strictures in dealing with research misconduct and it canvasses possible solutions. These include having allegations of research misconduct decided by a tribunal, as occurs for medical misconduct, or by a completely external agency as in Denmark (http://ufm.dk/en/research-and-innovation/councils-and-commissions/the-danish-committees-on-scientific-dishonesty) or by an external agency which oversees and directs local investigations as with the Office of Research Integrity in the USA (https://ori.hhs.gov/). We are in an era which expects increased transparency and the traditional approach to research misconduct in Australia is failing. It usually fails the whistle-blowers, protects the executives of universities and research institutes, and it ignores the moral principles by which the National Health and Medical Research Council alone spends more than $0.8 billion of taxpayer dollars annually on health and medical research. Institutions conducting research with such external funding can no longer take several years to conduct investigations, conduct them in complete secrecy, fail to report their outcomes to the public and hide behind enterprise agreements which ensure that findings cannot be obtained by those who really paid for the research, and whose lives may ultimately be affected by its outcomes.

Breen makes a compelling case to set up some form of national office for research integrity in Australia. We should be able to adopt the best of the systems operating overseas to establish strong, effective research governance for the first time. This is critical to protect the interests of researchers and research patients, and to maintain the confidence of the public.

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Letters to the Editor

Research integrity investigation is one of the most unpleasant situations people will experience. It is stressful, difficult, time-consuming and thankless, and in Australia there is little guidance or support for any of the participants, for most of whom it will be their first and (hopefully) only experience. Unless those involved are indemnified, they also risk legal suits from disgruntled protagonists, yet once lawyers become involved, costs spiral.

There are growing numbers of examples where the governance of medical research has gone badly wrong. In the US, anaesthetist Scott Reuben was found to have faked data in 25 studies. In 2009 he was sentenced to prison. The editor of the journal Anesthesia & Analgesia, Paul White, said Reuben’s studies affected the way millions of people were treated for pain during and after orthopaedic surgery, and led to the sale of billions of dollars worth of the COX2 inhibitors celecoxib and rofecoxib for applications whose benefits/risks are now in question.2

In France, the trial of the drug BIA 1–2474 led to the death of one volunteer and the hospitalisation of five others. After the first volunteer was hospitalised with headaches and blurred vision, the other participants were not informed, but were given another dose of the drug. The critical mistake was the failure to inform participants in the trial that one of the volunteers had suffered severe side effects. Because they were not fully informed, they could not re-assess their willingness to continue.3 As outlined in the Declaration of Helsinki, providing informed consent is a cornerstone of ethics in clinical trials, and yet the governance of human research ethics is even weaker in Australia than in France prior to the Biotrial disaster.

In one Australian clinical trial, where there was an ongoing independent investigation into prima facie evidence that the preclinical data had been falsified, and concerns about patient safety were raised, the trial was not suspended pending the outcome of the investigation, and none of the patients was informed at any stage. When concerns were raised about patient safety with the NHMRC, these were referred to the ‘Business Support Branch’, which provided assurances that ‘the NHMRC is monitoring the situation’ and ‘the NHMRC takes its responsibilities for the development of ethical standards relating to the conduct of research extremely seriously’, but there was no evidence of any action, such as halting the trial pending the outcome of the ongoing research integrity investigation.

According to Professor Ian Olver, Chair of the Australian Health Ethics Committee, this NHMRC committee has no regulatory role, and can only provide guidance of a general nature. It does not provide advice on specific matters relating to decisions taken by individual ethics committees, or decisions taken by individuals at particular research institutions.

As Breen says, the role of the Australian Research Integrity Committee (ARIC) is also limited. It can only review whether an institution has followed the procedures laid down in the Australian Code for the Responsible Conduct of Research. It cannot consider the merits of a case; or take rapid (potentially life-saving) action, because it will not consider cases while institutional processes are still underway.

A national body, such as the Office of Research Integrity in the United States, the Research Integrity Office in the UK, or the The Netherlands Board on Research Integrity (Landelijk Orgaan Wetenschappelijke Integriteit) would not be a panacea, but could fulfil several functions. It could provide advice to whistle-blowers, institutions, and those accused; offer education and training; collect data; update the Australian Code for the Responsible Conduct of Research; keep lists of experienced, independent investigators and panel members; provide oversight; provide an avenue for appeal; and ensure that the literature is corrected.

The integrity of research conduct is the cornerstone of good research practice. The recent Lancet Commission on waste in medical research4 highlights some of the issues relating to reproducibility of research results and the importance of transparency of data collection and evaluation. In the discipline of medicine we have made great strides with the issue of patient safety through careful development of quality systems, checklists and protocols. Similarly, we need to ensure that all researchers ensure that the integrity of data is the best it can be, collected appropriately, transformed carefully to ensure no manipulation, interrogated carefully and transparently and subject to internal and external audit if required.

We must ensure this level of integrity if we are to maintain our confidence in medical research, and to continue to use research as the basis for change in practice. Australia needs a national office or ombudsman with overarching responsibility for issues related to research integrity. Such a body would support institutional governance, enhance reproducibility and hence efficiency, and maintain and enhance public confidence in research.

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Documentation and identification of substitute decision-makers/persons responsible in residential aged care facilities in Victoria

Several recent Australian\textsuperscript{1,2} and American studies\textsuperscript{3,4} describe differences between documented ‘next of kin’ (NOK) or emergency contacts\textsuperscript{4} and patients’ nominated or preferred substitute decision-makers (SDM) in the medical records. Each state in Australia has its own laws governing medical treatment decisions and who is the correct SDM. In Victoria, the legal appointment of a SDM for medical decisions can be a medical power of attorney (POA-MT) or guardian with healthcare powers (GHCP).

We conducted a retrospective file audit of NOK and available SDM documentation at two residential aged care facilities in metropolitan Melbourne in April and November 2012 where 88 consecutive files of current residents were examined. Significant discrepancies were found between the listed NOK and the SDM for medical treatment decisions with deficiencies in SDM documentation.

A POA-MT or GHCP was noted for 14.8\% of all residents, with only 15.4\% of these having supporting legal documents in their file. For 26.1\% of residents, admission forms were unclear regarding the existence of a SDM for medical treatment decisions. Of these, 34.8\% were confirmed to have a medical POA or GHCP by review of their paper and electronic records and, if required, by information from the Victorian Civil and Administration Tribunal (VCAT). In the remaining 59.1\%, no POA-MT or GHCP was noted. Of these, 1.9\% were found to have a POA-MT.

Where a POA-MT or GHCP was confirmed with photocopies in the paper medical records or by VCAT, the appointed SDM was identical with 73\% of listed first NOK on the resident personal details forms.

For residents without a confirmed POA-MT or GHCP, the listed first NOK was a potential person responsible (PR) as outlined in the Guardianship and Administration Act 1986 (GAA)\textsuperscript{5} in 74.3\% of cases. 48\% of the potential PR were confirmed by the audit as the correct SDM/PR as per GAA. Difficulties in identifying a correct PR included the presence of multiple potential PR of unclear availability, willingness and ability to act as a SDM. Of the total audited group, 36.4\% of listed first NOK were consistent with the PR as per GAA.

Incomplete or incorrect SDM documentation and unavailable supporting legal documents may compromise patient care in emergency situations when a PR cannot readily be identified.

Healthcare professionals need to be aware that a listed NOK is not necessarily the PR, for example, the SDM for medical treatment decisions. Legal and ethical problems may arise when a NOK who is not the SDM/PR is approached for medical decision-making.\textsuperscript{4} In this study, 80.7\% of residents were noted to have cognitive impairment on admission by their general practitioner, indicating a high potential need for surrogate decision-making, thus confirming the importance of accurate SDM documentation and identification.

Lack of knowledge around legislation governing substitute decision-making has been described in laypersons and healthcare professionals.\textsuperscript{6,7} The Victorian Powers of Attorney Act 2014 consolidates an enduring POA and enduring power of guardianship into a single POA with powers for financial and/or personal matters. POA-MT continue to be regulated under the Medical Treatment Act 1988.\textsuperscript{8}

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References


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