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In 2004–2005, the New Zealand Institute of Economic Research (NZIER) predicted that, on the basis of the ageing of the population alone, New Zealand would need between 40 and 70% more healthcare workers by 2021 to maintain then standards of healthcare. This prediction was based on a range of disease projections and in turn on the success or otherwise of measures to compress morbidity in the later years of life. It was also based on an assumption of stable healthcare worker productivity. The work that NZIER has underway in 2012 for the National Health Board also assumes a healthcare worker productivity growth of zero over the next decade.

The assumption that we will see no change in the productivity of the healthcare workforce is both important and, if anything, optimistic. Relatively small changes in productivity can make a big difference to workforce demand and overall cost growth, especially if productivity gains are sustained over time. Unfortunately, however, the limited data we have suggest that our relevant record has been poor. The productivity of our public hospitals actually declined in the decade from 2000, a decline that is only now just beginning to level off.

Reversing this recent poor productivity record is essential given likely trends in the supply of healthcare workers. The New Zealand Medical Council’s annual work surveys indicate that there has already been a reduction in the working hours of general medical practitioners, including both normal and after-hours work. While there are several factors behind this decline, it is plausible that the introduction of capitated funding is a significant contributor. Looking forward, both the NZIER and similar Australian work suggest that across the health sector more broadly, population ageing will reduce the supply of the healthcare workforce at the same time as it increases the demand for their services. Both Australia and New Zealand already have an unsustainable reliance on immigrant healthcare workers, so improving the productivity of the healthcare workforce will be critical in filling this gap, as will policies that encourage workforce to stay vocationally active for longer.

We suspect that the falling productivity-rising cost conundrum of the past decade was in part a consequence of a dislocation of health service governors/managers and clinicians, and, therefore, clinicians will need to lead any response to the demand-supply-affordability challenge if it is to be even moderately successful.

The paper by Dr. John Cullen and his colleagues from the Waitemata District Health Board (WDHB) in this month’s Internal Medicine Journal is a demonstration of just such a clinician-led lift in productivity. They report on the outcome of a piloted new model of care for total hip and knee arthroplasties that is ‘an incentive – based, clinically – led model in which the surgeons and anaesthetists were responsible for increasing surgical elective throughput.’ While the authors acknowledge that the new model introduced many changes simultaneously, clinical leadership is at the heart of the change. The gains in outputs and outcome quality, and the reduced cost of providing those services are triumphs for the clinician leaders involved. To paraphrase, the WDHB, and the community that it serves, got more and better for less.

The balance of this editorial then is to identify the key elements of the WDHB ‘process’ that we consider to underpin this success and to encourage the adoption of this ‘formula for success’ as much as and as widely as is possible.

The first element is an ‘action research’ methodology. This approach is based on an agreed outcome – quantitative and qualitative – and where the measured variable set is what has to be done to achieve that outcome. The alternative is to agree changes in practice and then assess the impact of each change on outcomes, if any – a process that is not driven by an agreed goal. The latter is bedevilled by problems in restraining clinicians to rigid protocols and the risk of the ‘reform’ failing – especially in a health system that already has difficulty in meeting expectations. The ‘action research’ approach brings comfort to funders and politicians, and to hospital governors as long as the ‘target’ is real world (achievable) and clinically agreed. The use of local and relevant private-facility outputs to derive a public hospital target quantum in this context ensured both of the latter.

The second element was the identification and appointment of a clinical champion to lead the programme; in this context, a well-known and respected orthopaedic surgeon and former Olympian. This champion was not only the ‘public face’ of the initiative but was central to project governance and management. There are many personal qualities that such a champion needs – not the least of which is courage, especially when
colleagues often portray those who take on these wider leadership roles negatively.1\(^1\) Hopefully, this barrier will lessen as healthcare professions ‘reclaim’ the broader roles inherent in best-practice individual patient care in a population health-centred context and as more ‘clinical champions’ are successful and consequently become influential role models. It also needs to be acknowledged that any clinician engagement here was facilitated by the nature of the senior leadership at WDHB; both the Board Chair and the Chief Executive are medical graduates. Although they have long been in health system management, they have the highly desirable combination, to quote one of them, of ‘the mind of a manager and the heart of a doctor’.

The third element was the recruitment of a ‘coalition of the willing’ to form the surgical teams. The motivation that underpins such coalitions varies and may not always be or need to be altruistic. Sometimes, the coalition will only enable a small-scale operation. The latter is preferable to ‘reforms’ imposed on an unwilling and or sceptical healthcare workforce. To be most effective, the coalitions should be multidisciplinary and take-up the reform agenda ‘as their own’. Again, courage and determination are necessary qualities of these coalitions and it is the role of system governors/managers to provide necessary support and to ensure that any service-load implications of the reform process are accommodated without adverse impact on the rest of the healthcare workforce.

The fourth and final element was that of some core tactical measures to enable the ‘flexible process evolution’ – that is, the teams operated at a new campus and learners were excluded from the teams. The slowdown effect of any learners is debatable, but, the significance here is that it provides a milieu in which a sudden lift in productivity is not only possible but also is acceptable and does not intrinsically lead to a pejorative view of previous practice.

The WDHB is to be congratulated then on this innovation – more of a good thing at a higher quality and at less cost. The lessons to be learned here apply well outside the boundaries of the District Health Board, the discipline of orthopaedics and the actual procedures. We need to do more to ensure that successful pilots like this one are adopted more widely. Our health system is ‘littered with successful pilots’ that have shown promise or real utility and then gone nowhere. As a general principle, we will be reluctant to support funding of innovative trials or pilots or demonstrations that do not have such a final broad take-up phase.

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REVIEW

Towards a vaccine for chronic obstructive pulmonary disease

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Abstract

This review discusses chronic obstructive pulmonary disease as an outcome of two pathogenic pathways: the first resulting from inhalation of toxins and the second a consequence of bacterial colonisation of damaged airways. Earlier assessment of the role played by bacteria in acute exacerbations was compromised by a deficiency of quality data and the use of parameters more relevant to invasive infection. Data are reviewed to support a hypothesis that states intrabronchial inflammation reflects an excessive and inappropriate host response (largely mediated by Th17 cells derived from gut-associated lymphoid tissues) to colonising bacteria acting as an ‘antigen sump’ (in essence, a hypersensitivity reaction). It is proposed that both viral and bacterial infections exacerbate inflammation through a common pathway that involves colonising bacteria. An oral vaccine containing inactivated non-typeable Haemophilus influenzae augments a protective loop that involves the aspiration of bronchus content into the gut and reduces the severity of acute exacerbations including the need for hospital admission by reducing the ‘load’ of bacteria comprising this final common path. The positive clinical results from trials using oral NTHi support both the concept that bacterial colonisation of damaged airways is a potent second pathogenic pathway and that oral immunotherapy provides a significant therapeutic advance in limiting damage in chronic obstructive pulmonary disease.

Introduction and background to chronic obstructive pulmonary disease

A second pathogenic pathway in chronic obstructive pulmonary disease (COPD) dependent on bacterial colonisation of damaged airways, in particular non-typeable Haemophilus influenzae (NTHi), is not a new idea. However, interest waned due to a lack of data of therapeutic value. This review focuses on NTHi as a keystone in understanding the importance of bacterial colonisation in provoking exacerbations of COPD, in part as a result of studies that suggest benefit from an oral mucosal vaccine that reduces the load of bacteria in damaged airways.

Twenty-five years ago, an oral inactivated NTHi vaccine was shown to reduce the frequency and severity of exacerbations in smoking-related airways disease (SRAD).1 This was followed by three further vaccine studies2–4 and a Cochrane Report5 supporting benefit, with no reported significant adverse events. These studies recorded a reduction of all pathogens in sputum but did not detect an increase in secretary immunoglobulin A (IgA) antibody in saliva. In these studies, several unselected organisms were used possibly accounting for a variation in results with only five of six studies showing protection.1–4 At that time, there was little interest in the idea of a vaccine for a disease where inhalation of toxins was widely considered to be the sole cause of damage and IgA antibody was the required marker of mucosal immunity. This was consistent with a longstanding negativity and neglect with respect to SRAD, which was regarded as a self-induced disease of the elderly, for which nothing could be done; however, these circumstances have changed. Recognition of the potential of a vaccine to limit damage in COPD can best be understood in the context of change in acceptance of the importance of bacterial colonisation of damaged airways as a second major cause of airways damage in COPD. Four stages in this process will...
be discussed: evolution of ideas on the nature of SRAD, the importance of acute exacerbations, the role of bacteria and then the host response in determining acute episodes, and the evidence that an oral vaccine can downregulate inflammation.

In assessing the value of any ‘oral vaccine’, it is important to consider a number of often opposing receptor-response pathways that contribute to the ‘net response’ involving both innate and adaptive immune systems. Most microbes present both specific (antigenic) and ‘pattern’ recognition units to mucosal antigen-presenting (or dendritic) cells (APCs), to trigger cytokine-mediated upregulation – and downregulation – of the inflammatory response. Any particular ‘net outcome’ depends on characteristics of the stimulus and the manner in which it is presented, and to the ‘state’ of the mucosa. For example, constant, low-dose, soluble antigen presentation leads to a non-responsive or tolerant state, while an intermittent bolus of particulate antigen stimulates net immunity throughout the mucosal system. With respect to the ‘state’ of mucosa, variations include the level of inflammation present and whether or not the subject is atopic. In the presence of pathological inflammation, the IgA antibody response is suppressed and replaced by a Th17 response – mucosal colonisation is then controlled by the neutrophil flux. Atopic subjects express IgEFCR on the surface of mucosal APCs that can trigger a Th2 or Treg cell response depending on circumstances of allergen presentation.

In summary, mucosa-associated bacteria can either trigger a low level of inflammatory response when conserved ‘patterns’ ligate surface Toll-like receptors (commensals), or by also binding intracellular receptors (such as NOD), they induce an excessive inflammatory response and tissue damage (pathogens). In addition, bacteria-associated antigens are processed to induce uncommitted CD4 T cells in mucosa-associated lymphoid tissue to differentiate into Th1, Th2, Th17 and Treg cells depending on the characteristics of APCs and cytokine milieu. The outcome of net immunity, hypersensitivity (inappropriate Th2-IgE secretion, inappropriate Th17-neutrophil recruitment) or tolerance (Treg) reflects the balance between these T-cell subsets. These concepts underpin innovative approaches to immunotherapy: sublingual desensitisation for allergy; helminth-induced suppression of chronic inflammation, including Crohn’s disease and multiple sclerosis; downregulation of infection-related bronchospasm in children following low-dose polybacterial lysate mixes; and by regulating Th1/Th2 balance to optimise mucosal protection using probiotics. It is within this framework that durable immunity within the airways (seen as a reduction in bacterial antigen load) following cyclic ingestion of high-dose particulate bacteria can be both understood and differentiated from separate net outcomes that follow these other immunotherapeutic products.

The term chronic obstructive pulmonary disease (COPD) was introduced to unify SRAD through the common denominator of progressive airways obstruction. This allowed a simple and objective diagnosis to be made, enabling the development of international consortia such as GOLD that could then promote optimal management strategies and develop diagnostic criteria for multinational clinical trials. There had been division across the Atlantic as to the nature of SRAD: in America, the focus was on changes in structure and function in emphysema thought to be exclusively caused by inhaled toxins, while in the United Kingdom, the focus was the influence of smog-initiated epidemiological studies of ‘chronic cough and sputum’ (or ‘simple bronchitis’), and its complications of ‘infection episodes’ and ‘chronic obstruction’. These clinical disorders may or may not be associated with the tissue changes of emphysema. Initially, the ‘infection episodes’ were considered to be caused by bacteria, especially NTHi and Streptococcus pneumoniae. However, a ‘poor fit’ with parameters derived from study of invasive infection including sputum bacteriology, serology and response to antibiotics, together with a lack of epidemiological support for the idea that acute episodes worsened airways obstruction, lessened interest in bacterial infection as a significant pathogenic factor in COPD. Recent intense interest in COPD derives from a recognition of the sheer magnitude of its human and economic costs, the realisation that intrabronchial inflammation provides new opportunities for therapeutic intervention and likely relates to new ideas on the lung microbiome and a re-evaluation of the importance of exacerbations in acute and chronic phases of COPD. Thus, COPD is the only major cause of death that is increasing in frequency with about 20% over 60 worldwide having COPD, there are immense economic costs, and in many countries, exacerbations of COPD are the major medical cause for hospital admission. Inflammation in COPD has been contrasted with that in asthma, substituting neutrophils for eosinophils but linking inflammation exclusively to inhaled toxins. The use of asthma therapy has been trialled (inhaled corticosteroid/ bronchodilator). The most substantial database is with fluticasone/salmeterol from two multicentre studies designed to detect retention of airflow or reduction in mortality. There was a significant reduction of about 40% in exacerbations requiring corticosteroid therapy, but reduction in hospital admissions was less clear, being recorded at 0% and 17%, respectively. In both of these studies, the incidence of antibiotic-treated episodes increased in the treated groups, consistent with the
proneness to infection recorded with long-term inhalation of corticosteroids. Any conclusion that inhalation of toxins is the sole cause of inflammation is conflicted by progression of disease in severe COPD, where most have long ceased smoking. Alternative ‘drivers’ of inflammation such as colonising bacteria, feedback loops based on enzyme-release from damaged tissue and autoimmunity must be considered.

**Acute exacerbations**

Exacerbations of COPD feared by patients, and the main precipitant of respiratory and cardiac failure, have been reassessed and are now known to promote progression of airways disease and its clinical sequelae. The idea of an ‘exacerbation phenotype’ has recently been confirmed, with more frequent exacerbations occurring in those with most severe disease. These clinical observations are consistent with the demonstration that there is an increase in inflammation in clinically stable COPD. Exacerbations represent an increase in inflammation above a threshold, representing a perceived increase in volume and purulence of sputum. The inflammatory process is continuous and unstable. Recognition that the ‘normal’ variations in level of inflammation provide a ‘background noise’, which complicates calculation of exacerbation frequency in clinical studies, led to exacerbations being defined as bronchitic symptoms that require a change in therapy.

Recently, a significant role for bacteria in the pathogenesis of at least some exacerbations has been accepted but not understood largely on the basis of meta-analyses of antibiotic trials, evidence that long-term use of macrolides may reduce exacerbations, and a series of studies in COPD where novel ‘exacerbation’ isolates of NTHi were detected in some subjects by identifying specific serological responses. These ‘exacerbation isolates’ caused more destruction than those isolated from sputum collected in stable disease. In a study of established smokers, specific systemic antibody response over a winter period significantly correlated with exposure to NTHi. NTHi was the pathogen most commonly cultured from sputum and when present was quantitatively dominant. This is consistent with data using non-culture methods to identify the microbiome that appears restricted in COPD. Recent studies indicate that most, if not all, with COPD are colonised by NTHi. A ‘Vicious-Circle’ hypothesis of infection and inflammation has been generated to account for progressive disease. The importance of the relationship between microbes and the host response (including the role of epithelial cells) is of current interest. A recent review has viewed direct interaction between a microbe and the epithelial cell as the role of the ‘healthy soldier’ and the distortion of these interactions as the response of the ‘wounded soldier’. The inflammatory response can thus be protective or damaging depending on the efficiency of host immunity. The concept of ‘colonisation’ and ‘infection’ differs from that associated with invasive disease – at the bronchus mucosa, these terms refer more to whether or not there is clinical disease. Yet, residual uncertainties about the role of bacteria in promoting exacerbations are compounded by finding that bacterial colonisation in COPD is polybacterial, that there is a similar frequency of detection of bacteria in sputum collected in an exacerbation as in specimens taken from stable disease and that many exacerbations appear to be triggered by a virus infection. We hypothesise that the continuous presence of bacterial antigen in damaged airways stimulates a mucosal immune response that restricts expansion of colonisation. The level of inflammation within the airways is in part a dynamic reflection of the balance of a host–parasite relationship – if the inflammatory exudate exceeds a particular threshold, it is detected as an increase in volume and purulence of sputum (or an ‘exacerbation’ of COPD). An ‘exacerbation’ occurs when the mucosal immune response fails to contain colonisation, which then stimulates an inappropriate and excessive inflammatory response; in other words, purulent sputum reflects a hypersensitivity response to intrabronchial bacteria. Hypersensitivity responses with non-specific damage caused by an excessive recruitment of innate immune mechanisms in essence reflect a deficient adaptive-innate response to antigen, failing to clear that antigen, with the consequence of an excessive activation and accumulation of the innate components. These are well recognised for IgE (acute allergic reaction), IgG (arthus reaction) and Th1 (granulamatous reaction) responses. When this involves Th17 cells, the ‘hypersensitivity’ response is characterised by an accumulation of neutrophils (here, at a mucosal site). This hypothesis is supported by the demonstration that effector immune responses relevant to the control of bacterial colonisation are mediated by T lymphocytes generated from the gut-associated lymphoid tissue (GALT) in both rodent models and humans. These T cells relocate in the respiratory tract where they recruit and activate phagocytic cells, especially neutrophils. Recent studies in rodent models confirm that T cells from GALT that localise in lung tissue are Th17 cells. This subset of T cells is now recognised as being critical for lung protection by secreting interleukin 17 (IL-17) that acts on airways epithelium to induce neutrophil-specific chemokines and antibacterial substances. Neutrophils recruited into the bronchus undergo phenotypic change secreting large amounts of IL-8, tumour necrosis factor-α and IL-1,
which maintain lumenal protection through additional neutrophil recruitment, enhanced phagocytosis and prolongation of cell lifespan through autocrine mechanisms. IgA antibody appears irrelevant to protection as it is stimulated only over a narrow dose range and suppressed in the presence of inflammation. The relationship between bacteria and viruses in the respiratory tract is complex, but in addition to direct damage by virus, mechanisms of synergy are being described. For example, co-infection of mice with NTHi and influenza virus shows an interdependence with an increase in titre of both microbes, thus influencing the bacterial load. Accrediting an exacerbation to either ‘bacterial’ or ‘viral’ infection fails to recognise this synergy. Colonising bacteria – in particular NTHi – may be a final common path influencing the severity of both ‘bacterial’ and ‘viral’ infections. Studies using ‘infection-prone’ and ‘non-infection-prone’ phenotypes, as probes, have shown that those ‘prone’ to recurrent exacerbations have distinctive characteristics with respect to handling of colonising bacteria, which could influence clinical outcomes. Recent studies in smokers have demonstrated a ‘loop’ of gut-driven protection of the airways by showing an increase in NTHi-specific T cells through a winter season because of aspiration of bronchus content (including bacteria) into the gut (Fig. 1), confirming a unique antigen delivery system. Detection of elevated IgE antibodies against NTHi antigens in the serum of most with COPD (and many with steroid-resistant asthma) suggests that an allergic reaction to colonising bacteria may account for bronchospasm often noted in exacerbations. These observations support the old idea known as the ‘Dutch Hypothesis’ that intrinsic asthma and COPD are forms of the same disease.
A mucosal NTHi vaccine

The clinical trials described earlier used a high dose (3 × monthly cycles of six tablets, each tablet containing 10^{11} bacteria) of inactivated NTHi that did not stimulate a mucosal lgA antibody response in either normal subjects or those with chronic bronchitis but did stimulate a specific T-cell response. In rodent models, oral immunisation also selectively stimulated a specific T-cell response, which could transfer immunity to naive recipients. In human studies, a 3-log reduction in NTHi colonisation density followed oral immunisation with three cycles of NTHi. In other studies, there was a significant reduction in frequency of pathogen detection in sputum. The duration of this reduction was about 6–9 months, which was similar to the period of clinical benefit, indicating a need for annual pre-winter oral NTHi. Taken together with data from studies of recurrent acute bronchitis (earlier), these data are consistent with the idea that vaccine-induced reduction in colonisation in colonisation reduces the inflammation drive, providing a buffer to limit an inflammatory response to an intercurrent infection. The clinical evidence of vaccine-induced protection is clearest in subjects with moderate-to-severe COPD – the level of protection in either mild COPD or in other forms of septic airways disease requires further study.

Early studies of an oral NTHi vaccine in COPD used different uncharacterised isolates and gave variable benefit, with five of six studies showing protection when exacerbations were defined as ‘an increase in volume and purulence of sputum’. The most consistent benefit was a significant reduction in antibiotic usage: the only early study that included data on admission into hospital showed a significant reduction at about 90%. To improve the vaccine to react more broadly with NTHi isolates and be less dependent on concomitant colonisation, rat models of intratracheal or intestinal immunisation followed by respiratory infection challenge were used to screen vaccine candidates to identify HI-164 as broadly protective against a panel of NTHi isolates. The vaccine isolate HI-164 prevents penetration of NTHi into small airways and reduces parameters of inflammation in the airways of smokers. In subjects with COPD, protection is greatest against the most severe episodes that were defined as requiring corticosteroid therapy and/or admission into hospital in those with the most severe disease. A parallel study included subjects with less severe COPD and showed less dramatic benefit than in those with severe disease (unpublished data) possibly because a similar quantum of reduction in inflammation would have more clinical impact in those with the most compromised airways. Significant protection against recurrent exacerbations, duration of exacerbations and a reduction in antibiotic usage were recorded in those treated with the NTHi vaccine. In this trial, subjects continued on their background therapy, with about 90% on inhaled corticosteroid/bronchodilator combinations. Thus, observed benefit is additional to any current best practice therapy. There was a significant reduction in the isolation rate of all pathogens in sputum supporting earlier conclusions that enhanced protection is based on specific activation of sensitised T cells, which in turn enhances phagocytosis, a non-specific effector mechanism. While activation of mucosal protection is specific, the effector mechanism is non-specific, that is, phagocytes reduce all pathogens creating an ‘antisepsis’ environment within the bronchus lumen. In the mouse model of co-infection with NTHi and influenza virus, the synergistic increase in titre of both organisms was abrogated by pretreatment with oral NTHi. By reducing the level of inflammation within the airways, there is a shift in the severity of exacerbations. The apparent protection in the majority of those immunised reflects the high frequency of T-cell sensitisation in COPD. Protection by oral NTHi must not be confused with the oral polybacterial products used in Europe. The bacterial content of these latter products is about 1% of that in the NTHi oral vaccine. They are often lysates less geared to uptake into Peyer’s patches. They are short-lived polyclonal activators acting as super antigens inducing Treg cells, with no evidence of enhancing mucosal immunity and without proven benefit in COPD. In a direct comparison with oral NTHi vaccine, a polybacterial product was significantly less effective at preventing exacerbations of COPD.

Conclusion and future studies

This review discusses two major mechanisms that contribute to airways damage in COPD: one consequent on the other. The second involves bacterial colonisation of toxin-damaged airways, and the hypothesis presented that acute exacerbations in COPD reflect a particular outcome of the host–bacteria relationship. A critical part of the argument is that an oral NTHi vaccine downregulates intrabronchial inflammation protecting the patient from acute exacerbations. A central role for NTHi is postulated in the hypothesis providing a final common pathway for many, if not most, exacerbations irrespective of cause suggested by the size of the shift away from severe exacerbations following oral NTHi immunotherapy. A major task is to confirm these clinical observations in large clinical trials – such a study is current across 21 sites in Australia with 320 subjects with severe COPD. Any downside of oral immunotherapy remains to be
identified – to date, there is no evidence of bacterial replacement, immune tolerance or hypersensitivity reactions, but these must be carefully screened as more subjects are exposed to these new therapies. Of similar interest is testing the idea that oral NTHi alleviates symptoms in ‘treatment-resistant’ asthma. The basis of this postulate is reduction in recurrent episodes of recurrent wheezy bronchitis following oral NTHi, the presence of IgE anti-NTHi antibody in subjects with ‘treatment-resistant’ asthma (P. Howarth et al., unpubl. obs., 2010), a documented role for NTHi in promoting asthma in a rodent model and the reduction of NTHi ‘allergen’ in the lower airways following oral NTHi. Any effect of oral NTHi on progressive airways disease requires long-term study and the development of surrogate parameters. The use of culture-independent methods of quantitating the lung microbiome in such studies will be invaluable. The use of imaging technology may assist evaluating oral therapy on local disease because of microanatomic changes in bacterial communities. Technology is now available to study mechanisms of action as a molecular level for T-cell subsets, cytokine patterns, markers of inflammation and changes in the microbiome. NTHi is particularly able to form biofilms of structured extracellular DNA that may have particular relevance to hypersensitivity reactions, making assessment of the effect of enhanced immunity an important goal. In addition, the sequence of activation of tissue repair genes related to collagen deposition around small bronchi and bronchioloes, and destruction of support elastic tissue can be studied following oral NTHi. Thus, an oral vaccine that induces quantitative change in the pulmonary microbiome can be used not only to analyse changes in the microbiology but also as a probe on mechanisms of damage and repair in COPD and perhaps other lung diseases. As similar characteristics of inflammation occur in other diseases of both lower airways (e.g. bronchiectasis and cystic fibrosis) and upper airways (e.g. otitis media and recurrent sinusitis), as seen in COPD, these diseases may benefit from oral vaccines that reduce bacterial load, and these ideas need to be tested.

The most important management of COPD remains the cessation of smoking. Now, it may become possible to direct more effective therapy for those many with moderate-to-severe COPD who have long ceased smoking but continue with severe recurrent exacerbations and progressive airways disease. Indeed, as smoking can on occasion be perceived to reduce acute episodes, an oral vaccine may aid the process of giving up smoking. The disappointing history of identifying useful surrogate markers may improve as we gain a better understanding of relationship of the microbiome to the host response and the benefits of intervention strategies that modulate these relationships.

References


Clinical aspects of adult syphilis

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Abstract

Syphilis has been resurgent in Australian cities for the last decade. The varied presentation of this infection requires the physician to consider syphilis in the differential diagnosis of a broad range of conditions. Most cases are in men who have sex with men, young people in remote Aboriginal communities, or travellers from high-prevalence countries. The diagnosis and staging of syphilis require a sexual history, physical examination and interpretation of serological and microbiological findings. Penicillin remains the mainstay of effective treatment and has been used successfully for over 65 years. Treatment failure is rare, whereas reinfection is common. The interaction of syphilis and human immunodeficiency virus is complex, but standard therapy remains curative, and lumbar puncture is rarely required. Regular testing of high-risk individuals, contact tracing with empirical treatment and serological follow up are important components of syphilis control.

Introduction

Syphilis has been known to western medicine for over five centuries, but it remains with us despite the availability of a cheap single-dose cure for 65 years. The clinical manifestations of the capricious causative micro-organism, Treponema pallidum subspecies pallidum, continue to confound and elude physicians.

In Australia, the incidence of syphilis was at a historical low from the 1980s to the early 2000s, resulting in little clinical exposure to this previously common disease for most physicians in training. However, syphilis has resurfaced in our cities requiring that physicians include the possibility of syphilis in their differential diagnosis once again.

Therefore, the purpose of this review is to highlight the common and not-so-common clinical appearances of syphilis in adults, to review the role of diagnostic tools, to describe treatment options and to discuss modern controversies, such as the effects of human immunodeficiency virus (HIV) co-infection and the indications for lumbar puncture.

Epidemiology of syphilis in Australia

Prior to modern antibiotics, syphilis was widespread in the Australian community, with incidence rates of almost 200 per 100 000 reported in most states.\(^1\) The incidence dramatically dropped after the introduction of penicillin and was further reduced in the wake of the HIV epidemic, with only 4.2 notified cases of infectious syphilis per 100 000/year in 2004.\(^2\) However, since 2001, the number of reported cases in Australian cities has increased more than tenfold. In Sydney, six cases of infectious syphilis were reported in 1999, rising to 162 in 2003. This rise has been mirrored in other cities and is concentrated in men who have sex with men, a half of whom are also HIV positive.\(^3\) While the notifications have reached a plateau, 1098 cases of infectious syphilis were diagnosed nationally during 2010, 416 of which were in New South Wales.\(^2\)

In New Zealand, a similar pattern has emerged. Cases of syphilis increased by 150% between 2008 and 2009, predominantly in Auckland; however, surveillance is hampered as syphilis is not a notifiable disease in New Zealand.\(^4\)

The situation for Aboriginal and Torres Strait Islander Australians, particularly those living in remote settings, has historically been very different. In 2006, incidence rates were over 100 times that of the general Australian population and equivalent to the rates seen in the...
Serological tests for syphilis

Screening for syphilis in Australia utilises sensitive and specific treponemal tests, such as enzyme immune assay (EIA) that may contain both immunoglobulin G and immunoglobulin M components. These are then confirmed by supplementary specific tests, such as Treponema pallidum particle agglutination assay (TPPA) or the fluorescent treponemal antibody absorption test (FTA-abs). These tests do not, however, give any indication of disease activity and will normally remain positive for life regardless of treatment. Therefore, a non-specific test (sometimes called non-treponemal test), such as the rapid plasma reagin (RPR), or Venereal Disease Research Laboratory (VDRL) test, is used to provide a titre (e.g. 1:8, 1:16, and 1:32) that can be used to stage the infection, assess treatment response and detect reinfection. The RPR and VDRL are less sensitive for screening, are sometimes slower to rise in primary disease and may miss latent infection. All tests may produce false-positive results, so at least two types of test need to be positive in an asymptomatic person.

Clinical manifestations

Primary syphilis

The classic solitary chancre (ulcer) of primary syphilis is described as typically appearing between 9 and 90 days after exposure to the disease, with a median of between 21 and 30 days. It occurs at the point of inoculation, and thus may develop on the penis, vulva, cervix, anus or oral cavity depending on the type of sexual exposure. Because chancres are usually painless, many may not be noticed by the patient. Chancres are often associated with painless local lymphadenopathy. Multiple chancres may occur, and up to one quarter may be painful, especially if superinfected with skin flora, or with herpes simplex virus. Non-genital lesions may be mistaken for oral aphthous ulceration or perianal fissures, thus a sexual history and a high index of suspicion are required.

Within a few days of initial infection, T. pallidum begins to spread systemically and is detectable by polymerase chain reaction (PCR) in the blood in over 20% of those with primary disease. The chancre usually heals without scarring in 2–6 weeks, but it can recur (‘chancre redux’).

Immediate diagnosis may be made by dark-ground microscopy (not recommended for oral lesions due to commensal spirochaetes), but this is a dying art. A chancre swab collected for T. pallidum PCR testing is highly sensitive and specific, available in several reference laboratories and approved by the National Association of Testing Authorities, Australia. Direct immunofluorescence is an alternative. Syphilis serology should be performed but may be falsely negative in up to 10% of cases of primary syphilis, so it should be repeated if suspicion remains high.

Secondary syphilis

Secondary manifestations of syphilis may begin 3–5 months after infection, and in a third of patients with secondary disease, a residual chancre will be present. Untreated secondary syphilis may recur up to 2 years after infection, with 90% of recurrences in the first year. The list of possible features of secondary syphilis is vast. However, the majority of patients will have some evidence of systemic involvement, such as headache, malaise, mild fever, lymphadenopathy or sore throat. The typical maculopapular and subsequently scaly rash affecting the palms and soles occurs in over 75% of cases. In the pre-antibiotic era a variety of pustular and psoriatic forms of this rash were described and may still be seen today.

Other features of secondary disease include condylomata lata (pale elevated papules that develop at moist body orifices), patchy alopecia, oral mucosal erosions, mild hepatosplenomegaly and raised liver function tests, in particular alkaline phosphatase. Cardiovascular, bone and renal complications are all occasionally seen.

Neurological and ophthalmological complications can occur in secondary syphilis. Acute syphilitic meningitis is a cause of a lymphocytic meningitis and may result in transient cranial nerve deficit, the eighth cranial nerve being the most frequently affected. Uveitis, iritis, retinitis and optic neuritis are also described, and thus syphilis serology is a routine investigation for these disorders. At least 25% of patients with secondary disease will have cerebrospinal fluid (CSF) abnormalities if lumbar puncture is performed. However, in the absence of neurological or ophthalmological symptoms or signs, lumbar puncture is not necessary because standard treatment is curative.

Both specific treponemal serology and RPR/VDRL are universally positive in cases of secondary syphilis, and negative tests essentially rule out the diagnosis. Dark ground microscopy or T. pallidum PCR may be used to
detect directly the organism from abraded secondary skin lesions or condylomata lata, but both tests are less sensitive for dry lesions.

**Latent syphilis**

Latent syphilis is arbitrarily divided into early or late latent infection. For a case to be considered early latent, the patient must have no signs of primary or secondary disease and have positive syphilis serology, preceded by negative serology within the last 2 years (1 year in the USA)\(^1\) or recent contact with an infectious case. Early latent syphilis is considered infectious to sexual partners, whereas late infection is probably not. Asymptomatic patients with no evidence of recent negative serology or previous treatment are classified as having late latent infection, or syphilis of unknown duration. Because syphilis serology may remain positive for life even after successful treatment, reasonable effort should be applied to excluding prior infection.

In the pre-antibiotic era, one third of patients with syphilis progressed to symptomatic late disease (tertiary syphilis).\(^1\) This may manifest as neurosyphilis, cardiovascular syphilis or late benign syphilis (gummatous disease).

**Neurosyphilis**

This is perhaps the most feared complication of syphilis, and in the pre-antibiotic era, it affected 10% of men and 5% of women.\(^1\) CSF abnormalities may be present in the absence of symptoms or signs of neurological disease, and this is termed asymptomatic neurosyphilis. However, because lumbar puncture is not routinely recommended in early or latent disease in the absence of such symptoms or signs, this diagnosis is of limited clinical relevance. A detailed classification of neurosyphilis was proposed by Merritt in 1946.\(^1\)

Meningovascular neurosyphilis, typically occurring 5–12 years after initial infection (but occasionally as early as the first year), may cause a stroke-like syndrome. The territory of the middle cerebral artery is commonly affected, but meningeovascular syphilis can cause infarction secondary to endarteritis in any vessel, including those of the spinal cord. Focal or generalised seizures have also been documented. Syphilis serology should therefore be included in the work-up of young patients, or those from high-risk groups or high-risk countries.

Parenchymatous neurosyphilis is the cause of general paresis of the insane. During the interwar years, this disease was present in 10% of psychiatric admissions in Australia and led to over 200 deaths annually.\(^1\) Early symptoms include irritability, memory loss, personality change and insomnia. These may progress over many years to result in depression, confusion and disorientation, delusions of grandeur, paranoia and seizures. The symptoms may be combined with physical signs of facial tremors, papillary abnormalities, expressionless faces and hyperreflexia. Dementia progresses to death within months to years.

Tabes dorsalis is the other major consequence of untreated parenchymatous neurosyphilis. It peaks around 20 years after initial infection, but along with the other manifestations of neurosyphilis, it is now very rare in the western world. It is characterised by lightning pains, reduced deep tendon reflexes, paraesthesiae, sensory abnormalities of vibration and joint position sense, Charcot’s joints, and Argyll-Robertson pupils. Bladder and bowel disturbances are common. The classic visceral crises of tabes may result in severe gastrointestinal pains or laryngeal pain and hoarseness.

**Laboratory diagnosis of neurosyphilis**

Specific syphilis serology, such as EIA or TPPA, will be detectable in serum, and the serum RPR/VDRL will normally be positive. However, CSF analysis is required to confirm a case of neurosyphilis. The CSF white cell count (usually lymphocytes) is typically raised at >5 cells/mm\(^3\), protein levels are increased, and glucose normal or reduced. CSF VDRL confirms the diagnosis if positive, but it does not exclude active disease if negative. Some experts believe that a negative FTA-abs test on the CSF excludes the possibility of neurosyphilis.\(^1\) The interpretation of these results in patients with a bloody CSF tap requires caution, and the presence of coexisting HIV infection may itself impact on the CSF white cell count and protein. When considering lumbar puncture, it is worth reflecting that the likelihood of discovering CSF abnormalities if the serum RPR/VDRL is negative is reportedly very low.\(^1\) As early neuroinvasion by *T. pallidum* is common in the absence of abnormal CSF, the role of CSF PCR is yet to be determined.

**Cardiovascular syphilis**

Cardiovascular syphilis classically results in proximal aortic aneurysm and aortic regurgitation after 15–30 years of clinical latency. It previously accounted for 25% of those patients with symptomatic late infection,\(^1\) but it is rarely seen in high-income countries since the advent of effective antibiotics. Men are disproportionately affected at a ratio of 3:1. Because the aneurysms are associated with vascular wall thickening, they do not commonly dissect.
A routine chest X-ray in patients with syphilis serology over 55 years of age was once recommended, but studies have not found this to be of great utility in asymptomatic patients, so reserve it for those with signs of aneurysm or regurgitation. Other imaging modalities, such as echocardiogram or computed tomography, may be more sensitive if aneurysm is suspected.

Late benign syphilis (gumma)

Gummas are proliferative granulomatous lesions thought to represent an inflammatory response to small numbers of treponemes. They may occur cutaneously, when ulceration is common, or within any viscera or bone. They have become unusual in the antibiotic era, but it should be included in the differential diagnosis in patients with recalcitrant cutaneous ulcers or space occupying lesions and positive syphilis serology. Gummas may occur as early as the first year, but usually the incubation period is over 5 years.

Treatment of syphilis

Penicillin has remained the first line treatment for all stages of syphilis for over 65 years (Table 1). Oral doxycycline is an alternative in those who are penicillin allergic, intolerant of injections or non-pregnant. Azithromycin has shown to be at least as effective in producing serological cure as penicillin, but initial enthusiasm has waned with the demonstration of high levels of azithromycin resistance in regions where macrolide use is high. In Sydney, the prevalence of the azithromycin resistance gene A2058G on the 23 s ribosome of T. pallidum was present in over 85% of samples. Ceftriaxone has also shown to be successful at generating serological cure, but the data are more limited.

Pregnant women should receive the usual adult dose of penicillin and may require desensitisation to facilitate this. Patients with proven or probable symptomatic neurosyphilis, including those with ophthalmic signs, should receive a regimen that achieves high treponemocidal drug levels in the CSF.

Treatment response is monitored using the RPR or VDRL titres, and a fourfold (two-titre) reduction within 6–12 months is considered a cure. Non-response or rising titres after treatment are most commonly due to reinfecion. While most patients treated for infectious syphilis will have negative RPR/VDRL results at 12–24 months post treatment, a significant minority may have persistent low-level ‘serofast’ titres. Patients treated for late disease may exhibit static RPR/VDRL titres post treatment, particularly if the titre was very low (1:1, 1:2) prior to treatment.

The Jarisch–Herxheimer reaction is a post-treatment febrile cytokine-mediated reaction caused by endotoxin release from spirochaete lysis. It occurs 3–12 hours after treatment and is more common in secondary (60%) and primary (30%) infections than the other stages. Rigors and headache may also develop, and secondary lesions may transiently worsen. The reaction is managed by advising the patient in advance, non-steroidal anti-inflammatory as needed, and usually passes within 24 hours. In pregnant women, it may induce uterine contractions leading some authorities to recommend brief hospital admission during this period. The reaction has not, however, been associated with adverse pregnancy outcomes. Because the transient worsening of lesions might have serious consequences in important small vessels, such as those around the coronary ostium or optic nerve, British guidelines advise consideration of oral prednisolone therapy beginning 24 hours prior to antibiotic treatment in those with optic nerve or

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**Table 1** Recommendation for antibiotic treatment of syphilis (abbreviated from the British Association for Sexual Health and HIV (BASHH) 2008 guidelines)

<table>
<thead>
<tr>
<th>Stage of syphilis</th>
<th>Preferred treatment</th>
<th>Alternative treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary/secondary or early latent</td>
<td>1.8 g (2.4 MU) IM benzathine penicillin G single dose</td>
<td>Doxycycline 100 mg twice daily orally for 14 days Or Ceftriaxone 500 mg IM daily for 10 days</td>
</tr>
<tr>
<td>Late latent, cardiovascular or gummatous disease</td>
<td>1.8 g (2.4 MU) IM benzathine penicillin G 3x doses at weekly intervals</td>
<td>Doxycycline 100 mg twice daily orally for 28 days</td>
</tr>
<tr>
<td>Neurosyphilis†</td>
<td>2.4 g (2.4 MU) IM procaine penicillin G daily plus probenecid 500 mg 4 times a day orally for 14–17 days‡</td>
<td>Doxycycline 200 mg twice daily orally for 28 days</td>
</tr>
<tr>
<td></td>
<td>Or</td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td>3–4 MU benzyl penicillin IV every 4 hours for 14–17 days</td>
<td>Ceftriaxone 2 g IM or IV daily for 10–14 days</td>
</tr>
</tbody>
</table>

†Including ophthalmic disease.
‡Prefilled syringes with the correct dose for this regimen are difficult to obtain in Australia.
cardiovascular involvement in an attempt to dampen the inflammatory response. However, this has never been proven to be effective in reducing such a response, and the USA guidelines do not therefore make this recommendation.\textsuperscript{13}

**HIV and syphilis co-infection**

Syphilis is certainly more common in HIV-positive than in HIV-negative people in Australia,\textsuperscript{24} with theoretical concerns about immunodeficiency and reduced spirochete clearance from the CSF. Some studies suggest that HIV-positive individuals with syphilis are more likely to exhibit atypical manifestations, such as multiple changes\textsuperscript{25} or CSF abnormalities.\textsuperscript{26} However, these phenomena were well documented by syphilologists in the pre-HIV era. RPR/VDRL seroreversion after treatment may also be slower, leading to confusion about whether cure has been achieved. Intercurrent syphilis may temporarily increase HIV viral load and reduce CD4 count,\textsuperscript{27,28} although this will resolve after treatment. Raised viral load, along with the presence of mucosal lesions, may help explain the impact of syphilis on onward HIV transmission.

The main area of debate concerns whether neurosyphilis is more common in HIV-positive patients, and thus whether different treatment and investigation algorithms are required. One of the difficulties in interpreting the data, which is usually case series-level evidence, is that HIV itself can cause a host of neurological phenomena, and may cause a raised CSF white cell count and protein count. The diagnostic white cell count criteria for neurosyphilis in the context of HIV should accordingly be raised from &gt; 5 cells/mm\(^3\) to &gt; 20 cells/mm\(^3\).\textsuperscript{26} Furthermore, studies reporting neurological relapse of syphilis in HIV-positive patients after standard treatment rarely take into account the high rate of reinfection in this population. As in the HIV-negative host, HIV-positive patients with early syphilis frequently show CSF abnormalities. CSF abnormalities are more common with a CD4 &lt; 350 or an RPR &gt; 1:32 and less common on antiretroviral therapy. However, there are no longitudinal studies to determine the significance of these findings.

Given these findings, and the necessity of achieving high drug concentrations in the CSF to treat neurosyphilis, enhanced treatment protocols have been studied in HIV-positive patients. One study used standard therapy augmented with high-dose amoxicillin and probenecid, yet failed to show improved treatment responses.\textsuperscript{12} Current treatment guidelines recommend the same antibiotic regimens in both HIV-positive and HIV-negative patients.

Over the last 30 years, many thousands of HIV-positive patients (aware of their HIV status or not) have been treated with benzathine penicillin. If this regimen was ineffective, confirmed neurosyphilis would not be the rarity it is today. If HIV-positive patients display unusual neurological signs despite treatment for syphilis and exclusion of other pathology, they might be better served by commencing antiretroviral therapy; such therapy has shown to reduce significantly the risk of being diagnosed with neurosyphilis.\textsuperscript{29}

We believe therefore that lumbar puncture is indicated in HIV-positive patients with syphilis only in the presence of neurological or ophthalmological signs or lack of treatment response when reinfection has been excluded. This scenario is very uncommon in our service.

Given the high syphilis incidence in HIV-positive men who have sex with men, syphilis serology should be part of routine HIV monitoring bloods.\textsuperscript{30}

**Contact tracing and follow up**

Contact tracing is the responsibility of the diagnosing clinician, although it is usually done by the patient. The diagnosing clinician needs to support patients to inform sexual partners of their exposure and to provide the tools to achieve this. Online notification services can provide anonymity for those unwilling to make personal contact, for example, http://www.thedramadownunder.info, and sexual health services can assist with provider referral in difficult or complex cases. Contacts presenting within 3 months of exposure to infectious syphilis should be empirically treated as a case of incubating syphilis with the same regimen as for primary syphilis because serology may be falsely negative during this period. Contacts from greater than 3 months ago can defer treatment until serology results are known. How far back to contact trace depends on the disease stage and is summarised in Table 2.\textsuperscript{31}

Patients treated for syphilis should have repeat RPR/VDRL samples taken at 3, 6 and 12 months post-
treatment to ensure serological cure and to identify reinfection. If at ongoing risk, then at least an annual RPR testing is advised. All patients with syphilis should have a sexual health screen performed, including an HIV test.

**Conclusion**

The increase in cases of syphilis over the last decade necessitates renewed awareness of this infection and its varied manifestations. This is particularly so for patients from higher risk populations. Diagnostic and treatment algorithms are fortunately well established and offer high sensitivity, specificity and cure. Despite an interesting debate around the interaction of HIV and syphilis, there is little evidence to suggest HIV-positive patients who acquire syphilis should receive non-standard antibiotic regimens or be encouraged to undergo lumbar puncture in the absence of conventional indications. Regular screening, contact tracing and treatment remain important tools in identifying asymptomatic carriers, reducing the infectious period and preventing reinfection.12

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6 Communicable Diseases Branch, Queensland Health. Statewide communicable diseases surveillance report. 21 November 2011.


28 Read PJ, Fox J. Infectious syphilis unmasking drug resistance in an individual with long term virological
Increasing productivity, reducing cost and improving quality in elective surgery in New Zealand: the Waitemata District Health Board joint arthroplasty pilot

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Key words
elective surgery, quality, productivity, reducing cost, arthroplasty, performance.

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Abstract

Background: In 2010, Waitemata District Health Board piloted a new model of care for total hip and knee arthroplasties. The pilot was incentive based and clinically led. The participating surgeons and anaesthetists were responsible for increasing surgical throughput. The pilot aimed to increase productivity, reduce cost and increase quality for patients.

Aim: To compare costs and outcomes for elective hip and knee arthroplasties carried out at the pilot site (Waitakere Hospital) compared with the main District Health Board hospital site (North Shore Hospital (NSH)).

Methods: A retrospective matched cohort study of hip and knee replacements discharged between 1 July 2010 and 31 March 2011, comparing costs and outcomes at the pilot site compared with the NSH site. Only non-complex procedures were included, and routinely collected data were used.

Results: One hundred and seventy-seven hip replacements (77 NSH, 100 pilot) and 158 knee replacements (88 NSH, 70 pilot) were analysed. Total inpatient event costs were 12% and 17% lower for hip and knee replacements, respectively, at the pilot site compared with NSH. Significant reduction in operation length (39% hip, 36% knee) and length of stay (38% hip, 39% knee) were found in the pilot groups compared with NSH.

Conclusion: Implementation of an innovative new model in a public hospital setting has produced significant increases in productivity and reduced overall costs. This model could potentially be used in other public healthcare settings for non-complex elective surgery.

Introduction

Increasing financial constraints within a context of increasing healthcare demand necessitate the introduction of more efficient and productive models for delivering healthcare.1 In elective surgery, the need to increase productivity and reduce costs while maintaining or improving patient outcomes has become a focus of research.2-7

In New Zealand, improved access to elective surgery is one of the six key health targets introduced by the New Zealand Government.8 In 2010, the Waitemata District Health Board piloted a new model of care for total hip and knee arthroplasties. The pilot was incentive based and clinically led. The participating surgeons and anaesthetists were responsible for increasing surgical throughput. The pilot aimed to increase productivity, reduce cost and increase quality for patients.

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Conclusion: Implementation of an innovative new model in a public hospital setting has produced significant increases in productivity and reduced overall costs. This model could potentially be used in other public healthcare settings for non-complex elective surgery.

Funding: None.
Conflict of interest: None.
The District Health Board (DHB) was faced with the challenge of increasing the surgical intervention rate within a fixed capitated budget. This triggered a clinician-led proposal fundamentally to review how elective surgery services were being provided. WDHB undertook an extensive investigation of productive operating models through literature review and site visits. Several key points were noted from this investigation: first, leadership is an important driver for creating change; second, the financial impact of incremental improvements to operating room delays is only realised if overtime payments are reduced or additional procedures can be performed within the same timeframe; and third, incentives need to be aligned with defined outputs.

WDHB piloted a new model of elective surgery commencing in April 2010 for total hip joint arthroplasties and expanded it in July 2010 to include total knee joint arthroplasties. The aim of the pilot was to improve access to elective surgery for the Waitemata population and improve the level of care provided to patients while reducing costs. Increasing throughput was to be achieved through creating radical rather than incremental improvement.

A previously unutilised operating theatre was commissioned at Waitakere Hospital (WTH) in West Auckland. This site was chosen, as elective events would not be interrupted by acute surgery as can occur at WDHB’s main site, North Shore Hospital (NSH). This paper presents a matched cohort analysis that compares total costs and outcomes for elective joint arthroplasties performed at WTH (pilot) and NSH for the period 1 July 2010 through 31 March 2011.

Methods

Study design and setting

The design was a retrospective matched cohort study of hip and knee replacement patients at the pilot site compared with the NSH site. Only non-complex, elective events were undertaken at the pilot site. The inclusion criteria were therefore designed to ensure that similar cases were selected for comparison.

Selection of hip replacement participants

Inpatient events were selected, which met the following criteria:
- Discharge date between 1 July 2010 to 31 March 2011
- Procedure performed at pilot site or NSH
- The theatre event had a primary theatre procedure of ‘hip replacement’
- Elective admission type (from waiting list)
- Coded to the diagnosis-related group (DRG) I03C: hip replacement without catastrophic or severe comorbidities or complications
- American Society of Anaesthesiologists (ASA) Grade <3

Patients meeting the earlier criteria, with long lengths of stay (>11 days) were individually evaluated to ensure that they presented as non-complex cases. One NSH case meeting the earlier criteria and with a length of stay of 35 days was excluded due to complexity (a congenital chronic dislocated hip).

Selection of knee replacement participants

Inpatient events were selected, which met the following criteria:
- Discharge date between 1 July 2010 to 31 March 2011
- Procedure performed at pilot site or NSH
- One theatre visit only within the inpatient stay (two excluded from NSH sample and none from pilot sample on this criterion)
- The theatre event had a primary theatre procedure of ‘joint replacement – knee’
- Elective admission type (from waiting list)
- Coded to the DRG I04Z: knee replacement and reattachment. (This DRG does not distinguish complex from non-complex; therefore, ASA grade and age were used as inclusion criteria.)
- ASA grade <3
- Age <80 years. Initial analysis showed that the two knee subgroups were not comparable in age because the pilot group had very few patients aged 80+ years (n = 3), while NSH had many (n = 27), and therefore, this criterion was added to improve comparability.

Patients meeting the earlier criteria with a patient comorbidity and complication level of 4 (high) were individually evaluated by reading the electronic discharge summary to ensure that they presented as non-complex cases. Six NSH cases were excluded due to complexity, specifically chronic kidney disease, psoriatic arthritis, stroke (postoperatively), femur fracture, trauma and elevated body mass index. Knee revisions and bilateral knee replacements were excluded through the theatre procedure criterion earlier.

Data collection

Routinely collected data were used for this study. Patient events meeting the earlier criteria were...
extracted from the patient management system, Patient Manager v1.86. The following data were extracted:
- Patient and clinical characteristics: age, ethnicity, ASA grade, complexity and comorbidity level, DRG, weighted inlier equivalent separation (WIES); the case weighting applied to each case based on DRG and length of stay.
- Outcome measures: in-theatre minutes (the time from when the patient is wheeled into theatre until they are wheeled out), length of stay, total cost per procedure, acute readmissions within 28 days, and community physiotherapy and occupational therapy referrals.

The following costing data were extracted from the WDHB costing system for the sample of inpatient events and then grouped into five cost categories:
- Medical costs, Surgical Department – an apportionment of the total Surgical Department costs (mainly Senior Medical Officer (SMO), registrar and house surgeon costs) based on length of time in theatre, presence of a pre-admission clinic appointment and time on a ward. It includes theatre time and ward time.
- Medical costs, Anaesthetic Department – an apportionment of the total Anaesthetic Department costs (mainly SMO and registrar costs) based on length of time in theatre and presence of an anaesthetic pre-admission clinic appointment. It includes theatre time and pre-admission clinic time.
- Theatre costs – includes nurses, anaesthetic technicians, theatre consumables and theatre overheads allocated based on length of time the patient was in theatre.
- Ward costs – includes nurses and other ward staff, ward consumables (excluding implant costs), and ward overheads allocated based on the number of days the patient was in hospital.
- Other costs – includes radiology, pharmacy, allied health and clinical records handling.

The costing system uses full absorption costing, which means all service costs, including management overheads, are allocated to patient events. Costs at both sites contain a share of DHB overhead cost.

Costing system costs were used for all cost groups apart from two:
- For the pilot cases, theatre and ward medical time costs were replaced with a package of care fee paid to consultants under the contract.
- Implant cost. The costing system applies a weighted average cost for implants to orthopaedic events divided into four categories: major, minor laparoscopic, minor other and mini. The sample events, all categorised as ‘major’, received an implant cost of $4781 through the costing system. More accurate differential costing was available from only one of the two sites (NSH), where implant costs are recorded per procedure into a database.

The average cost of hip implants for the NSH sample was $5361, substantially higher than the costing system allocation. There was no reason to believe that the WTH site hip implants would be less expensive, and therefore, the costing allocation was replaced with the higher cost for both sites.

Additional data were extracted to analyse theatre utilisation. The procedures in the sample were performed on theatre sessions that included non-sampled patients because they did not fit the inclusion criteria. While pilot sessions were exclusively hips and knees, NSH procedures were performed on mixed orthopaedic lists. All theatre sessions in the sample were extracted and also the WIES value, length of stay and primary procedure for all theatre procedures in those sessions. The duration (full day/half day) of the sessions was also extracted.

All pilot sample events were examined to identify transfers back to the main hospital, NSH. The WTH is not equipped to handle acute or complex surgical events. Therefore, if patients seen under the pilot programme required complex care, they were transferred back to NSH. Costs for inpatient events at NSH as a result of a WTH transfer were added to the WTH pilot event costs.

Data analysis
Descriptive analyses included calculation of means, medians and percentages. Tests of mean difference were undertaken using student’s t-test or Kruskal–Wallis test if appropriate. All analyses were performed using Stata 9.2 (Statacorp LP, College Station, TX, USA) and SAS 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results
Patient and clinical characteristics
Three hundred thirty-five patient events were analysed: 177 hip replacements (77 NSH, 100 pilot) and 158 knee

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hip replacements</th>
<th>Knee replacements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pilot n = 100</td>
<td>NSH n = 77</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>63.1</td>
<td>64.9</td>
</tr>
<tr>
<td>Range</td>
<td>25–92</td>
<td>36–85</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European (%)</td>
<td>85.0</td>
<td>79.2</td>
</tr>
<tr>
<td>Other (%)</td>
<td>15.0</td>
<td>20.8</td>
</tr>
<tr>
<td>Gender female (%)</td>
<td>50</td>
<td>57</td>
</tr>
<tr>
<td>ASA 1 and 2 (%)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

ASA, American Society of Anaesthesiologists; NSH, North Shore Hospital.
replacements (88 NSH, 70 pilot). The mean ages in both procedures were similar between the pilot and NSH groups (P-values 0.35 and 0.27 respectively). The distributions of events by ethnicity showed no significant differences in the pilot and NSH groups (Table 1).

### Outcome measures

The median operation length was significantly shorter in the pilot groups compared with the NSH group (100 minutes pilot vs 166 minutes NSH for hips, 109 minutes pilot vs 173 minutes NSH for knees). Median length of stay was significantly shorter in the pilot group compared with the NSH group for both cohorts (three vs five for both hip and knee). Twenty-five patients were readmitted within 28 days. Reasons for readmission included suspected or actual infection (four pilot, two NSH), suspected or actual deep vein thrombosis (five pilot, four NSH), cardiac (one pilot, two NSH), medical other (two pilot, two NSH), and other (three NSH). The study did not have the power to show a significant difference in readmission between sites. Fewer of the pilot events required follow up by community physiotherapy and occupational therapy compared with the NSH events – see Table 2.

The 335 patients underwent their procedures on 176 theatre sessions. An additional 272 procedures were also performed in those theatre sessions. Analysis of all procedures in the theatre sessions was undertaken to compare the number of procedures per list between the pilot and NSH sites. The pilot site averaged 4.0 procedures per full day session (all arthroplasties), while the NSH site averaged 3.2 procedures per full day session, of which arthroplasties constituted 64%. That is, the average NSH list had two joint arthroplasties plus one or two lower WIES procedures. The mean WIES value of sessions in the pilot site was 14.1: 53% more than the NSH mixed sessions that earned a mean WIES value of 9.2. The difference in average length of stay between the sites (3.3 pilot, 4.9 NSH) indicates that the additional WIES value in the pilot lists did not arise from longer lengths of stay (Table 3). The creation of specific surgeon-anaesthetist teams in the pilot site is evidenced in the number of surgeon/anaesthetist combinations; the pilot procedures were performed by 16 combinations, while the NSH procedures had 98 combinations.

### Cost and revenue

Two knee replacement patients transferred from the pilot site to NSH. The costs of their NSH inpatient event were added to their WTH inpatient event costs. Total inpatient event costs were 11% lower for hip replacements and 17% lower for knee replacements at the pilot site (P-values both <0.0001). The costs of surgical service time was significantly higher on the pilot site for both cohorts ($2200 vs $1579 hip, $2225 vs $1754 knee, P-values for both <0.0001), while the cost of anaesthetic service time was slightly lower in the pilot ($1200 vs $1219 hip, $1200 vs $1295 knee, P-values 0.3962 and 0.0003 respectively). Theatre costs were far lower in the

<table>
<thead>
<tr>
<th>Measure</th>
<th>Hip replacement</th>
<th>Knee replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in theatre (minutes, mean)</td>
<td>104</td>
<td>166</td>
</tr>
<tr>
<td>Time in theatre (minutes, median)</td>
<td>100</td>
<td>166</td>
</tr>
<tr>
<td>Length of stay (days, mean)</td>
<td>3.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Length of stay (days, median)</td>
<td>3.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Readmissions within 28 days (%)</td>
<td>8.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Community physiotherapy after discharge (%)</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>Community occupational therapy after discharge (%)</td>
<td>32</td>
<td>79</td>
</tr>
</tbody>
</table>

†On test of median difference (Kruskal–Wallis test) at 95% confidence level. NSH, North Shore Hospital.

### Table 3 Theatre throughput and team measures – all procedures on the sample theatre sessions

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pilot</th>
<th>NSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of full day theatre sessions (of sample events)</td>
<td>52</td>
<td>124</td>
</tr>
<tr>
<td>Total number of procedures in sessions</td>
<td>207</td>
<td>400</td>
</tr>
<tr>
<td>Procedures in selected sessions also in sample (%)</td>
<td>82.1</td>
<td>41.3</td>
</tr>
<tr>
<td>Mean number of procedures in each session</td>
<td>4.0</td>
<td>3.2</td>
</tr>
<tr>
<td>WIES value per session (mean)</td>
<td>14.1</td>
<td>9.2</td>
</tr>
<tr>
<td>Procedures in sessions that are arthroplasties (%)</td>
<td>98.0</td>
<td>63.8</td>
</tr>
<tr>
<td>ALOS of all procedures on these lists</td>
<td>3.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Surgeon/anaesthetist combinations</td>
<td>16</td>
<td>98</td>
</tr>
</tbody>
</table>

ALOS, average length of stay; NSH, North Shore Hospital; WIES, weighted inlier equivalent separation.
pilot theatres ($2321 vs $3828 hip, $2336 vs $4057 knee, P-values for both <0.0001) because of higher throughput, shorter operating times and fewer in-theatre staff. Ward costs were about one-third lower in the pilot ($1324 vs $1860 hip, $1387 vs $2103 knee, P-values for both <0.0001) because of shorter ward stays (Table 4). Any difference in implant cost was not measurable because implant costs are not individually tracked to each theatre event at the pilot site (see Methods).

**Discussion**

Overall, the new model of care significantly increased elective productivity while reducing costs for total hip and total knee arthroplasty at the pilot site compared with the NSH site. This project was clinician driven. Clinicians rose to the challenge of creating a model of care that could reduce the overall cost of surgery performed and the speed at which it could be done. Cost reduction was able to be achieved by increasing throughput (thereby reducing the allocation of fixed costs to each procedure), reducing bed days used and reducing staffing mix (by non-use of junior medical staffing). Overall costs were reduced even though the remuneration given to surgeons/anaesthetists participating in the pilot was considerably higher than standard medical contracts offered at the DHB.

Cost critical to cost reduction was the need to involve clinicians in the understanding of what the drivers of costs were and giving them the ability to influence those costs directly. The new model of care was different to that performed at NSH in that:

1. Specific surgeon–anaesthetist teams were created to perform the operating lists. These teams were accountable for driving the overall theatre throughput. At NSH, the operating team combinations often differ.
2. Surgeons and anaesthetists were contracted using an alliance-contracting arrangement. The alliance-contracting concept used in industry is defined as incentive-based relationship contracts characterised by risk-sharing, openness and an alignment of interests. This contracting arrangement provided the template for consultant-led clinical care for the entire patient episode, assigned surgeon/anaesthetist responsibility for throughput targets, and promoted a reduction in consumable costs. Consultants were paid a package of care fee for their service, negotiated in the knowledge of all costs of the episode of care that they could influence. The total costs had to fall below the envelope of the WIES value available. The WIES is a value assigned to each episode of inpatient care based on the expected cost of the case (used to derive a national price for each procedure). At NSH clinicians are paid according to a standard Multicollective Employment agreement. Remuneration for surgeons and anaesthetists at NSH is not specifically tied to surgical throughput.
3. No junior medical staff participated in the care of the patients either in the pre-admission workup, operating or postoperative care. The anaesthetist/surgeon team provided all necessary medical care during the inpatient admission. At NSH, junior staff often participates in the pre-assessment, operating and postoperative care of elective patients.
4. Nurses were upskilled as the main theatre assistants in the pilot operating rooms. At NSH, a combination of junior medical staff and nurses are often theatre assistants.

Table 4 Cost and revenue differences

<table>
<thead>
<tr>
<th>Cost/revenue group</th>
<th>Hip replacement</th>
<th>Knee replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pilot</td>
<td>NSH</td>
</tr>
<tr>
<td>n = 100</td>
<td></td>
<td>n = 77</td>
</tr>
<tr>
<td>Costs – mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgeon (and RMO)</td>
<td>2200 (0)</td>
<td>1579 (452)</td>
</tr>
<tr>
<td>Anaesthetist time – surgery</td>
<td>1200 (0)</td>
<td>1219 (223)</td>
</tr>
<tr>
<td>Anaesthetic pre-admit</td>
<td>171 (183)</td>
<td>218 (180)</td>
</tr>
<tr>
<td>Theatre</td>
<td>2321 (639)</td>
<td>3828 (668)</td>
</tr>
<tr>
<td>Implant</td>
<td>5361 (0)</td>
<td>5361 (0)</td>
</tr>
<tr>
<td>Ward</td>
<td>1324 (318)</td>
<td>1860 (855)</td>
</tr>
<tr>
<td>Other</td>
<td>1181 (251)</td>
<td>1369 (1439)</td>
</tr>
<tr>
<td>Total cost</td>
<td>13 758 (792)</td>
<td>15 434 (2397)</td>
</tr>
<tr>
<td>Revenue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case weights (mean WIES)</td>
<td>3.55</td>
<td>3.55</td>
</tr>
<tr>
<td>National price 2009/10 ($)†</td>
<td>15 657</td>
<td>15 657</td>
</tr>
</tbody>
</table>

†National price per WIES of $4410.38. NSH, North Shore Hospital; RMO, Resident Medical Officer; SD, standard deviation; WIES, weighted inlier equivalent separation; —, P-value not applicable.
5 There was a dedicated allocation of surgical beds to receive the patients post-surgery. At NSH, beds are not ring-fenced for elective procedures.

6 Patients with similar procedures were cohorted on theatre lists and then in the same four-bed room on the ward. This allowed surgeons to streamline theatre practice, and patients to support and even compete with each other in their recovery. Cohorting by procedure is not common at the main hospital.

The absence of junior staff undoubtedly contributed to the efficiency of the model. There is no suggestion by the authors that this model would be applicable to the complex elective patients. With junior staff, it is important to separate service requirements from teaching requirements. For the more complex and highly morbid patients, junior doctors are required to assist the management of those patients. In addition, the clinical leaders of this project recognise that training of junior staff is critical to the future workforce requirements of the profession. In addition, there are ethical imperatives including the Hippocratic Oath that require those in training to receive teaching from those more skilled and fully trained. To this end, the DHB is now investigating how best to give this training in a high throughput elective surgical environment.

The findings presented here are consistent with other findings identified from the international literature. For example, clinician-led team programmes in specialty surgical areas have led to significant cost savings elsewhere, and a team approach has been shown to increase productivity in areas such as total joint arthroplasty and neurosurgery.

McRoberts and Porteous, and Larsen et al. also reported significant reductions in length of stay because of arthroplasty service redesign. Reduced length of stay did not result in an increased readmission rate or increased morbidity, as reported by Larsen et al. and Hunt et al.

**Limitations**

The study has several limitations. Being a retrospective study, it was not possible to randomise patients to the pilot or standard models of care. Therefore unmeasured differences leading to confounding could exist between the sample groups. All routinely collected data that indicated complexity were considered when setting the inclusion criteria. Prospective data collection or randomisation to models of care would have reduced this potential bias.

The pilot introduced many changes simultaneously; site change, separation of elective from acute surgery, incentive payments for consultants, retraining for nursing staff, and the establishment of a dedicated team. It is unknown which of these factors contribute the most to the process and cost improvements, that is, which can be considered intrinsic to the model, and which, confounders. Further studies could try to quantify the impact that each variable had.

The allocation of costs through the costing system may not reflect actual resource consumption to a high degree of accuracy. For instance, ward costs allocate the same cost to each bed day, irrespective of actual nursing input on each day. As Viapiano explains, cost allocation schemes can over-cost or under-cost surgical procedures. However, the WDHB costing system conforms to national standards for costing practice, developed to allow inter-DHB comparative analysis of costs.

The mean WIES value difference per theatre list was reported to indicate whether the higher number of procedures per pilot list was due to the greater complexity of other procedures on the NSH site. However, the WIES value is an indicator of the complexity of the whole inpatient event, including the ward stay; not strictly a measure of theatre complexity. However, given that the average length of stay of the NSH events was longer than the pilot site events, these measures support the conclusion that the pilot site theatre sessions are substantially more productive than the NSH elective theatre sessions.

The sample was not large enough to determine whether the reduced length of stay was associated with a higher readmission rate. However, Chard et al. found poorer outcomes for patients in standard NHS care compared to independent sector treatment centres, when controlling for casemix.

The study only used available data, and therefore the reporting of patient outcomes was limited to readmissions and community allied health rehabilitation. Pilot cases were less likely to receive community physiotherapy and occupational therapy than standard care cases, but there has been no examination of the reasons for the difference.

**Contribution of the study to the international literature**

No other New Zealand study compares operating room throughput, in-theatre time, length of stay and costs between sites or models of care for joint arthroplasty. This study shows that innovation in elective surgery in a public hospital in New Zealand can lead to cost reductions across the whole inpatient event and a significant increase in productivity. This model could be applied in other public hospital settings. Issues such as the willingness of clinicians and managers to lead and participate in such a project, the capability of physically being able to separate
elective and acute surgical streams and the overall acceptability of this model both within and external to the specific hospital setting would need to be explored.

**Conclusion**

Implementing productive models of care into the public sector is challenging but possible. The Waitakere Pilot of non-complex arthroplasty cases has improved theatre throughput, reduced length of stay, and reduced overall costs, when compared to standard care. This model could potentially be extended to other publicly-funded hospital sites for non-complex elective surgery.

**Acknowledgements**

The authors thank the surgeons, anaesthetists, nurses and anaesthetic technicians who contributed to the success of this pilot study. William Leung of the University of Auckland provided valuable guidance for the creation of this study. Dr Lifeng Zhou of Waitemata DHB provided statistical analysis and advice.

**References**

Mediastinal staging of non-small-cell lung cancer among
Australasian thoracic physicians: clinical practice and
constraints on minimally invasive techniques

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Key words
non-small-cell lung carcinoma, endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA), mediastinal staging, access to health services.

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Abstract

Background/Aim: We determined current practice among Australasian thoracic physicians in the mediastinal staging of non-small-cell lung cancer (NSCLC). We focused on the availability of endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) and constraints to its use, as there has been no systematic analysis regarding the availability and uptake of this new technology among thoracic physicians.

Methods: Physician members of the Thoracic Society of Australia and New Zealand were emailed a survey seeking their current approach to three scenarios requiring mediastinal staging of NSCLC. Respondents were also asked for their preferred investigation for each scenario if any current constraints were removed. Relevant demographic information was sought.

Results: We received 164 responses from 512 Australasian physicians (34%). Without constraints, EBUS-TBNA was the preferred investigation for all three clinical scenarios, but only 33% of respondents had access to EBUS-TBNA. Constraints included lack of availability and lack of expertise. Reduced EBUS-TBNA access was associated with a number of clinician factors.

Conclusions: Australasian thoracic physicians prefer EBUS-TBNA for the mediastinal staging of NSCLC, but access to EBUS-TBNA services is limited. We recommend targeted measures to improve access to EBUS-TBNA use and optimise mediastinal staging of NSCLC.

Introduction

In patients diagnosed with non-small-cell lung cancer (NSCLC) without distant metastases, accurate mediastinal staging is critical for the selection of appropriate treatment. Traditionally, surgical mediastinoscopy, supported by conventional transbronchial needle aspiration (TBNA: otherwise known as Wang needle aspiration), has been the investigation of choice because computed tomography (CT) and positron emission tomography (PET) have significant false positive and false negative results.1 In the 1990s, endoscopic ultrasound-fine needle aspiration (EUS-FNA) was introduced, allowing ‘real-time’ minimally invasive mediastinal evaluation.2 A further development occurred in 2004 with endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA).3 This minimally invasive technique is able to evaluate the majority of mediastinal nodes necessary for NSCLC staging with the same accuracy as mediastinoscopy but far less morbidity.4 As a day-case procedure, it is less costly,3 and well tolerated.5

We sought to determine current Australasian practice regarding mediastinal staging and were particularly interested in the view of clinicians regarding the role of EBUS-TBNA, and whether there were any constraints to its use.

Methods

An email survey was conducted through the kind cooperation of the Thoracic Society of Australia and New Zealand, which represents thoracic physicians in Australasia. All adult physician members of the society were emailed a web link to the survey (Supporting Information Table S1) on three separate occasions between 28 October and 15 December 2009. The survey was closed after 3 months.

The survey invited responses on the clinicians’ scope of practice, availability of conventional TBNA (Wang needle
aspiration) and EBUS-TBNA as well as attendance at lung oncology multidisciplinary meetings (MDMs). Respondents were also asked to indicate their current staging approach to three clinical scenarios of NSCLC causing suspected malignant lymphadenopathy in different locations within the mediastinum (Fig. 1). Each scenario was framed to indicate that histological staging was necessary for patient management. We also surveyed their ideal staging investigation if there were no constraints to their choice. Respondents could indicate the constraints that limited their choice of investigation.

Only responses from specialist physicians practising in Australasia were analysed as the focus of our study was on Australasian clinical practice.

Ethics approval was not required as no patients were involved and the survey was anonymous.

Results are presented using summary statistics. Results were analysed by Stata version 11 (StataCorp, College Station, TX, USA) using a Chi-squared test with a two-sided significance level of 0.05.

Results

Clinician practice

We received 164 responses out of a total 512 specialists practising adult respiratory medicine in Australia and New Zealand on the Thoracic Society of Australia and New Zealand roll (response rate 32%). The majority of respondents practised in a tertiary metropolitan hospital (59.8%), whereas 12% of respondents were based in rural/regional hospitals (Table 1). 27% of respondents saw more than 20 patients per year with mediastinal lymphadenopathy that required tissue diagnosis (Table 2). Of respondents involved in the care of lung cancer patients, 66% regularly attended a lung cancer MDM. Conventional TBNA was available to 66% of respondents, but EBUS-TBNA to only 34% of respondents (Table 2).

In general, location of practice, the volume of patients seen with mediastinal lymphadenopathy and MDM attendance predicted EBUS-TBNA availability. Tertiary metropolitan clinicians had the highest access to EBUS-TBNA, 49% compared with 11% for all other groups (P < 0.00001) (see Table 2). Of the respondents who saw more than 20 patients per year with mediastinal lymphadenopathy that required tissue diagnosis, 42% (22 of 53) had EBUS-TBNA available at their workplace compared with only 27% (30 of 113) of those who saw less than 20 such patients (P = 0.0527). Clinicians who attended a lung cancer MDM had greater access to an EBUS-TBNA service 42% (41 of 97) than those who did not 14% (7 of 51) (P = 0.0004).

Figure 1 Survey respondents were asked to first indicate which procedure a patient would undergo in their current practice for the three illustrated scenarios. Respondents were then asked to identify the procedure they would choose if there were no constraints to their procedural selection. (a) A patient is diagnosed with left-sided non-small-cell lung cancer. A staging computed tomography-positron emission tomography (CT-PET) reveals a 20-mm right hilar (Station 10R) lymph node requiring tissue diagnosis. (b) A patient is diagnosed with right-sided non-small-cell lung cancer. A staging CT-PET reveals a 20-mm right para-tracheal (Station 4R) lymph node requiring tissue diagnosis. (c) A patient is diagnosed with a non-small-cell lung cancer. A staging CT-PET reveals a 30-mm sub-carinal (Station 7) lymph node requiring tissue diagnosis.
There were clear links between clinician location, attendance at MDMs and volume of patients seen with mediastinal lymphadenopathy. Seventy-seven per cent of those who saw more than 20 patients per year with mediastinal lymphadenopathy requiring tissue diagnosis were based in tertiary metropolitan hospitals. Eighty-six per cent of those who saw more than 20 patients per year with mediastinal lymphadenopathy that required tissue diagnosis regularly attended an MDM compared with 53% of those who saw less than 20 such patients ($P = 0.0001$).

Rural practitioners had the least access to both EBUS-TBNA (5%) and a lung cancer MDM (30%; see Table 2). Interestingly, non-tertiary metropolitan hospital physicians had high MDM attendance rates (78.6%), but low EBUS-TBNA availability (0%).

### Clinical scenarios

Scenario 1 required pathologic evaluation of right hilar lymphadenopathy (station 10R – Fig. 1a). EBUS-TBNA was chosen by most respondents (46%) as their preferred investigation, but when constraints were removed, this increased to 90% of respondents (Fig. 2a).

Scenario 2 involved 20-mm right paratracheal lymphadenopathy, or station 4R (Fig. 1b). Mediastinoscopy was chosen by most respondents (52%) as their preferred investigation, but when constraints were removed, 92% chose EBUS-TBNA (Fig. 2b).

Scenario 3 involved 20 mm subcarinal lymphadenopathy, or station 7 (Fig. 1c). Conventional TBNA was chosen by most respondents (42%) as their preferred investigation, but when constraints were removed, 70% chose EBUS-TBNA (Fig. 2c).

The constraints preventing respondents from utilising EBUS-TBNA as their first investigation in their clinical practice were lack of availability (identified by over 90% of respondents), lack of expertise (over 50% of respondents) and increased cost (15%).

### Discussion

We draw five conclusions from our survey of Australian thoracic physicians. Firstly, EBUS-TBNA is the investigation of choice in the mediastinal staging of NSCLC in the minds of most respondents. Secondly, this enthusiasm for EBUS-TBNA is tempered by lack of available services. Thirdly, when EBUS-TBNA is not available, the approach to mediastinal staging is not standardised. Fourthly, availability of conventional TBNA is also limited, albeit not to the same degree as EBUS-TBNA. Lastly, a third of respondents who manage lung cancer do not regularly attend an MDM. On the basis of these findings, we recommend targeted measures to improve access to EBUS-TBNA services and streamline mediastinal staging of NSCLC patients.

Our results show EBUS-TBNA is the investigation of choice in the mediastinal staging of NSCLC among thoracic physicians. This preference for EBUS-TBNA reflects its advantages over alternative investigations. Compared with mediastinoscopy or thoracoscopy, costs and morbidity are lower. Unlike EUS-FNA, EBUS-TBNA can examine the hilar lymph node stations and the endobronchium. EBUS-TBNA also has a much higher accuracy than EUS-FNA in evaluating the right paratracheal region.

Despite clinician preference for EBUS-TBNA, there are major constraints to EBUS-TBNA access. Two-thirds of respondents report having no access to EBUS-TBNA services. It is understandable that clinicians at peripheral or rural locations do not have direct access to EBUS-TBNA, as such a service requires considerable expense and training, and adequate throughput to maintain procedural

### Table 1: Predominant workplace

<table>
<thead>
<tr>
<th>Predominant workplace</th>
<th>n  = 164</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary metropolitan hospital</td>
<td>98 (59.8%)</td>
</tr>
<tr>
<td>Non-tertiary metropolitan hospital</td>
<td>14 (8.5%)</td>
</tr>
<tr>
<td>Rural/regional</td>
<td>20 (12.2%)</td>
</tr>
<tr>
<td>Private hospital/clinic</td>
<td>32 (19.5%)</td>
</tr>
</tbody>
</table>

### Table 2: Availability of endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) and conventional TBNA, attendance at multidisciplinary meeting (MDM) and high volume of patients with mediastinal lymphadenopathy as determined by workplace

<table>
<thead>
<tr>
<th>All respondents (n = 157)</th>
<th>Tertiary metropolitan hospital (n = 93)</th>
<th>Non-tertiary metropolitan hospital (n = 14)</th>
<th>Rural/regional (n = 20)</th>
<th>Private hospital/clinic (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBNA available at workplace</td>
<td>53 (33.8%)</td>
<td>46 (49.5%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Conventional TBNA available at workplace</td>
<td>103 (65.6%)</td>
<td>68 (73%)</td>
<td>10 (71%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Regularly attend MDM</td>
<td>97 (61.8%)</td>
<td>71 (81%)</td>
<td>11 (79%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>High volumet practitioner</td>
<td>43 (27.4%)</td>
<td>33 (35%)</td>
<td>3 (21%)</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

†Reviews more than 20 patients per year with mediastinal lymphadenopathy requiring tissue diagnosis.
competence. What is more concerning is that many clinicians at tertiary metropolitan hospitals also indicate limited access to EBUS-TBNA (49.5%). The implication is that many patients requiring mediastinal staging of NSCLC may not receive an appropriate minimally-invasive staging procedure, even when managed at a tertiary metropolitan centre.

The main reasons for limited access offered by the respondents included lack of availability and lack of expertise. Cost was also considered a major barrier by approximately 15%; however cost-benefit analyses have suggested that, given the greater cost of mediastinoscopy, capital expenditure to establish EBUS-TBNA would be cost beneficial after as few as 16 procedures.

Certain clinician groups were particularly disadvantaged in accessing EBUS-TBNA. EBUS-TBNA was only available to 5% of rural practitioners and, notably, was not available to any non-tertiary metropolitan hospital.

**Figure 2** (a) Preferred procedure for obtaining tissue diagnosis for clinical Scenario 1 (see Fig. 1a). Fifty per cent of respondents indicated their choice of modality was limited by constraints and thus went on to choose a modality not limited by any constraints. (b) Preferred procedure for obtaining tissue diagnosis for clinical Scenario 2 (see Fig. 1b). Forty-seven per cent of respondents indicated their choice of modality was limited by constraints and thus went on to choose a modality not limited by any constraints. (c) Preferred procedure for obtaining tissue diagnosis for clinical Scenario 3 (see Fig. 1c). Thirty-six per cent of respondents indicated their choice of modality was limited by constraints and thus went on to choose a modality not limited by any constraints.
practitioner. Clinicians who did not attend an MDM and clinicians who saw less than 20 patients per year with mediastinal lymphadenopathy also had less access to EBUS-TBNA.

It is highly likely that the location of practice, the volume of patients seen with mediastinal lymphadenopathy and MDM attendance are not independent predictors of EBUS-TBNA availability, but rather act as covariates. For example, those who saw more than 20 patients per year with mediastinal lymphadenopathy were also mainly based at tertiary metropolitan hospitals and had greater access to MDMs.

Our survey highlights that 34% of respondents involved in the care on lung cancer patients do not regularly attend a lung cancer MDM. This should cause concern, as there is evidence that MDM care improves outcomes for lung cancer. Access to MDM care was lower among rural clinicians as well as clinicians in a private care setting.

We specifically surveyed MDM attendance because we suspected these meetings serve as a conduit for EBUS-TBNA referral. As we expected, in rural and private practice settings, low attendance rates at MDMs do in fact coexist with poor access to EBUS-TBNA. Unexpectedly, however, clinicians at non-tertiary metropolitan centres have high MDM attendance rates but poor access to EBUS-TBNA. We conclude that factors other than MDM attendance also influence EBUS-TBNA availability.

We found that when EBUS-TBNA is not available, the approach to mediastinal staging of NSCLC among clinicians in Australasia is variable. This is seen in the range of responses to each of our clinical scenarios. Scenario 1 presented right hilar lymphadenopathy. If EBUS-TBNA is not available, we agree that thoracoscopy or conventional TBNA would be reasonable alternatives. Although more respondents chose mediastinoscopy over either thoracoscopy or conventional TBNA, we are concerned that adequate access to the hilar nodes by mediastinoscopy may be technically difficult. EUS-FNA is clearly inappropriate for right sided lesions.

Scenario 2 involved right paratracheal lymphadenopathy. Without EBUS-TBNA availability, we agree that mediastinoscopy or conventional TBNA are appropriate alternatives. Scenario 3 involved subcarinal lymphadenopathy. Without EBUS-TBNA availability, most respondents chose conventional TBNA, although some opted for mediastinoscopy. The only published study to compare directly EBUS-TBNA with mediastinoscopy for staging of lung cancer indicated sensitivity of mediastinoscopy was inferior to EBUS-TBNA for evaluation of subcarinal LN. Given this, and the greater morbidity associated with surgical staging, we feel EBUS-TBNA (where available) or conventional TBNA should be considered the primary investigative modalities at this LN station.

Our data regarding conventional TBNA availability (66%) is more positive than European studies, where conventional TBNA is performed by only a minority of pulmonologists. Nevertheless, there is still room for improvement given one third of respondents are without access to such a service. Previously described barriers to widespread utilisation of conventional TBNA include inadequate training and a perception of poor utility among bronchoscopists. What role should conventional TBNA play in staging of NSCLC? Where EBUS-TBNA is available, we recommend it over conventional TBNA. In centres without EBUS-TBNA, we recommend that conventional TBNA be performed concurrently at the time of diagnostic bronchoscopy, as it has been shown to obviate the need for invasive staging in a significant proportion of patients. However, for patients with known NSCLC, we see little role for conventional TBNA as a dedicated staging procedure and patients should be referred directly for EBUS-TBNA instead.

We favour EBUS-TBNA over conventional TBNA for two reasons. While early studies describing diagnostic accuracy of conventional TBNA in expert hands reported excellent sensitivity comparable with that of EBUS-TBNA, subsequent studies have generally been unable to replicate this, and a recent meta-analysis of conventional TBNA for staging of NSCLC determined a pooled sensitivity of just 39%. Operator proficiency has a significant effect on diagnostic performance. Unlike EBUS-TBNA, several factors strongly influence the accuracy of conventional TBNA, including LN position and size, and prevalence of mediastinal metastases. No studies have previously compared accuracy of EBUS-TBNA against conventional TBNA for staging of lung cancer, however diagnostic yield of EBUS-TBNA for suspected sarcoidosis has been proven to be higher than conventional TBNA, despite use of a 19-gauge needle for conventional TBNA.

Furthermore, for NSCLC staging, the real costs of conventional TBNA may actually be greater than that of EBUS-TBNA. Recent cost analyses have demonstrated that because of the proportion of patients with known NSCLC undergoing staging with conventional TBNA that will require further procedures because of non-diagnostic TBNA, EBUS-TBNA is still cost-beneficial compared with TBNA.

**Implications for practice**

If optimal mediastinal staging of NSCLC is currently hampered by limited EBUS-TBNA access in Australasia,
should new EBUS-TBNA services be introduced more widely? Our survey results suggest that the rational answer to this question may hinge on clinician location.

Rural clinicians who responded to our survey had limited participation at lung cancer MDMs. We therefore suggest that rural physicians develop regional networks with tertiary metropolitan centres with EBUS-TBNA using teleconferencing technology. Involvement at MDMs in this manner should improve overall care and also facilitate appropriate EBUS-TBNA referrals. Private clinicians too had low attendance rates at lung cancer MDMs and should also be encouraged to participate in such meetings for the same reasons.

Non-tertiary metropolitan hospital practitioners had high rates of MDM attendance, but still reported limited access to EBUS-TBNA. Here, the best solution may be to establish links with a tertiary centre offering such services, perhaps within existing health networks.

Finally, half the survey respondents who worked in tertiary centres had no EBUS-TBNA available. Here there may be two alternatives. Firstly, the clinician could develop referral links with another tertiary centre with an EBUS-TBNA service. Alternatively, a new service could be introduced at that centre, depending on the availability of funding, clinician interest and adequate patient throughput.21

**Limitations**

We deliberately surveyed respondents by asking about ‘EBUS-TBNA availability at their workplace’ without differentiating on-site availability from off-site availability at a referral centre. It is therefore theoretically possible that a respondent might reply to this question in the negative, even if he routinely had access to EBUS-TBNA services in a nearby referral centre. However, we do not believe this to be the case in the majority of our respondents, as the lack of EBUS-TBNA availability was confirmed by the large proportion of survey respondents who changed their preferred investigation to EBUS-TBNA when current constraints to practice were removed.

While EBUS-TBNA access is clearly limited, our study cannot quantify the magnitude of this problem with accuracy. The survey was not designed to do so, and response rates were less than 50%. However, we feel it is unlikely that clinicians who did not respond to our survey would have had better access to EBUS-TBNA than the cohort that did respond.

We cannot prove that the factors associated with limited EBUS-TBNA availability in our survey play a causative role. However, we suggest the link between EBUS-TBNA availability and MDM attendance is an important one to consider, and improving MDM attendance is important in its own right to provide optimal lung cancer care.

Our results have been interpreted in the context of Australasian practice. In Australia and New Zealand, thoracic physicians are involved in the work-up of lung cancer patients. The use of CT-PET is widespread, and multidisciplinary-team management considered best-practice. Endoscopic techniques, such as EBUS-TBNA and EUS-FNA, are often carried out by physicians, but also sometimes by surgeons. The ‘tyranny of distance’ between major cities often necessitates self-sufficient services in each location, even when population density is not high. For all these reasons, caution must be exercised before extrapolating our findings and recommendations to other settings.

**Conclusion**

Australasian thoracic physicians demonstrate a preference for EBUS-TBNA for the mediastinal staging of NSCLC. This preference reflects the numerous advantages of this minimally-invasive technique. However, access to EBUS-TBNA services is currently limited, resulting in many patients undergoing more invasive staging procedures than are necessary. Factors limiting access include the lack of availability and expertise. Among rural and private clinicians, low attendance rates at a lung cancer MDM may also be contributory.

We recommend increasing access to appropriate EBUS-TBNA use in a step-wise fashion. Rural and private practitioners should develop links with tertiary lung cancer centres with EBUS-TBNA. Non-tertiary metropolitan centres without access to EBUS-TBNA should develop referral links to tertiary centres with EBUS-TBNA facilities. Tertiary metropolitan centres currently without access could either develop similar links, or consider the introduction of an EBUS-TBNA service at their own institution.

**References**


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### Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Survey questions

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Sleep, blood pressure and obesity in 22 389 New Zealanders


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Key words
sleep, blood pressure, obesity, human.

Abstract
Aim: To determine the relationship of sleep disorders with blood pressure and obesity in a large, relatively healthy, community-based cohort.

Methods: A cross-sectional study was undertaken using data from 22 389 volunteer blood donors in New Zealand aged 16–84 years. Height, weight, neck circumference and blood pressure were measured directly, and data on sleep and other factors were ascertained using a validated self-administered questionnaire.

Results: Even in a relatively young, non-clinical cohort, lack of sleep (34%), snoring (33%), high blood pressure (20%) and obesity (19%) are common. After adjusting for relevant confounders, participants at high risk of sleep apnoea had double the odds of having high blood pressure but only in participants over 40 years. Very low and high quantities of sleep are also associated with high blood pressure. Even after controlling for neck circumference, self-reported sleep apnoea, sleep dissatisfaction and low amounts of sleep are associated with a higher body mass index.

Conclusions: Obesity and hypertension have significant associations with a variety of sleep disorders, even in those less than 40 years of age and after adjusting for a wide range of potential confounders.

Introduction

There is growing evidence of a relationship between sleep and health.1,2,3 The direction of this relationship is uncertain, with conditions such as hypertension and obesity a possible cause and consequence of sleep disorders. For example, it is well recognised that obesity increases sleep apnoea4,5 and daytime sleepiness,6,7 but it has also been suggested that shortened sleep duration alters weight regulation, increasing obesity.8,9 Additionally, although some studies have shown associations between raised blood pressure and sleep disorders in those over 30 years of age,10,11 this relationship has not gained universal acceptance.12,13

Previous studies evaluating the association between sleep and health are primarily based on relatively small study samples or particular population subgroups, such as samples with predominantly middle-aged or older adults.5,10,11 Most previous studies have also been unable to examine the influence of potential confounding influences likely to affect associations between sleep and health, such as alcohol consumption and smoking.4,12-14

The current analysis of data from the New Zealand Blood Donors’ Health Study (NZBDHS) examines the relationship between participants at high risk for sleep apnoea and sleep complaints (sleep quantity, sleep satisfaction and insomnia) and both obesity and blood pressure in a large, relatively young, yet diverse, community-based sample.

Methods

Recruitment procedures and methodology of the NZBDHS are detailed elsewhere.15 In brief, 22 389 people volunteering to donate blood (81% response rate) aged 16 years or older were recruited into the study from April 1998 to October 1999 at blood collection points managed by the Northern Regional Blood Service in the Northland, Auckland, Waikato and Bay of Plenty regions of New Zealand.16 The criteria for accepting volunteer blood donation in New Zealand are in accordance with international guidelines (http://www.nzblood.co.nz). In general, the donor must be in good health to ensure the safety of both the donor and recipient. The study was approved by regional ethics committees, and all participants provided informed consent.
Height, weight, neck circumference and blood pressure were measured by study staff using strictly standardised procedures. Blood pressure, using a calibrated electronic monitor (Omron T2 (Omron Health Care, Vernon Hills, IL, USA)), was the average of two readings taken during the day, after the participant had been seated for at least 5 minutes. High blood pressure was classified as a systolic blood pressure (SBP) of 140 mmHg or more or a diastolic blood pressure (DBP) of 90 or more. A self-administered questionnaire was used to solicit details regarding the presence of snoring, sleep apnoea, sleep complaints (satisfaction, quantity and insomnia), alcohol consumption, smoking, use of marijuana or other illegal drugs and depression (Appendix I). Based on previous studies investigating the predictive power of questionnaire data for sleep apnoea, sleep questions were used to categorise two subgroups: one with a high likelihood and one with a low likelihood of sleep apnoea. Participants at high risk of sleep apnoea were defined as self-reported choking or stopping breathing whilst asleep and were referred to as self-reported sleep apnoea or participants at high risk of sleep apnoea throughout. Detailed instruments used in previous research and the pilot study informed its content. Participants were also asked (yes/no) if they had ever been told by a doctor that they have or have had a heart attack, a stroke, epilepsy, migraine or diabetes.

**Statistical analysis**

Associations between sleep disorders and both blood pressure and body mass index (kg/m²) (BMI) were assessed in two ways, reflecting the uncertainty in the causal pathway between sleep and these two major cardiovascular risk factors. First, mean SBP and DBP and BMI (all continuous variables) were compared between various sleep groups; for example, those with and without self-reported sleep apnoea. General linear models were used for these comparisons, adjusting for a multiple set of potential confounders: sex, BMI (excluded from analysis where BMI was the dependent variable), neck circumference, ethnicity, alcohol consumption, smoking, marijuana or other illicit drug use, depression, insomnia, marital status and certain medical conditions (heart disease, stroke, diabetes, epilepsy, migraines). Second, odds ratios (OR) for sleep disorders (e.g. sleep apnoea) were estimated, from logistic regression models, for ordinal categories of BMI and dichotomous categories for blood pressure (hypertension and non-hypertensive; for all other analysis, blood pressure remained continuous) using the same adjustments. In both analyses, interaction with age, sex, BMI and blood pressure was tested by adding interaction terms to the statistical models.24

**Results**

Demographic data and physical measurements were available from all 22 389 NZBDHS participants (Table 1). Completed questionnaires were received from 96% of the NZBDHS participants. Incomplete responders were not different to responders in age (mean difference: 0.1 years 95% confidence interval (CI), −0.3 to 0.5) or sex (male: full responders 46% vs missing 47%). The proportions of people in this study reporting major illness were very low (0.2% reporting a history of heart attack, 0.2% a history of stroke and 0.4% diabetes), compared with the general population as noted in the New Zealand Health Survey in 2002 (10.4% heart disease, 2.1% stroke, epilepsy, migraine or diabetes).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>12 012 (54)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10 377 (46)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>16–24</td>
<td>8040 (36)</td>
</tr>
<tr>
<td></td>
<td>25–39</td>
<td>5305 (24)</td>
</tr>
<tr>
<td></td>
<td>40+ (maximum 84)</td>
<td>9041 (41)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15–19</td>
<td>664 (3)</td>
</tr>
<tr>
<td></td>
<td>20–24</td>
<td>8901 (40)</td>
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<td></td>
<td>25–29</td>
<td>8382 (38)</td>
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<tr>
<td></td>
<td>30–34</td>
<td>3104 (14)</td>
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<td>Alcohol (CAGE)</td>
<td>Low risk</td>
<td>18 837 (86)</td>
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<tr>
<td></td>
<td>High risk</td>
<td>3035 (14)</td>
</tr>
<tr>
<td>Marital Status</td>
<td>Married or living with partner</td>
<td>10 750 (51)</td>
</tr>
<tr>
<td></td>
<td>Divorced/separated/never married</td>
<td>10 395 (49)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non-smoker</td>
<td>17 593 (85)</td>
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<td>Current smoker</td>
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<tr>
<td>Blood Pressure</td>
<td>Normotensive</td>
<td>15 425 (80)</td>
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<tr>
<td></td>
<td>Hypertensive†</td>
<td>3883 (20)</td>
</tr>
<tr>
<td>Depression</td>
<td>Not depressed</td>
<td>18 161 (83)</td>
</tr>
<tr>
<td></td>
<td>Depressed</td>
<td>3633 (17)</td>
</tr>
<tr>
<td>Sleep Quantity</td>
<td>&lt;one full night’s sleep per week</td>
<td>791 (4)</td>
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<tr>
<td></td>
<td>One to six full night’s sleep per week</td>
<td>15 788 (74)</td>
</tr>
<tr>
<td></td>
<td>&gt;six full night’s sleep per wk</td>
<td>4730 (22)</td>
</tr>
<tr>
<td>Snoring</td>
<td>Present</td>
<td>7322 (33)</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>Present</td>
<td>1382 (6)</td>
</tr>
<tr>
<td>Sleep satisfaction</td>
<td>Want more</td>
<td>13 111 (60)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Present</td>
<td>4511 (20)</td>
</tr>
</tbody>
</table>

Hypertension systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90, BMI, body mass index; CAGE, four clinical interview questions focusing on Cutting down, Annoyance by criticism, Guilty feeling and Eye-openers.
stroke, 4.3% diabetes). This study had a higher proportion of participants aged 16–39 years than the New Zealand Health Survey (60% vs 36% respectively). However, while the proportion of smokers was somewhat lower in the NZBDHHS compared with the New Zealand Health Survey (15% vs 23%), high blood pressure (20% vs 21%) and obesity (19% vs 21%) were similar (Table 1).

A total of 33% of NZBDHHS participants reported being told they snore loudly. Either breathing pauses or choking during sleep was reported by 6% (Table 1). Insomnia with sleep dissatisfaction and the absence of depression, alcohol dependence, self-reported sleep apnoea or illicit substance use (i.e. primary insomnia), was present in 20% (n = 4511).

### Sleep and blood pressure

Without adjusting for any potential confounders, snorers (compared with non-snorers) had higher SBP (mean difference 8.0 mmHg, 95% CI 7.5 to 8.5) and higher DBP (5.2 mmHg, 95% CI 4.9 to 5.5). However, snorers were older (mean difference: 9.0 years, CI 8.6 to 9.4), larger (BMI: 2.6 kg/m², CI 2.4 to 2.7), neck circumference: 2.6 cm, CI 2.5 to 2.7), more likely to be male (59% vs 39%), more likely to be alcohol dependent (four clinical interview questions focusing on Cutting down, Annoyance by criticism, Guilty feeling and Eye-openers (CAGE) (Appendix I): 12% vs 7%) and current smokers (18% vs 16%). Participants reporting sleep apnoea (compared with those not reporting sleep apnoea) also exhibit all of these characteristics and generally to an even greater degree than snorers (mean difference for participants with self-reported sleep apnoea compared with snorers: age 1.8 years, CI 0.9 to 2.8; BMI 0.4 kg/m², CI 0.2 to 0.7; neck circumference 0.8 cm, CI 0.6 to 0.1; male 67% vs 59%; CAGE 20% vs 12%; and current smoker 21% vs 18%). When adjusting for relevant confounders (including age, sex, BMI, neck circumference, ethnicity, alcohol consumption, smoking, marijuana or other illicit drug use, depression, insomnia, marital status, heart disease, stroke, diabetes, epilepsy and migraines). The number of full night’s sleep per week, that is zero full night’s sleep per week minus one to six full night’s sleep per week.. There was no significant interaction between age and BMI for any of the sleep disorders, therefore, a single mean value is presented across all ages.

### Table 2  Adjusted mean differences† (with 95% confidence intervals) for systolic blood pressure (SBP) and body mass index (BMI) in participants with or without various sleep disorders

<table>
<thead>
<tr>
<th>Age</th>
<th>Sleep apnoea (SA)</th>
<th>Sleep satisfaction</th>
<th>Insomnia (I)</th>
<th>Sleep quantity‡</th>
<th>Sleep quantity‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SA minus non-SA</td>
<td>Want more – Satisfied</td>
<td>I minus non-I</td>
<td>(0) – (1 to 6)</td>
<td>(7) – (1 to 6)</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–24</td>
<td>-1.4 (-3.6 to 0.7)</td>
<td>-1.4 (-2.3 to -0.5)</td>
<td>-1.0 (-1.9 to -0.1)</td>
<td>0.3 (-3.2 to 3.8)</td>
<td>0.6 (-0.5 to 1.7)</td>
</tr>
<tr>
<td>25–39</td>
<td>1.8 (-0.2 to 3.7)</td>
<td>-0.2 (-1.2 to 0.7)</td>
<td>-1.3 (-2.5 to -0.2)</td>
<td>0.7 (-1.8 to 3.2)</td>
<td>-0.2 (-1.3 to 0.9)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>2.3 (1.1 to 3.5)</td>
<td>-2.2 (-2.9 to -1.4)</td>
<td>-1.1 (-2.1 to -0.2)</td>
<td>2.8 (1.3 to 4.3)</td>
<td>2.3 (1.5 to 3.1)</td>
</tr>
<tr>
<td>BMI§</td>
<td>All ages</td>
<td>0.2 (0.0 to 0.5)</td>
<td>0.2 (0.1 to 0.3)</td>
<td>0.1 (-0.0 to 0.2)</td>
<td>0.3 (-0.1 to 0.6)</td>
</tr>
</tbody>
</table>

†Adjusted for sex, BMI (excluded from analysis as BMI was the dependent variable), neck circumference, ethnicity, alcohol, smoking, marijuana and illicit drug use, depression, insomnia, marital status, heart disease, stroke, diabetes, epilepsy and migraines. §The number of full night’s sleep per week, that is zero full night’s sleep per week minus one to six full night’s sleep per week. There was no significant interaction between age and BMI for any of the sleep disorders, therefore, a single mean value is presented across all ages.
Table 3  Adjusted odds ratios† (with 95% confidence intervals) for various sleep disorders for hypertensive compared with non-hypertensive participants by age group

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sleep apnoea (present)</th>
<th>Sleep satisfaction (want more)</th>
<th>Insomnia (present)</th>
<th>Sleep quantity (low)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>16–24</td>
<td>1.02 (0.55 to 1.88)</td>
<td>0.69 (0.53 to 0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–39</td>
<td>1.88 (0.95 to 3.69)</td>
<td>1.65 (1.19 to 2.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td>2.06 (1.12 to 3.81)</td>
<td>1.24 (0.94 to 1.65)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†See Table 2 (includes body mass index).

Sleep and BMI

After controlling for the same potential confounders (including neck circumference and interactive terms) to determine the relationship between self-reported sleep apnoea and BMI, participants reporting sleep apnoea had a higher BMI compared with those without self-reported sleep apnoea (mean difference 0.2 kg/m², CI 0.0 to 0.5) (Table 2). Without controlling for neck circumference, the difference was greater (1.4 cm, CI 1.1 to 1.7). Similarly, with respect to insomnia, BMI did not have an effect modification with age, but there was a trend for those with insomnia to have a higher BMI (0.1, CI –0.0 to 0.2). Participants who were not satisfied with the amount of sleep they obtained had a higher BMI (0.2, CI 0.1 to 0.3). There was an association between sleep quantity and BMI, such that the more full night’s sleep per week, the lower the BMI (no full night’s sleep per week: mean 26.2, CI 25.9 to 26.5; 1–6 nights per week: 26.0, CI 25.9 to 26.0; seven nights per week: 25.8, CI 25.7 to 25.9). Similar results were obtained with logistic regression where having a high BMI (35 kg/m² or more) was associated with higher odds of reporting sleep apnoea (1.55, CI 1.09 to 2.19), sleep dissatisfaction (1.47, CI 1.18 to 1.82), low sleep quantity (less than five full night’s sleep per week; 1.54, CI 1.26 to 1.88), but not insomnia (1.10, CI 0.87 to 1.39), compared with participants with BMI 20–24 kg/m² (Table 4).

Discussion

Even in this relatively young (60% less than 40 years of age), healthy sample, the prevalence of snoring, self-reported sleep apnoea and being overweight was remarkably high. One in three participants reported snoring, a finding within the range of previous studies often of older, less healthy samples.26–33 In addition, one in five exhibited high blood pressure, more than 50% were overweight, and one in five were obese.

High blood pressure has been proposed as an important link between sleep disorders and adverse vascular events.10,11 Previous large and well-designed studies have established a clear relationship between sleep apnoea and blood pressure in participants over 30 years34 and 40 years of age.1 We have been able to support and extend these findings with similar results for people aged 40 years and over. In addition, the large number of young participants in the NZBDHS allowed us to show the absence of this association in participants aged less than 40 years. We were also able to establish a relationship between sleep duration and blood pressure by showing that both very low and very high quantities of sleep are associated with high blood pressures. Again, this relationship was only evident in participants aged 40 years and over. Additionally, after controlling for the effects of multiple potential confounders, insomnia was associated with a small but significantly lower blood pressure compared with those without insomnia, with a similar effect for sleep dissatisfaction. There are limited data on the relationship between insomnia and blood pressure,35,36 and subsequently identifies an area for further investigation. Interestingly, while low sleep quantity was associated with higher blood pressure, both insomnia and sleep dissatisfaction were associated with lower blood pressures. Although there is a limited literature relating insomnia and high blood pressure, the strongest data in a smaller sample suggest that objective sleep duration of less than 6 hours is associated with an increased risk of developing hypertension.37 Complaints of insomnia but actual sleep greater than 6 hours were not associated with development of hypertension. In addition, complaints of sleep dissatisfaction (complaints of poor sleep without complaint of insomnia for 1 year) with sleep duration greater than 5 hours were also not associated

Table 4  Adjusted odds ratios† (with 95% confidence intervals) for various sleep disorders by body mass index (BMI) group (reference group: 20–24 kg/m²)

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Sleep apnoea (present)</th>
<th>Sleep satisfaction (want more)</th>
<th>Insomnia (present)</th>
<th>Sleep quantity (low)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–19</td>
<td>1.50 (0.92 to 2.45)</td>
<td>1.03 (0.82 to 1.28)</td>
<td>0.88 (0.70 to 1.12)</td>
<td>0.97 (0.78 to 1.19)</td>
</tr>
<tr>
<td>20–24</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>25–29</td>
<td>1.23 (1.02 to 1.47)</td>
<td>1.17 (1.07 to 1.29)</td>
<td>1.00 (0.91 to 1.11)</td>
<td>1.19 (1.08 to 1.30)</td>
</tr>
<tr>
<td>30–34</td>
<td>1.35 (1.06 to 1.73)</td>
<td>1.36 (1.18 to 1.57)</td>
<td>1.12 (0.96 to 1.31)</td>
<td>1.41 (1.23 to 1.61)</td>
</tr>
<tr>
<td>35+</td>
<td>1.55 (1.09 to 2.19)</td>
<td>1.47 (1.18 to 1.82)</td>
<td>1.10 (0.87 to 1.39)</td>
<td>1.54 (1.26 to 1.88)</td>
</tr>
</tbody>
</table>

†See Table 2. There were no significant interactions involving body mass index, therefore, values are presented across all ages. ‡Less than five full night’s sleep per week.
with developing hypertension. Our findings are congruent with these observations from smaller studies using objective polysomnography. The slightly lower blood pressure in those complaining of insomnia and sleep dissatisfaction was small but unexpected. It may reflect an atypical ‘insomnia’ group with a wide variety of confounders being excluded (including depression, alcohol and drug use) and both insomnia and sleep dissatisfaction being heavily influenced by patient perception, and not strongly associated with sleep quantity. Whilst these associations provide important information regarding sleep and blood pressure, they do not identify the mechanism for such changes, which may relate to complex bidirectional associations between sleep apnoea, sleepiness, inflammation and insulin resistance.

This study also provides strong supporting evidence for the role of body habitus (BMI, neck circumference) in sleep apnoea. Interestingly, increasing BMI was associated with both snoring and self-reported sleep apnoea in a clear dose–response relationship, even after controlling for neck circumference. This result may indicate a non-localised or indirect effect of increased adiposity on sleep apnoea risk, in addition to the local physical effect of a large neck compressing the airway, or an influence of adiposity on respiratory regulation. Reduced sleep quantity and insomnia were also associated with higher BMI, supporting a previous smaller study conducted in primary care. Excessive loss of sleep leading to hormonal changes and higher BMI has been suggested as a causative mechanism. Unlike the association between various sleep disorders and blood pressure, the association between sleep disorders and BMI did not differ with age. This result may reflect a more immediate biochemical or mechanical effect of BMI on blood pressure compared with the associations between some sleep disorders and high blood pressure, which appear to take more time to develop, hence the association was only evident after 40 years of age.

Limitations of this study relate to the recruitment strategy, daytime measurement of blood pressure only, the inherent inability of cross-sectional studies to determine causal relationships and the reliance on self-reporting of many lifestyle behaviours and sleep disorders. While blood donors may not be representative of the broader population, they are a large, diverse, non-clinical, community-dwelling sample. Blood pressure measurements in the current project were taken predominantly during the day, and we cannot exclude the possibility that these may differ from blood pressure measurements taken at night. Unfortunately, due to the large number and geographical distribution of participants, it was not possible to perform polysomnography. Instead, we used questionnaire data to categorise patients into high and low likelihood of sleep apnoea groups. Questions on loud snoring and stopping breathing during sleep predicted an apnoea index of greater than 10, with a sensitivity of 83% and a specificity of 63%. Other investigators showed subjects reporting never snoring and no observed apnoea were 35 times less likely to have sleep apnoea than subjects with positive responses. Crocker et al. found that observed apnoea in sleep-clinic patients was the most powerful predictor of an apnoea index greater than 15, and these patients were nearly 20 times more likely to have OSA than those subjects not reporting this symptom in a non-clinical sample. In a population study in Australian men, 10% of men that have reported never snoring or have not witnessed apnoea had a respiratory disturbance index greater than 5, in contrast to 66% of men with a history of frequent snoring and apnoeas. Whilst many studies have confirmed self-reported apnoea as one of the most powerful predictors of sleep apnoea, the sensitivity and specificity have been lower (60% sensitivity, 63% specificity). Additionally, a systematic review of various predictors of sleep apnoea showed similar sensitivity and specificity to self-reporting, utilising non-questionnaire techniques, such as oximetry (sensitivity 87%, specificity 65%). Therefore, despite the varying sensitivities and specificities in the earlier studies and the variable source of data (both community and clinic cohorts), it is likely that the division into high- and low-likelihood sleep apnoea groups using questionnaire data would produce two groups with markedly different prevalence in sleep apnoea. Furthermore, the inherent misclassification of some participants in comparison with polysomnography is likely to have diluted the magnitude of the observed effects, and subsequently, under-represent the true deleterious effects of sleep apnoea. These potential limitations are offset by accessing the largest cohort examining these sleep disorders, blood pressure and BMI to date with a high response rate, direct measurement of height, weight, neck circumference and blood pressure, and incorporating a detailed self-administered questionnaire covering multiple lifestyle behaviours.

Even in a large, relatively young and healthy sample, sleep disorders, obesity and hypertension are common. There is a significant association between high blood pressure and sleep disorders evident after 40 years of age. Additionally, higher BMI is associated with various sleep disorder, even when accounting for the effects of neck circumference. However, unlike blood pressure, the relationship between sleep disorders and obesity appears to be evident at an early age.
References

Appendix I

Sleep disorders (Yes/No)
1. Have you ever been told that you snore loudly?
2. Have you ever been told that you stop breathing while you sleep?
3. Have you even been told that you appear to choke while you sleep?

Sleep apnoea was defined as either stopping breathing or choking while asleep.

Sleep complaints:
- **Sleep satisfaction**
  How do you feel about the amount of sleep you normally get? (1. Nowhere near enough; 2. Could do with a lot more; 3. Could do with a bit more; 4. Get the right amount; 5. Get plenty)
  Responses were dichotomised into dissatisfied (1, 2, 3) and satisfied (4, 5).

- **Sleep quantity**
  On average, how many nights during a week do you get a full night’s sleep (i.e. at least 7 to 8 hours)?
  Responses were categorised as 0 nights per week; 1–6 nights per week; 7 nights per week.
  For logistic regression categories were <5 nights per week; and 5–7 nights per week.

- **Insomnia**
  Please indicate how often (number of times per month) you experience each of the following (0, 1, 2–4, 5–15, 16–30 times per month):
  - Have trouble falling asleep.
  - Wake up during the night and have difficulty getting back to sleep.
  - Wake up too early in the morning and be unable to get back to sleep.

Insomnia was defined as having at least one of these sleep complaints at least weekly, and being dissatisfied with sleep, in the absence of depression, alcohol dependence, sleep apnoea, or illicit substance use.

Alcohol
Do you currently drink alcohol once a month or more? Yes/No
If yes, how often do you drink alcohol?
6–7 days a week/4–5 days a week/2–3 days a week/once a week/once every 2 weeks/once a month.

On an average day when you drink alcohol, how many drinks would you usually have in total?
Alcohol consumption was dichotomised into high and low risk based on the CAGE questionnaire. Two positive answers have a sensitivity exceeding 85% and a specificity approaching 90% for the diagnosis of alcohol abuse or dependence.

Smoking
Do you smoke cigarettes (not cigars/pipe) now? Yes/No
How many manufactured cigarettes do you usually smoke each day?
Non-smokers were assigned ‘0’ where smokers were assigned a value based on the number of cigarettes smoked per day.

Marijuana
During the past 12 months how often did you use marijuana (also know as grass, pot, cannabis, hashish, hash oil)?
Did not use/less than once a month/once a month/once every 2 weeks/once a week or more often.

Other illegal drugs
During the past 12 months how often did you use other illegal drugs? (that is drugs not prescribed by your
doctor or bought from a chemist, such as cocaine, LSD, amphetamines or speed, heroin, morphine.

Did not use/less than once a month/once a month/once every 2 weeks/once a week or more often.

Depression
Have you ever had two weeks or more when you felt sad or depressed nearly every day? Yes/No.

Did it interfere a lot with you, life, work or activities? Yes/No.
Subjects who responded positively to both of these questions constituted one group (high risk for depression), all others constituted the other group. Questions relating to depression were based on the CIDI-SFMD.45

Body mass index, sexual difficulties and sexual satisfaction among people in regular heterosexual relationships: a population-based study

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Key words
body mass index, obesity, physiological sexual dysfunction, psychological sexual dysfunction, Australia.

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Abstract

Background/Aims: The aims of this study were to clarify the relationship between body mass index (BMI) and sexual difficulties and to investigate if BMI influenced sexual satisfaction, over and above the effects of sexual difficulties.

Methods: Cross-sectional analyses of a nationally representative computer-assisted telephone interview. Eight thousand, six hundred and fifty-six respondents were recruited by random digit dialling in 2004–2005. Only those in a sexually active, heterosexual relationship were included in the current analyses.

Results: After adjustments for demographic factors, both overweight and obese male and female participants were more likely to report worrying during sex about whether their body was unattractive. Among women, associations were also found between higher BMI and lack of interest in sex. No other significant associations between BMI and sexual difficulties were evident. There was an association between BMI and extreme physical pleasure for women but not men over and above the effects of sexual difficulties, with obese women being more likely than normal weight women to report extreme physical pleasure. No associations were found for either men or women between BMI and whether or not they reported extreme emotional or sexual satisfaction with their relationship.

Conclusions: With the exception of body image difficulties, there is little association between BMI and self-reported sexual difficulties. Furthermore, extreme sexual and emotional satisfaction appeared to be associated with the presence or absence of sexual difficulties and not overly influenced by BMI. Overall, clinicians and patients should be aware that being overweight is not necessarily detrimental to sexual functioning.

Introduction

The World Health Organization projections in 2005 indicated approximately 1.6 billion adults were overweight (body mass index (BMI) ≥ 25 kg/m²) and at least 400
million adults were obese worldwide (BMI ≥ 30 kg/m²).\textsuperscript{1} Higher BMI has been associated with serious health consequences, such as increased cardiovascular disease, musculoskeletal disorders and some types of cancer.\textsuperscript{1} BMI may also be associated with sexual difficulties and sexual satisfaction but the limited research available has not been conclusive.

To date, the literature for men has primarily focused on associations between obesity and erectile dysfunction, with most studies before 2007 reporting a positive association between the two.\textsuperscript{2} Similarly, a recent community-based study in Denmark found that higher BMI in men aged 20–45 increased the prevalence of erectile dysfunction but not premature ejaculation, retarded ejaculation or sexual desire disorders.\textsuperscript{3} Several other studies have reported a U-shaped relationship – higher levels of erectile dysfunction in both underweight and obese respondents.\textsuperscript{4,5} Yet in these studies, the association between higher BMI and erectile dysfunction disappeared when lifestyle factors were allowed for. The relationship between BMI and sexual satisfaction in men has been little studied. A Swedish population-based study concluded sexual satisfaction levels varied widely among overweight and obese adults, who were not significantly different from normal weight men.\textsuperscript{6} Studies have shown obese women experienced greater impairment in enjoyment and desire and were less likely to have sexual encounters than men.\textsuperscript{7} The 2007 review of sexual function and obesity found female sexual dysfunction was not sufficiently described in the literature for any conclusions to be drawn.\textsuperscript{2} Since then, studies among women have reported conflicting findings. Several studies have reported a positive association between higher BMI and sexual difficulties\textsuperscript{8–10} and sexual/partner dissatisfaction,\textsuperscript{11–13} whereas other studies have found no association between obesity and sexual dysfunction\textsuperscript{14–16} or satisfaction.\textsuperscript{6}

A recent population-based study on sexuality and obesity among men and women aged 18–39 conducted in France found no association of BMI with painful intercourse, lack of sexual desire and arousal dysfunction in women. Among men, those who were underweight were more likely to report premature ejaculation and lack of sexual desire, whereas overweight and obese men were more likely than normal weight men to experience erectile dysfunction often. There was no association between the respondents’ BMI status and being very satisfied with their sexual life.\textsuperscript{17}

Given the large and ever increasing proportion of overweight and obese adults in countries such as Australia, the aim of our study is to investigate further the relationship between BMI and a range of sexual difficulties in both men and women using a large nationally representative survey. In addition, our study will investigate the effect of BMI and sexual difficulties on sexual and emotional satisfaction.

\section*{Methods}

\subsection*{Setting and participants}

The present study was a component of the Australian Longitudinal Study of Health and Relationships.\textsuperscript{18} While the Australian Longitudinal Study of Health and Relationships surveyed 4290 men and 4366 women in all states and territories of Australia, only respondents in a relationship with a regular opposite-sex partner and who had had sex in the previous 12 months were included in the analysis.

\subsection*{Survey}

Participants were asked a range of socio-demographic questions including age, education, occupation, cohabitation status, residential location, language spoken at home and country of birth. Health questions included current use of tobacco and alcohol, and use of cannabis in the last 12 months.

A series of questions assessed the presence of eight different sexual difficulties for at least 1 month during the previous 12 months. These were: whether the respondent lacked interest in having sex; was unable to come to orgasm; came to orgasm too quickly; took too long to orgasm; experienced physical pain during intercourse; did not find sex pleasurable; felt anxious about ability to perform sexually; and had trouble keeping an erection (men only); or trouble with vaginal dryness (women only). Participants were also asked ‘during sex do you worry about whether your body looks unattractive?’

Three questions assessed the degree of satisfaction in relation to the main opposite-sex partner. Respondents were first asked to rate how physically pleasurable they found sex with their current regular partner to be (not at all pleasurable, slightly, moderately, very or extremely pleasurable), then asked how satisfied they were with the sexual relationship overall and how emotionally satisfying they found the relationship (not at all satisfied to extremely satisfied).

Finally, height without shoes and weight without clothes were reported. Both metric and imperial measurements were accepted.

\subsection*{Procedure}

Approval for this study was granted by the human research ethics committees of La Trobe University, the
University of New South Wales and Deakin University. It was conducted during 2004 and 2005 using computer-assisted telephone interviewing. Participants were first contacted through random digit dialling and, after having the study explained to them, either gave their verbal consent to be interviewed or refused. Of those contacted, 56.0% agreed to participate. Age was the only selection criterion used in this study; participants were aged between 16 and 64 years inclusive. Where two or more eligible respondents lived in a household, only one was randomly chosen to be interviewed. All interviews were conducted in English.

Statistical analysis

The three satisfaction measures were recoded to indicate extreme satisfaction or not. This was necessary because of the skewed distribution of the variables and is consistent with previous research on sexual and relationship satisfaction.19

BMI was calculated as weight in kilograms divided by height in metres squared. Participants were placed in one of four BMI categories corresponding to the current World Health Organization recommendations: underweight, BMI < 18.5 kg/m²; normal weight, BMI = 18.5 to 24.9 kg/m²; overweight, BMI = 25 to 29.9 kg/m² and obese, BMI ≥ 30 kg/m².20

Multinomial logistic regressions assessed the socio-demographic correlates of different BMI categories. Multivariate male and female models were tested that included socio-demographic variables significant at $P \leq 0.25$ in bivariate models with BMI. Variables were excluded from the models one at a time based on non-significant $P$-values ($P > 0.05$), low cell counts and on inconsistencies between bivariate and multivariate relative risk ratios and standard errors. Non-significant socio-demographic variables were re-tested in the final multivariate model. Variables from the final models were used in subsequent analyses to adjust for socio-demographic differences.

Odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regressions were also computed to assess associations between BMI categories and a range of sexual difficulties, and to assess the effect of BMI and sexual difficulties on physical pleasure in sex with the partner and sexual and emotional satisfaction taking into account the significant socio-demographic variables. Finally, we examined the effect of BMI on pleasure and satisfaction after allowing for any sexual difficulties and socio-demographic variables associated with BMI. When the association with weight category was ordered, we tested for a linear trend relationship by fitting weight category as a continuous variable.

All associations between variables were treated as statistically significant at $P < 0.05$. All analyses were conducted using Stata, version 10.1 (StataCorp, College Station, TX, USA) and were weighted by the number of eligible household members.

Results

Of the 8656 people (women, 50.4%; men 49.6%) who completed the survey, 6448 provided at least one viable sexual satisfaction response and were involved in a sexually active relationship with a main opposite-sex partner. Of these people, 104 participants failed to provide adequate information to enable BMI calculation. The BMI status of the remaining sample was: underweight 2.1% (women 3.7%; men 0.5%); normal 42.5% (women 49.9%; men 35.2%); overweight, 37.9% (women 28.9%; men 46.7%); and obese 17.6% (women 17.5%; men 17.6%). Respondents in the underweight category were excluded from further analyses because of small numbers. After considering missing data on BMI and the above exclusions, the following analyses are based on a weighted sample of 2884 women and 3043 men.

Socio-demographic profile

Table 1 displays the results of multivariate modelling of the association between socio-demographic characteristics and BMI and shows the weighted numbers and percentages of men and women according to their socio-demographic background.

Adjusted relative risk ratios show that BMI was significantly associated with age and education in both men and women. Women were more likely to be overweight or obese as age increased, whereas for men the risk stopped increasing after age 45. Both men and women were less likely to be overweight or obese as education increased.

Cohabitation status, language spoken at home, frequency of use of alcohol, use of tobacco and cannabis were also associated with BMI among men. Men who lived separately from their female partners were less likely to be obese than men who lived with their partner. Men who spoke a language other than English at home were also less likely to be overweight or obese, as were current smokers, whereas current cannabis users were less likely to be obese. Finally, men who drank alcohol occasionally (less often than weekly) were more likely to be obese than men who did not drink.

Among women, BMI was also associated with country of birth and frequency of alcohol use. Compared with women born in Australia, those born overseas were less
### Table 1 Demographic correlates of body mass index (BMI)

#### BMI categories – men

<table>
<thead>
<tr>
<th>Age (3041)§</th>
<th>P &lt; 0.001</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
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</thead>
<tbody>
<tr>
<td>16–24 (311)</td>
<td></td>
<td>61.3‡</td>
<td>31.8</td>
<td>6.8</td>
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<tr>
<td>25–34 (508)</td>
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<td>35–44 (745)</td>
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<td>45–54 (871)</td>
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<td>31.7</td>
<td>48.2</td>
<td>20.1</td>
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<td>55–64 (606)</td>
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<td>32.8</td>
<td>47.5</td>
<td>19.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education (3041)§</th>
<th>P &lt; 0.001</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary/ lower secondary (643)</td>
<td>31.6</td>
<td>45.9</td>
<td>1.13 (0.89, 1.42)</td>
<td>22.5</td>
</tr>
<tr>
<td>Secondary or equivalent (1592)</td>
<td>35.4</td>
<td>46.7</td>
<td>1.00</td>
<td>17.9</td>
</tr>
<tr>
<td>Post-secondary (806)</td>
<td>42.1</td>
<td>45.5</td>
<td>0.74 (0.61, 0.90)</td>
<td>12.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupation (3030)‡‡</th>
<th>P = 0.13</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional (1304)</td>
<td>34.8</td>
<td>47.1</td>
<td>1.00</td>
<td>18.1</td>
</tr>
<tr>
<td>Assoc. professional (556)</td>
<td>35.4</td>
<td>50.1</td>
<td>1.08 (0.85, 1.37)</td>
<td>14.5</td>
</tr>
<tr>
<td>Tradesperson (860)</td>
<td>35.5</td>
<td>46.2</td>
<td>0.92 (0.73, 1.16)</td>
<td>18.4</td>
</tr>
<tr>
<td>Unskilled (310)</td>
<td>45.8</td>
<td>36.5</td>
<td>0.72 (0.50, 1.02)</td>
<td>17.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohabitation status (3040)§</th>
<th>P = 0.003</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live together (2613)</td>
<td>33.5</td>
<td>47.5</td>
<td>1.00</td>
<td>19.0</td>
</tr>
<tr>
<td>Live separately (427)</td>
<td>53.9</td>
<td>39.1</td>
<td>0.82 (0.61, 1.09)</td>
<td>6.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Residential location (3007)‡‡</th>
<th>P = 0.22</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cities (1532)</td>
<td>39.1</td>
<td>45.6</td>
<td>1.00</td>
<td>15.3</td>
</tr>
<tr>
<td>Regional/remote (1475)</td>
<td>33.1</td>
<td>47.1</td>
<td>1.09 (0.91, 1.30)</td>
<td>19.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Language spoken at home (3042)§</th>
<th>P = 0.009</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>English (2894)</td>
<td>35.5</td>
<td>46.6</td>
<td>1.00</td>
<td>17.8</td>
</tr>
<tr>
<td>Other (148)</td>
<td>52.2</td>
<td>38.3</td>
<td>0.62 (0.42, 0.92)</td>
<td>9.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country of birth (3040)‡‡</th>
<th>P = 0.32</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (2310)</td>
<td>35.9</td>
<td>45.9</td>
<td>1.00</td>
<td>18.2</td>
</tr>
<tr>
<td>Overseas (730)</td>
<td>37.6</td>
<td>47.5</td>
<td>1.06 (0.86, 1.31)</td>
<td>15.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current smoker (3039)§</th>
<th>P = 0.002</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (2313)</td>
<td>34.6</td>
<td>47.3</td>
<td>1.00</td>
<td>18.2</td>
</tr>
<tr>
<td>Yes (726)</td>
<td>42.0</td>
<td>43.0</td>
<td>0.73 (0.59, 0.89)</td>
<td>15.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current alcohol use (3041)§</th>
<th>P &lt; 0.001</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (337)</td>
<td>39.7</td>
<td>44.5</td>
<td>1.00</td>
<td>15.8</td>
</tr>
<tr>
<td>Less often than weekly (790)</td>
<td>31.2</td>
<td>46.1</td>
<td>1.26 (0.91, 1.73)</td>
<td>22.7</td>
</tr>
<tr>
<td>Weekly (1183)</td>
<td>38.7</td>
<td>45.9</td>
<td>0.96 (0.71, 1.30)</td>
<td>15.4</td>
</tr>
<tr>
<td>Daily (731)</td>
<td>36.5</td>
<td>47.9</td>
<td>0.95 (0.69, 1.30)</td>
<td>15.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cannabis last 12 months (3038)§</th>
<th>P = 0.01</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (2740)</td>
<td>35.2</td>
<td>46.7</td>
<td>1.00</td>
<td>18.2</td>
</tr>
<tr>
<td>Yes (298)</td>
<td>47.8</td>
<td>42.5</td>
<td>0.80 (0.60, 1.06)</td>
<td>9.7</td>
</tr>
</tbody>
</table>

#### BMI categories – women

<table>
<thead>
<tr>
<th>Age (2882)††</th>
<th>P &lt; 0.001</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>16–24 (268)</td>
<td></td>
<td>66.9‡</td>
<td>23.0</td>
<td>10.1</td>
</tr>
<tr>
<td>25–34 (603)</td>
<td></td>
<td>58.5</td>
<td>24.5</td>
<td>17.0</td>
</tr>
<tr>
<td>35–44 (816)</td>
<td></td>
<td>53.5</td>
<td>30.4</td>
<td>16.1</td>
</tr>
<tr>
<td>45–54 (761)</td>
<td></td>
<td>46.4</td>
<td>33.8</td>
<td>19.8</td>
</tr>
<tr>
<td>55–64 (434)</td>
<td></td>
<td>40.1</td>
<td>33.9</td>
<td>26.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education (2884)††</th>
<th>P &lt; 0.001</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary/ lower secondary (749)</td>
<td>42.4</td>
<td>32.7</td>
<td>1.13 (0.91, 1.41)</td>
<td>25.0</td>
</tr>
<tr>
<td>Secondary or equivalent (1363)</td>
<td>51.2</td>
<td>30.6</td>
<td>1.00</td>
<td>18.0</td>
</tr>
<tr>
<td>Post-secondary (772)</td>
<td>62.3</td>
<td>25.7</td>
<td>0.71 (0.58, 0.88)</td>
<td>12.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupation (2847)§§</th>
<th>P = 0.62</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional (1065)</td>
<td>55.7</td>
<td>28.2</td>
<td>1.00</td>
<td>16.1</td>
</tr>
<tr>
<td>Assoc. professional (1131)</td>
<td>50.8</td>
<td>30.5</td>
<td>1.14 (0.93, 1.41)</td>
<td>18.6</td>
</tr>
<tr>
<td>Tradesperson (129)</td>
<td>51.3</td>
<td>31.6</td>
<td>1.21 (0.76, 1.93)</td>
<td>17.1</td>
</tr>
</tbody>
</table>
likely to be overweight or obese, whereas women who drank weekly or daily were less likely to be obese than those who did not drink.

**Association between BMI and sexual difficulties**

Table 2 displays the results of a series of logistic regressions examining the association between BMI and reported sexual difficulties that lasted at least 1 month during the previous year (unless otherwise specified), after adjusting for significant socio-demographic variables. There was little association between BMI and sexual difficulties. The exception was an increased likelihood of worrying during sex about whether body looked unattractive for men ($F_{2,3162} = 10.14, P < 0.001$) and women ($F_{2,3088} = 29.08, P < 0.001$) who were overweight (men, OR 1.77, CI 1.26–2.49; women, OR 1.74, CI 1.44–2.10) or obese (men, OR 2.46, CI 1.65–3.66; women, OR 2.61, CI 1.73–2.70). Additionally, trend analysis revealed a significantly increased likelihood of reporting a lack of interest among both overweight (OR 1.13, CI 1.02–1.25) and obese women (OR 1.27, CI 1.04–1.56).

**Association between sexual difficulties, extreme satisfaction and BMI**

The associations between BMI, sexual difficulties, and three domains of relationship satisfaction were examined (extreme physical pleasure in sex (Table 3), sexual satisfaction (Table 4) and emotional satisfaction (Table 5)) by a series of logistic regressions adjusted for socio-demographic characteristics. Overall, results demonstrated a strong association between sexual difficulties and extreme satisfaction and a weak association between BMI and extreme satisfaction after adjusting for sexual difficulties.
Table 2: Adjusted odds ratios for the association between body mass index (BMI) categories (reference category normal BMI) and sexual difficulties for 1 month or more in the previous year

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weighted n</td>
<td>%</td>
<td>Adjusted OR (95% CI)†</td>
<td>Weighted n</td>
</tr>
<tr>
<td>Lacked interest in having sex</td>
<td>Normal</td>
<td>1098</td>
<td>17.1</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1407</td>
<td>18.2</td>
<td>1.08 (0.87, 1.35)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>528</td>
<td>16.5</td>
<td>0.94 (0.71, 1.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.56</td>
<td></td>
</tr>
<tr>
<td>Unable to come to orgasm</td>
<td>Normal</td>
<td>1097</td>
<td>3.7</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1405</td>
<td>3.9</td>
<td>0.98 (0.63, 1.52)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>528</td>
<td>4.4</td>
<td>1.06 (0.62, 1.83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.95</td>
<td></td>
</tr>
<tr>
<td>Came to orgasm too quickly</td>
<td>Normal</td>
<td>1094</td>
<td>11.0</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1400</td>
<td>12.9</td>
<td>1.11 (0.85, 1.44)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>528</td>
<td>14.9</td>
<td>1.26 (0.91, 1.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.39</td>
<td></td>
</tr>
<tr>
<td>Took too long to orgasm</td>
<td>Normal</td>
<td>1093</td>
<td>6.6</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1402</td>
<td>5.5</td>
<td>0.88 (0.62, 1.25)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>528</td>
<td>7.0</td>
<td>1.11 (0.71, 1.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.51</td>
<td></td>
</tr>
<tr>
<td>Physical pain during intercourse</td>
<td>Normal</td>
<td>1100</td>
<td>1.6</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1405</td>
<td>1.6</td>
<td>1.07 (0.52, 2.22)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>529</td>
<td>1.7</td>
<td>1.24 (0.51, 3.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.89</td>
<td></td>
</tr>
<tr>
<td>Did not find sex pleasurable</td>
<td>Normal</td>
<td>1102</td>
<td>2.7</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1402</td>
<td>3.1</td>
<td>1.18 (0.71, 1.97)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>530</td>
<td>3.9</td>
<td>1.27 (0.69, 2.34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.71</td>
<td></td>
</tr>
<tr>
<td>Felt anxious about ability to perform sexually</td>
<td>Normal</td>
<td>1101</td>
<td>10.8</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1403</td>
<td>9.5</td>
<td>0.87 (0.66, 1.16)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>530</td>
<td>10.9</td>
<td>0.95 (0.66, 1.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.63</td>
<td></td>
</tr>
<tr>
<td>Had trouble keeping an erection</td>
<td>Normal</td>
<td>1102</td>
<td>6.6</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1401</td>
<td>8.7</td>
<td>1.26 (0.90, 1.75)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>528</td>
<td>8.4</td>
<td>1.08 (0.71, 1.65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.39</td>
<td></td>
</tr>
<tr>
<td>Had trouble with vaginal dryness</td>
<td>Normal</td>
<td>1102</td>
<td>6.9</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1405</td>
<td>10.2</td>
<td>1.77 (1.26, 2.49)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>527</td>
<td>13.1</td>
<td>2.46 (1.65, 3.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

†Odds ratio and 95% confidence interval adjusted for age group, educational attainment, cohabitation status, language spoken at home, frequency of use of alcohol and use of tobacco and cannabis. ‡Odds ratio and 95% confidence interval adjusted for age group, educational attainment, country of birth and frequency of use of alcohol. §Trend analysis. ¶Time limit not specified.
The majority of sexual difficulties were associated with the three measures of sexual satisfaction. Among men, lacking interest in sex, coming to orgasm too quickly, not finding sex pleasurable, feeling anxious about ability to perform sexually and having trouble keeping an erection were all individually associated with decreased likelihood of extreme physical pleasure, extreme sexual and emotional satisfaction. Taking too long to reach orgasm and worrying during sex about body attractiveness were associated with being less likely to report extreme physical pleasure and extreme sexual satisfaction, whereas worrying during sex about body unattractiveness was associated with being less likely to report extreme sexual satisfaction and extreme emotional satisfaction. Among women, coming to orgasm too quickly was not associated with any of the three satisfaction measures.

For women, lacking interest in sex, being unable to come to orgasm, physical pain during intercourse, not finding sex pleasurable, and feeling anxious about ability to perform sexually were all individually associated with being less likely to report extreme physical pleasure, extreme sexual and emotional satisfaction. Taking too long to reach orgasm and trouble with vaginal dryness were both individually associated with being less likely to report extreme physical pleasure and extreme sexual satisfaction, whereas worrying during sex about body unattractiveness was associated with being less likely to report extreme sexual satisfaction and extreme emotional satisfaction. Among women, coming to orgasm too quickly was not associated with any of the three satisfaction measures.

After allowing for socio-demographic variables and those sexual difficulties associated with BMI, there was only one significant association between BMI and the three extreme satisfaction measures. Obese women were more likely to report extreme physical pleasure (OR 1.36, CI 1.07–1.72) than women with normal BMI. This association, however, was not significant without adjustments for sexual difficulties and socio-demographic characteristics ($P = 0.15$). On the other hand, unadjusted odds ratios suggested a negative association between BMI

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Adjusted odds ratios for the association between extreme physical pleasure and sexual difficulties (for 1 month or more in the previous year) and BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual difficulty</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Adjusted OR (95% CI)‡</td>
</tr>
<tr>
<td>Lacked interest in having sex</td>
<td>0.39 (0.31, 0.49)</td>
</tr>
<tr>
<td>Unable to come to orgasm</td>
<td>0.69 (0.46, 1.06)</td>
</tr>
<tr>
<td>Come to orgasm too quickly</td>
<td>0.73 (0.58, 0.93)</td>
</tr>
<tr>
<td>Took too long to orgasm</td>
<td>0.73 (0.52, 1.02)</td>
</tr>
<tr>
<td>Physical pain during intercourse</td>
<td>1.17 (0.63, 2.18)</td>
</tr>
<tr>
<td>Did not find sex pleasurable</td>
<td>0.21 (0.11, 0.39)</td>
</tr>
<tr>
<td>Felt anxious about ability to perform sexually</td>
<td>0.71 (0.54, 0.92)</td>
</tr>
<tr>
<td>Had trouble keeping an erection</td>
<td>0.56 (0.40, 0.77)</td>
</tr>
<tr>
<td>Had trouble with vaginal dryness</td>
<td>–</td>
</tr>
<tr>
<td>Ever worried during sex about whether body looked unattractive¶</td>
<td>0.90 (0.69, 1.18)§</td>
</tr>
<tr>
<td>BMI††</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1.07 (0.90, 1.28)‡‡</td>
</tr>
<tr>
<td>Obese</td>
<td>1.12 (0.89, 1.41)</td>
</tr>
</tbody>
</table>

†Odds ratio (and 95% confidence interval) for extreme physical pleasure if sexual difficulty present, adjusted for age group, educational attainment, cohabitation status, language spoken at home, frequency of use of alcohol and use of tobacco and cannabis. ‡Odds ratio (and 95% confidence interval) for extreme physical pleasure if sexual difficulty present, adjusted for age group, educational attainment, country of birth and frequency of use of alcohol. §Also adjusted for BMI. ¶Time limit not specified. †Reference category = normal BMI. ‡‡Also adjusted for ‘ever worried during sex about whether body looked unattractive’. §§Also adjusted for ‘lacked interest in having sex’.
and extreme emotional satisfaction among women ($P = 0.008$), which was no longer significant ($P = 0.13$) after adjustments for sexual difficulties and socio-demographic characteristics.

**Discussion**

It was important to clarify the relationships between BMI, sexual difficulties and sexual satisfaction given divergent results in previous research. In this population-based Australian study, BMI was not strongly associated with sexual difficulties in either men or women. The exceptions to this were that men and women who were overweight or obese were more likely to report that they worried during sex about how attractive their bodies looked. This is not surprising, given reported associations between poor body image and obesity. In addition, overweight and obese women were more likely to lack interest in sex than women with normal BMI. Although it is possible that BMI affects sexual interest, it may be that women who enjoy sex more are better motivated to maintain normal weight.

Overall, the weak association between BMI and sexual difficulties for women is consistent with the limited previous research demonstrating no association in women. The results contrast with some studies that have reported associations between obesity and sexual dysfunction, including reductions in arousal, lubrications, and orgasm. However, in contrast to the population-based sample used in our study, the majority of previous studies has reported on severely obese women, including women being evaluated for weight loss surgery.

The lack of association between BMI and trouble keeping an erection, however, contrasts with the majority of studies indicating that BMI and erectile dysfunction in men are positively associated or that the relationship is U-shaped among men who were not physically active. Larsen et al.'s review of sexual function and obesity suggested that direct comparison of studies was difficult.

---

**Table 4** Adjusted odds ratios for the association between extreme sexual satisfaction and sexual difficulties (for 1 month or more in the previous year) and body mass index (BMI)

<table>
<thead>
<tr>
<th>Sexual difficulty</th>
<th>Men Adjusted OR (95% CI)†</th>
<th>Women Adjusted OR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacked interest in having sex</td>
<td>0.40 (0.32, 0.51)</td>
<td>0.38 (0.32, 0.45)§</td>
</tr>
<tr>
<td>Unable to come to orgasm</td>
<td>0.55 (0.35, 0.87)</td>
<td>0.37 (0.29, 0.46)</td>
</tr>
<tr>
<td>Come to orgasm too quickly</td>
<td>0.60 (0.46, 0.78)</td>
<td>1.19 (0.85, 1.69)</td>
</tr>
<tr>
<td>Took too long to orgasm</td>
<td>0.61 (0.43, 0.88)</td>
<td>0.67 (0.54, 0.83)</td>
</tr>
<tr>
<td>Physical pain during intercourse</td>
<td>0.80 (0.41, 1.58)</td>
<td>0.56 (0.42, 0.75)</td>
</tr>
<tr>
<td>Did not find sex pleasurable</td>
<td>0.24 (0.13, 0.47)</td>
<td>0.29 (0.22, 0.38)</td>
</tr>
<tr>
<td>Felt anxious about ability to perform sexually</td>
<td>0.53 (0.39, 0.71)</td>
<td>0.43 (0.32, 0.57)</td>
</tr>
<tr>
<td>Had trouble keeping an erection</td>
<td>0.51 (0.36, 0.72)</td>
<td>–</td>
</tr>
<tr>
<td>Had trouble with vaginal dryness</td>
<td>–</td>
<td>0.62 (0.50, 0.79)</td>
</tr>
<tr>
<td>Ever worried during sex about whether body looked unattractive¶</td>
<td>0.59 (0.43, 0.80)§</td>
<td>0.74 (0.62, 0.89)§</td>
</tr>
</tbody>
</table>

BMI†† | Overweight 1.02 (0.86, 1.23)‡‡ | 0.96 (0.79, 1.17)§§ |
| Obese | 1.10 (0.86, 1.39) | 1.17 (0.93, 1.47) |
| | $P = 0.75$ | $P = 0.27$ |

†Odds ratio (and 95% confidence interval) for extreme sexual satisfaction if sexual difficulty present, adjusted for age group, educational attainment, cohabitation status, language spoken at home, frequency of use of alcohol and use of tobacco and cannabis. ‡Odds ratio (and 95% confidence interval) for extreme sexual satisfaction if sexual difficulty present, adjusted for age group, educational attainment, country of birth and frequency of use of alcohol. §Also adjusted for BMI. ¶Time limit not specified. ††Reference category = normal BMI. ‡‡Also adjusted for ‘ever worried during sex about whether body looked unattractive’. §§Also adjusted for ‘lacked interest in having sex’. © 2011 The Authors

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because of the variation in the criteria used to define erectile dysfunction. For example, we asked a single question about whether the respondent had trouble (for at least a month within the previous 12 months) keeping an erection when he wanted to. The current study most likely assesses erectile difficulty rather than diagnosing erectile dysfunction. Overall, caution should be used when comparing our results with studies that use multi-item diagnostic measures.

The lack of association between BMI and erectile difficulty is consistent with two studies that failed to find a positive association when lifestyle factors were allowed for.4,5 Both studies reported a U-shaped relationship among the inactive before adjusting for lifestyle factors. Yet among the physically active, and after adjustments were made for lifestyle factors, comorbid diseases and medication use, the relationship between obesity and erectile dysfunction became non-significant. Similarly, the results from the current study were also fully adjusted for socio-demographic differences across BMI categories, and also differences in tobacco, alcohol and cannabis use.

We also did not find a strong association between BMI and physical pleasure in sex and sexual and emotional satisfaction. This is consistent with the findings of Adolfsson,6 who found that overweight and obese people did not differ in sexual satisfaction from people of normal weight. In addition, a recent French population-based study also reported no differences in the percentage of respondents who were very satisfied with their sexual lives across different BMI categories.17 After adjusting for significant socio-demographic characteristics and sexual difficulties, the only significant association between BMI and satisfaction in our study was that obese women were more likely to report extreme physical pleasure than women of normal BMI. This contrasts with studies demonstrating that obese women were less satisfied with their sexual lives7,11 and relationships.12,13 which has been found among specific subpopulations, including the class III obese (BMI > 40 kg/m²).7 older women

<table>
<thead>
<tr>
<th>Sexual difficulty</th>
<th>Men Adjusted OR (95% CI)†</th>
<th>Women Adjusted OR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacked interest in having sex</td>
<td>0.51 (0.42, 0.63)</td>
<td>0.60 (0.51, 0.70)§</td>
</tr>
<tr>
<td>Unable to come to orgasm</td>
<td>0.69 (0.46, 1.05)</td>
<td>0.69 (0.57, 0.83)</td>
</tr>
<tr>
<td>Come to orgasm too quickly</td>
<td>0.59 (0.47, 0.75)</td>
<td>1.00 (0.71, 1.40)</td>
</tr>
<tr>
<td>Took too long to orgasm</td>
<td>0.66 (0.47, 0.92)</td>
<td>0.95 (0.79, 1.15)</td>
</tr>
<tr>
<td>Physical pain during intercourse</td>
<td>1.11 (0.61, 2.05)</td>
<td>0.74 (0.58, 0.95)</td>
</tr>
<tr>
<td>Did not find sex pleasurable</td>
<td>0.28 (0.16, 0.50)</td>
<td>0.51 (0.41, 0.63)</td>
</tr>
<tr>
<td>Felt anxious about ability to perform sexually</td>
<td>0.62 (0.47, 0.81)</td>
<td>0.76 (0.60, 0.97)</td>
</tr>
<tr>
<td>Had trouble keeping an erection</td>
<td>0.71 (0.53, 0.96)</td>
<td>–</td>
</tr>
<tr>
<td>Had trouble with vaginal dryness</td>
<td>0.71 (0.53, 0.96)</td>
<td>0.91 (0.75, 1.12)</td>
</tr>
<tr>
<td>Ever worried during sex about whether body looked unattractive¶</td>
<td>0.74 (0.56, 0.98)§</td>
<td>0.67 (0.56, 0.79)§</td>
</tr>
<tr>
<td>BMI††</td>
<td>1.05 (0.88, 1.25)‡‡</td>
<td>0.84 (0.70, 1.01)§§</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.19 (0.95, 1.49)</td>
<td>0.86 (0.70, 1.08)††</td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td>0.32</td>
</tr>
</tbody>
</table>

†Odds ratio (and 95% confidence interval) for extreme emotional satisfaction if sexual difficulty present, adjusted for age group, educational attainment, cohabitation status, language spoken at home, frequency of use of alcohol and use of tobacco and cannabis. ‡Odds ratio (and 95% confidence interval) for extreme emotional satisfaction if sexual difficulty present, adjusted for age group, educational attainment, country of birth and frequency of use of alcohol. §Also adjusted for BMI. ¶Time limit not specified. ††Reference category = normal BMI. ‡‡Also adjusted for ‘ever worried during sex about whether body looked unattractive’. §§Also adjusted for ‘lacked interest in having sex’.
(40–69 years), young women (18–23 years) and small numbers (n = 57) of dating and married couples. Many past studies, however, have not adjusted for demographic characteristics.

Overall, sexual difficulties were associated with lower ratings of satisfaction, with some exceptions. Coming to orgasm too quickly was not associated with satisfaction among women. This may be because in the typical sexual scripts of Australians, the woman’s orgasm is not assumed to end the encounter. In men, physical pain during intercourse was not associated with satisfaction, possibly because of it being rare and having varied causes not related to other sexual difficulties.

Strengths of the current study include the population-based sampling and wide age range, thereby providing a large representative sample of Australians aged 16–64 in a regular, sexually active, heterosexual relationship. This study, however, does not give any insight into men and women who do not have a regular partner, nor does it provide any information on men and women with same-sex partners. Other limitations include survey-based issues such as self-report and social desirability biases, relating to the sensitive nature of the material and the known biases associated with self reports of weight and height. For example, men and women have been shown to overestimate their height and underestimate their weight compared with actual measurements; this effect has also been reported in computer-assisted telephone interview studies similar to ours. Our results may underestimate respondents’ BMI, thus potentially affecting associations. Finally, the exclusion of the underweight category demonstrates the difficulty in obtaining adequate sampling in all four categories of the BMI. The inclusion of this category in future research would add to the current findings.

Conclusion
The main finding of the study is that independent of social circumstances, BMI is not a major driver of sexual functioning and satisfaction for people in regular relationships. Although it is undoubtedly important for clinicians to include criteria such as body fat in the overall health profile of patients, when treating those reporting sexual dysfunction or lack of satisfaction, BMI may not be an important clinical evaluation measure. Similarly, clinicians should also be aware of the strong associations between sexual difficulties and physical pleasure and sexual and emotional satisfaction.

Acknowledgements
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Detection of patients presenting with adverse drug events in the emergency department


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Key words
adverse drug event, emergency department, severity, preventability.

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Abstract

Background: Adverse drug events (ADE) have been studied widely in hospitalised and emergency department (ED) patients. Less is known about the ED visits of drug-related injury in Taiwan. This study seeks to determine the incidence, risk and patient outcomes of ADE in an ED population.

Methods: We conducted a prospective observational cohort study of patients 18 years and older presenting to the ED of an urban, tertiary medical centre. ED visits between 1 March 2009 and 28 February 2010 identified by investigators for suspected ADE were further assessed by using the Naranjo Adverse Drug Reaction probability scale. Outcomes (ED disposition, injury severity and preventability) and associated variables (triage, gender, drug category, number of drugs, Charlson comorbidity index score and ADE mechanism) were measured.

Results: Of 58,569 ED visits, 452 patients (0.77%) had physician-documented ADE. 24% of patients with ADE were hospitalised with life-threatening conditions, with a mortality rate of 10.0%. The majority of ADE were considered preventable (73.4%), and the unintentional overdose was the most common cause. Cardiovascular agents accounted for the most ADE (25.8%) and consisted of 65.3% of ADE in patients aged 65 years and older. Risk factors for ADE-related hospitalisation were elderly age (odds ratio (OR) 1.9, 95% confidence interval (CI) 1.1–3.4), severity of ADE (OR 6.9, 95% CI 3.3–14.5) and higher Charlson comorbidity index scores (OR 3.4, 95% CI 2.0–5.7).

Conclusion: ADE-related ED visits are not uncommon in Taiwan and many cases are preventable. ED-based surveillance may provide useful information for monitoring outpatient ADE.
Introduction

Recent years have seen increased attention given to adverse drug events (ADE) in the patient safety arena of pharmacotherapy.1-3 A growing number of research studies is now available to shed light on the drug-related emergency visits in many countries.4-6 These studies have noted that ADE not only result in significant causes of mortality and morbidity, but also impact on healthcare resource utilisation, including emergency department (ED) visits, medication use, diagnostic test and hospital admission.7,8

The majority of research in ADE has focused on hospitalised patients, and ADE has been estimated to constitute 0.2-25% of all hospital admissions.1,9,10 However, little is known about ADE-related emergency room visits. Kaufman et al. investigated that 81% adults take at least one medication, and many take multiple agents weekly.4 In the United States, ADE-related injury accounts for 37.3% of ED visits; approximately threefold more patients are treated in EDs than are admitted to hospitals (13%) each year.11 The national systematic surveillance of ADE for outpatients in Taiwan has not been well established. To better understand the medication safety issues and build a safer healthcare system, more studies on ED visits for outpatient ADE are crucial and needed.

Our study investigates the incidence of ADE in adults presenting to ED, describes demographic and clinical factors associated with ADE and identifies the severity and preventability of ADE in a tertiary medical centre in northern Taiwan.

Materials and methods

The study consisted of a prospective cohort design. With an average of 81 000 annual ED visits and 2800 inpatients beds, the study site ED is in an academic hospital that serves as a tertiary referral centre in northern Taiwan. All patients registered at the study site ED from 1 March 2009 to 28 February 2010 were eligible for this cohort study. This study was approved by the Institutional Review Board of the study hospital. Board-certified emergency attending physicians, emergency resident physicians and on-duty resident physicians collaboratively involved in the direct care of these patients were notified of the study by a special announcement asking them to identify potential ADE patients. We defined an ADE case as ED visit by a patient age 18 years or older, from 1 March 2009 to 28 February 2010, for a condition that the treating physician explicitly attributed to the use of a drug or a drug-specific effect.9 Interviews were conducted by trained research assistants using standardised data collection forms. The assistants were instructed to examine the physician diagnoses recorded in the clinical chart and followed each patient’s progress in diagnosis and therapy. The following data were recorded for each individual patient: demographic factors (gender, age, education, ethnic group), cigarette or alcohol use, diagnosis, drug history, type of ADE, chronic comorbidities and in the case of hospitalised patients, details of clinical progress and outcome were also included. We used the Charlson comorbidity index score to classify comorbid conditions and weigh the seriousness of comorbid disease.12

ADE cases were defined as persons who sought ED care for injuries linked to the outpatient use of a drug or drug-specific adverse effects (e.g. hypotension in a person taking diuretics). The case definition of ADE included the following mechanisms of injury: allergic reactions (immunologically mediated effects), adverse effects (undesirable pharmacologic effects at recommended doses) and unintentional overdoses (toxic effects linked to excess dose or impaired excretion).13 Exclusion criteria for this study were: intentional self-harm (e.g. suicide attempts); drug therapeutic failures; drug withdrawal; drug abuse; drug non-adherence; and trauma (e.g. motor vehicle accidents and falls) caused by drug effect. Follow-up visits for an ADE previously diagnosed and treated were also excluded. Drugs were defined as prescription medications, over-the-counter medications, vaccines, vitamins and nutritional supplements. Alcoholic beverages, tobacco products, illicit substances and cosmetics were not included.

All clinical signs, symptoms, systemic complications and deaths were recorded as individual event counts for each occurrence. The diagnosis of an ADE was first made by emergency physicians, and subsequently corroborated by sub-specialists, such as cardiologists, nephrologists, gastroenterologists or clinical toxicologists. In determining whether an ADE had occurred, the research team considered the temporal relation between the drug exposure and the event, as well as whether the event reflected a known effect of the drug. The process of defining ADE has been used in numerous prior studies relating to ADE across various clinical settings. We used Naranjo scores14 to quantify and assign causality into four categories: certain, probable, possible or unlikely. A case was considered as certain ADE if the clinician attributed the cause of adverse effect to the action of a drug, and no other plausible cause was identified (Naranjo scores: ≥9). A case was considered as probable ADE if the clinician associated the adverse effect to the action of a drug, and...
no other plausible cause was identified (Naranjo scores: 5–8). A case was considered as possible ADE if the clinician documented that the link between the adverse effect and the drug was possible, or if there were other possible contributing causes of the adverse effect in addition to the drug (Naranjo scores: 1–4).15 If no link between an adverse effect and a drug was documented, the episode was not considered a case (Naranjo scores: <1).

The clinical outcomes measured were disposition from the ED, preventability of ADE and severity of ADE. Preventability was classified as definitely preventable, possibly preventable or not preventable.16,17 We defined a preventable ADE as an adverse effect that is related to wrong dosage, poor monitoring, poor drug selection or incorrect administration.15 Any dispute regarding the culprit drug or drug–drug interactions was resolved by the entire research team. The severity of ADE according to the World Health Organization definition is categorised as fatal, life-threatening, moderate or mild. The diagnosis during ED visits and any associated diseases were classified using the International Classification of Disease 9th revision (World Health Organization’s Ninth Revision, International Classification of Diseases). Drugs were classified using the Anatomical Therapeutical Chemical system.

All collected data were recorded into the Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) and the Statistical Product and Service Solutions (SPSS for Windows, Version 10.0, SPSS Inc., Chicago, IL, USA) was used to analyse the data. We first used the descriptive statistics and contingency tables to demonstrate the primary demographic characteristics, clinical manifestations and drug categories among ADE patients. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as the proportion in percentage (%). Independent t-test was used to examine the statistical significance of continuous variables, and chi-squared test was used to evaluate categorical variables. A P-value less than 0.05 was considered statistically significant.

We further used univariate and multivariate logistic regressions to estimate the odds ratios of potential predictors of preventability of ADE and ADE-related hospitalization. The odds ratios were expressed as crude and adjusted odds ratio with 95% confidence interval (CI). Independent variables for the multivariate logistic regression included age, gender and those variables with a P-value less than 0.05 with physician-documented ADE were identified (0.77% of all patients). Nearly two-thirds were elderly and two-thirds were males. Nearly one-fourth of total ADE were hospitalised. The majority (75.9%) of ADE were observed, treated and released from ED (Table 1).

The 452 emergency physician-documented ADE visits were classified into three categories: certain (n = 279, 61.7%), probable (n = 146, 32.3%) and possible (n = 27, 6.0%). Most cases (n = 425, 94%) were at least probable ADE. Of the 27 possible ADE, the study physicians also

Results
A total of 58 569 non-traumatic patients was presented to our ED during the study period. Of these, 452 cases were physician-documented ADE. Of these, 452 cases

| Table 1: Characteristics in 452 patients with adverse drug event (ADE) |
|-----------------------------------------------|------------------|------------------|
| Patients characteristics | Patients with ADE (n = 452) | No. (%) |
| Age, years | ≥65 | 295 (65.3) |
|           | <65 | 157 (34.7) |
| Gender | Male | 275 (60.8) |
|         | Female | 177 (39.2) |
| Triage | 1 + 2 | 166 (36.7) |
|         | 3 + 4 | 286 (63.3) |
| Disposition | Observed, treated and discharged in ED | 343 (75.9) |
|         | Admitted | 109 (24.1) |
| Charlson comorbidity index scores† | Mean ± SD | 2.64 ± 2.17 |
|         | Median, range | 2, 0–11 |
| No. of intake drugs | Mean ± SD | 7.1 ± 4.1 |
|         | Median, range | 7, 1–21 |
| Clinics of prescription | Tertiary medical centre | 368 (71.2) |
|         | Non-tertiary medical centre | 84 (21.8) |
| Prevention of ADE | Definitely preventable | 16 (3.5) |
|         | Possibly preventable | 316 (69.9) |
|         | Not preventable | 120 (26.5) |
| Seriousness of ADE | Death | 8 (1.8) |
|         | Life-threatening | 37 (8.2) |
|         | Need to be treated | 343 (75.9) |
|         | No need to be treated | 64 (14.2) |
| Injury mechanism of ADE | Unintentional overdose | 182 (40.3) |
|         | Adverse effect | 181 (40.0) |
|         | Allergic reaction | 89 (19.7) |

†Diseases of Charlson comorbidities include myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumour, leukaemia, lymphoma, moderate or severe liver disease, metastatic solid tumour, AIDS, ADE, adverse drug event, ED, emergency department, SD, standard deviation.
A multiple logistic regression was used to examine possible independent predictors of patient’s prognosis. Table 4 reports the results of the multivariate logistic regression model for hospitalisation. We found that advanced age (adjusted OR = 1.9, 95% CI 1.1–3.4), more serious ADE (adjusted OR = 6.9, 95% CI 3.3–14.5) and higher Charlson comorbidity index scores (adjusted OR = 3.4, 95% CI 2.0–5.7) were associated with ADE-related hospitalization.

We also evaluated factors related to the preventability of ADE by using multivariate regression analyses. Seriousness of ADE (fatal and life-threatening; OR 2.6, 95% CI 1.1–6.3), the need of hospitalisation (OR 2.0, 95% CI 1.1–3.4) and drugs requiring close monitoring either by measurement of serum concentrations (e.g. digoxin, theophylline, lithium and anticonvulsants) or check-up of indicators of therapeutic/adverse effects (e.g. plasma

<table>
<thead>
<tr>
<th>Categories of chief complaints</th>
<th>Overall No. (%)</th>
<th>Hospitalization No. (%)</th>
<th>Death No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash (itching, eyelid swelling or angioedema)</td>
<td>74 (16.4)</td>
<td>11 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>49 (10.8)</td>
<td>14 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Dizziness or vertigo</td>
<td>47 (10.4)</td>
<td>6 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy (gum bleeding, haematuria, ecchymosis or bloody stool)</td>
<td>44 (9.7)</td>
<td>5 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Altered mental status (coma or confusion)</td>
<td>29 (6.4)</td>
<td>15 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Vomiting or nausea</td>
<td>28 (6.2)</td>
<td>5 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Tarry stool</td>
<td>20 (4.4)</td>
<td>9 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>19 (4.2)</td>
<td>7 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>19 (4.2)</td>
<td>11 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Chest tightness or pain</td>
<td>17 (3.8)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15 (3.3)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>14 (3.1)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Cold sweating</td>
<td>13 (2.9)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (2.2)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9 (2.0)</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (1.8)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Poor appetite</td>
<td>7 (1.5)</td>
<td>3 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (1.3)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Acute urine retention</td>
<td>6 (1.3)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>18 (4.0)</td>
<td>3 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>452 (100)</td>
<td>109 (100)</td>
<td>8 (100)</td>
</tr>
</tbody>
</table>
glucose, prothrombin time, liver and renal function and electrolytes) (OR 7.6, 95% CI 3.6–16.2) were associated with the preventability of ADE.

Discussion

Our investigation is the first prospective study in Taiwan to estimate the number of and risk factors for ADE among adults presenting to ED. Our study found that ADE accounted for 0.77% (452/58,569) of non-traumatic ED visits, of which 73.5% (332/452) were considered preventable. Few of the ADE were fatal or life threatening, with most (75.9%, 343/452) requiring treatment in ED. ED plays an important role in screening and management of ADE.

The proportion of ADE found in our ED (0.77% of all ED visits) is somewhat lower than the proportion reported in previous studies, which has ranged from 0.86% for adverse drug reactions to 3.9% for medication-related problems.19–21 A similar range has been reported for inpatient ADE (0.7–6.5%).5,22 This variability may be attributed to differences in study populations, methodology and inclusion/exclusion criteria of ADE. Our result is similar to a study conducted in the United States using a national surveillance system (0.7% of all ED visits).23

Our finding showed that ADE-related ED visits are frequently associated with the clinical presentations of skin rash (16.4%), fatigue (10.8%), dizziness or vertigo (10.4%), coagulopathy (9.7%) and altered mental status (6.4%). Many patients with ADE had metabolic and gastrointestinal diagnoses, such as hypoglycaemia, peptic ulcers, coagulopathy, hypotension and imbalance of electrolytes; there are certain similarities between our findings and previous research in an ED setting.15 However, the result is different from other inpatient studies that showed that central nervous system ADE were more common than metabolic ADE.24,25 Further studies are warranted to evaluate whether the presenting symptoms of ADE are truly different between ED patients and inpatients.

We found a majority of serious ADE (39/45, 87%) and hospitalisation (90/109, 83%) could possibly be prevented. Among 332 preventable ADE, cardiovascular agents were the most frequently implicated (107/332, 32.2%). A study confined to the elderly outpatients found that life-threatening and fatal ADE were more likely to be preventable than less severe events in the ambulatory setting.17 The ADE-related hospitalisation proportion in our study was 24.1% (109/452), which was lower than the 30.9% reported by Hafner et al. in the United States5 and slightly higher than a study conducted in ED in Italy (19.1%).26,27 By preventing life-threatening ADE, hospitalisation could also be prevented. Our findings also suggested that close monitoring of certain drugs that have a narrow therapeutic window (e.g. digoxin) or an easily detectable indicator of therapeutic/adverse effects (e.g. plasma glucose and electrolytes) could potentially prevent ADE and subsequent hospitalisations.

Several studies have suggested that elderly people may have increased risk for ADE. Hohl et al. investigated ADE among the elderly presenting to the ED and showed that 10.6% of ED visits were because of ADE.28

<table>
<thead>
<tr>
<th>Table 4: Adjusted odds ratios (ORs) for hospitalisation for 452 patients with adverse drug events (ADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>≥65</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Triage</td>
</tr>
<tr>
<td>1 + 2</td>
</tr>
<tr>
<td>Charlson comorbidity index scores‡</td>
</tr>
<tr>
<td>≥3</td>
</tr>
<tr>
<td>No. of intake drugs</td>
</tr>
<tr>
<td>≥8</td>
</tr>
<tr>
<td>Seriousness of ADE</td>
</tr>
<tr>
<td>Serious (death &amp; life-threatening)</td>
</tr>
<tr>
<td>Injury mechanism of ADE</td>
</tr>
<tr>
<td>Unintentional overdose</td>
</tr>
<tr>
<td>Adverse effect</td>
</tr>
</tbody>
</table>

†Adjusted variables include patient age, patient gender, triage, adverse event mechanism, seriousness of ADE and the Charlson comorbidity index scores. ‡Diseases of Charlson comorbidities include myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumour, leukaemia, lymphoma, moderate or severe liver disease, metastatic solid tumour, AIDS.

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higher proportion of ADE (295/20 628, 1.4%) in the aged population (≥65 years old). Such finding could be explained by the use of multiple drugs in treating multiple comorbidities, which is more common among the elderly.29 A few studies have shown that comorbidities or the number of concurrent medical problems are associated with ADE.30,31 Although there is debate in the literature as to whether age itself is a risk factor for an ADE-related ED visit or hospitalisation,11 our study showed that patients aged 65 years or older were more likely to be hospitalised than younger patients. In addition, patients with more serious ADE and higher Charlson comorbidity index scores (≥3) were more likely to be hospitalised.

In Taiwan, the current system for reporting outpatient ADE is not well established. Most reported ADE are inpatient and rely on healthcare providers, especially nurses or pharmacists. Our current study can provide useful information for processing national surveillance of ADE in adult outpatient ED visits. At present, it is unlikely that such screening will directly change clinical practice. However, we believe that further efforts could be implemented to reduce ADE by professional education focusing on the importance of pharmacovigilance among healthcare providers.

The study had some limitations. First, patients with less serious ADE might have been treated in other settings (e.g., primary clinics and local hospitals) or might not have been treated in any healthcare setting, which would lead to an underestimate of the prevalence of ADE. Second, although we had tried our best to ameliorate the possibility of under-diagnosis of ADE that could theoretically result from the differences in the detection of ADE between emergency physicians, we did not have data to quantify the magnitude of such an effect. Third, we did not include ADE-related traumatic patients (e.g., falls) that could also underestimate the actual occurrence of ADE. Fourth, as some of the data were collected by patient interviews, recall bias might be present. Finally, as our study was limited to only a tertiary care facility, our results might not be applicable to other settings, such as a rural ED.

**Conclusion**

ADE are common in the ED and older patients. The majority of ADE is preventable and deserves more attention. Compared with other developed countries, a national active surveillance programme for outpatient ADE is pivotal in Taiwan.

**Acknowledgements**

The authors would like to thank all the physicians and monitors participating in the data collection for this study. We would also like to thank Susan Sheu, MD for her critical review and editing of the manuscript. We are grateful to Ms Te-Yu Lo for data collection.

**References**


Evaluation of iron deficiency anaemia in tertiary hospital settings: room for improvement?

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Key words
iron deficiency anaemia, endoscopy, hospital, cancer.

Abstract

Background: Iron deficiency anaemia (IDA) is a marker of occult blood loss from gastrointestinal (GI) lesions and requires thorough GI evaluation. Aim: This study aimed to determine frequency and findings of GI endoscopy in patients with IDA attending a tertiary hospital, and associations of endoscopy with patient and clinician-related factors and results of faecal occult blood tests (FOBT).

Methods: Retrospective audit of 621 subjects identified with definite and probable IDA (serum ferritin <15 ug/L and 16–50 mg/L respectively) between 1 January 2006 and 31 December 31 2008. Subjects were analysed as males >18 years and females ≥45 years of age with definite (group A, n = 180) or probable (group B, n = 353) IDA, and females <45 years of age with definite or probable IDA (group C, n = 88).

Results: Endoscopy of any type was documented in 310 (50%) of patients with oesophagogastroduodenal endoscopy, and colonoscopy rates being significantly higher in group A patients (61% and 56% respectively) than in group B (39%, 37%) and group C (30%, 31%; P < 0.01 for all comparisons). Endoscopy rates ranged from 96% of patients seeing gastroenterologists to 31% of those seeing nephrologists. In patients undergoing colonoscopy, cancer and high-risk adenomas were detected in 51 patients (20%), ranging from 27/100 (27%) of group A, 23/130 (18%) of group B and 1/27 (4%) of group C. Lesion prevalence was similar (19–24%) regardless of whether FOBT yielded positive or negative results or had not been performed.

Conclusions: Almost one in two patients with IDA were not documented as undergoing GI endoscopy. More intense guideline promulgation, improved endoscopy access and ongoing practice audits are required to improve endoscopy rates.

Introduction

While considerable attention has recently been given to community-based screening for colorectal cancer in asymptomatic persons, patients identified in hospital settings as having iron deficiency anaemia (IDA) are high-risk patients deserving thorough gastrointestinal (GI) evaluation. In the absence of overt GI bleeding, IDA is diagnosed in between 4% and 7% of patients admitted to hospital or attending outpatient clinics. The prevalence of GI lesions causing occult blood loss or impaired iron absorption in patients with IDA varies from 70% to 90%, with serious lesions, such as colorectal cancer occurring in 6–29% of cases. Serum ferritin is the best marker of iron deficiency compared with low serum iron, increased total iron binding capacity and low percentage transferrin saturation. Values <50 ug/L are diagnostic or highly suggestive of IDA, while values >100 µg/L predict a very low likelihood of IDA and a prevalence of colonic neoplasia similar to that of asymptomatic, non-anaemic patients (1.7% vs 1.2%). While elevated levels of serum transferrin receptors may be helpful in cases of falsely elevated serum ferritin due to inflammatory disease, such assays are not standardised, and their sensitivity and clinical utility remain uncertain.

In some studies, older age, low red cell mean corpuscular volume (MCV) and positive faecal occult blood tests (FOBT) predict a greater likelihood of GI bleeding in patients with IDA. However, current Australian guidelines recommend that all adult male patients and postmenopausal female patients with IDA and no overt blood loss or other obvious cause should be referred for oesophagogastroduodenal (OGD) endoscopy and/or colonoscopy. Which endoscopic procedure should be done first and whether a second procedure should only be performed if the first procedure is non-contributory
remain controversial. Studies showing a much higher yield of malignancy from colonoscopy compared with OGD endoscopy would favour the former as first procedure \(^{15}\) and, if non-contributory, be followed by the latter.\(^ {16}\) However, because some reports reveal as many as 23% of patients, particularly older subjects, can have both upper and lower GI lesions,\(^ {17}\) some guidelines recommend dual endoscopy.\(^ {18}\) Previous hospital-based audits have shown that only 30–50% of eligible patients with IDA undergo GI endoscopy,\(^ {19,20}\) with positive FOBT results predicting greater use of endoscopy in some studies.\(^ {21}\) Guidelines also recommend iron replacement therapy and restricted use of red cell transfusions while patients await endoscopic evaluation, but no studies of adherence to these recommendations currently exist.\(^ {22}\)

The aims of this study were to (i) determine the frequency with which a cohort of tertiary hospital patients with IDA were referred for GI endoscopy and received iron supplementation; (ii) characterise the endoscopic and histological findings among endoscoped patients; (iii) determine whether the yield of malignant or precancerous lesions varied according to results of FOBT; and (iv) compare patient characteristics and clinician-related factors between patients who underwent endoscopy and those who did not.

**Methods**

**Patients**

This retrospective study included all adult patients (age >18 years) admitted to, or receiving outpatient care at, a 640-bed tertiary hospital in Brisbane between 1 January 2006 and 31 December 2008 in whom blood tests for iron studies had been performed as identified through interrogation of the hospital pathology database. Based on published guidelines, values of serum ferritin \(\leq 15\) \(\mu g/L\) and 16–50 \(\mu g/L\) were defined as definite and probable iron deficiency respectively.\(^ {10,23,24}\) In patients with iron deficiency, anaemia was considered present if the haemoglobin (Hb) was below the hospital laboratory reference range of 115 g/L in women, 120 g/L in men aged 65 years or older, and 135 g/L in men aged less than 65 years. Patients were excluded if they failed to meet our definition of anaemia or, on chart review, were receiving regular therapeutic venesection, or had known coeliac disease, colonic polyps or cancer under surveillance.

**Data collection**

Medical records were retrieved on all patients with definite or probable IDA, and clinical and laboratory data were collected regarding patient characteristics, haematology (values of Hb and MCV) and biochemistry results, specialty of treating clinician, results of FOBT (if performed), frequency of GI endoscopy (either OGD endoscopy, colonoscopy or both), lesions seen on endoscopy, histology of biopsied lesions and follow-up care. Values of MCV categorised anaemia into normocytic (MCV 80–100 fl), microcytic (MCV < 80 fl) and macrocytic (MCV > 100 fl); results of estimated glomerular filtration rate (eGFR) categorised patients with chronic kidney disease (CKD) into stages 1–5.\(^ {25}\)

**GI causes of occult bleeding**

On the basis of large cohort studies,\(^ {24,26–28}\) GI lesions seen on endoscopy or confirmed histologically, which were accepted as potential causes of IDA, included gastric or duodenal ulcer, GI malignancies (in the oesophagus, stomach, colon and rectum), high-risk polyps (adenoma >1 cm diameter, villous or tubulovillous, high-grade dysplasia), coeliac disease, vascular malformations, portal hypertension (oesophageal varices, portal hypertensive gastropathy), inflammatory bowel disease and large hiatus hernia predisposing to Cameron ulcers. Gastritis, duodenitis, oesophagitis, Barrett’s oesophagus, small hiatus hernia, diverticulosis and hyperplastic polyp were not considered lesions causing IDA.

**Statistical analysis**

Statistical analyses involved the total study cohort and three subgroups: all males >18 years and females \(\geq 45\) years of age with definite (group A) or probable (group B) IDA, and all females <45 years of age with definite or probable IDA (group C). Differences between subgroups were analysed using chi-square tests for proportions or analysis of variance for means. Statistical significance was denoted by \(P < 0.05\). Ethical approval for the study was received from the Metro South Human Research Ethics Committee.

**Results**

**Patient characteristics**

During the study period, 2355 measurements of serum ferritin were performed, of which 1396 (59%) returned values \(\leq 50\) \(\mu g/L\) and 736 were associated with anaemia. Of those 736 tests, 101 comprised multiple measurements on the same patient. Of 635 patients with IDA, review of medical records found 10 patients to be receiving regular venesection, 2 had known coeliac disease and 2 were under surveillance for colonic polyps. Excluding these cases resulted in a study sample of 621 patients,
with IDA comprising 266 (43%) inpatients and 355 (57%) outpatients, of whom 180 were group A (29%), 353 group B (57%) and 88 group C (14%). Baseline patient characteristics for all groups are listed in Table 1. There were no significant differences between groups A and B in terms of age, Hb, MCV or eGFR. Within the total cohort, anaemia was normocytic in 456 patients (74%), microcytic in 123 (20%) and macrocytic in 37 (6%). Stage 1–3 CKD was seen in 82% of patients, and stages 4 and 5 in the remaining 18%.

**Endoscopy utilisation**

Endoscopy of any type was undertaken in 310 patients (50%), with 272 (44%) undergoing OGD endoscopy, 257 (41%) colonoscopy and 218 (35%) both procedures (Table 2). The rate of OGD endoscopy was significantly higher in group A patients (61%) compared with group B (39%) and group C (30%, \( P < 0.01 \) for both comparisons). Similar rates were seen for colonoscopy: group A 56% versus group B 37% versus group C 31% (\( P \leq 0.01 \)). The proportion of patients undergoing both OGD endoscopy and colonoscopy decreased significantly according to group: 49% for group A, 31% for group B and 25% for group C (\( P < 0.01 \) for linear trend).

Of the 311 patients in whom no endoscopy (upper or lower) was performed, 60 (19%) were in group A, 194 (62%) in group B and 57 (18%) in group C. Among groups A and B combined (254 patients), the mean age was 64 years, male (58%), female (42%), with mean Hb 105 g/L and mean serum ferritin value of 27 ug/L. These baseline characteristics were not dissimilar to those of the total cohort.

Among this combined group of 254 patients, 25 (10%) were receiving renal dialysis, 19 (7%) had undergone renal or liver transplantation, 17 (7%) had advanced non-GI malignancy, 31 (12%) underwent bone marrow examination with haematological malignancies confirmed in 15 (6%), and 17 (7%) were assigned alternative diagnoses (haematuria, menorrhagia, mesenteric infarction, cardiac valve haemolysis, nutritional deficiency or anaemia of chronic disease). Referrals for further GI investigation were made to gastroenterologists (public or private) or general practitioners in 34 (13%) and 27 (11%) patients, respectively, while 5 (2%) were referred to other specialties. Endoscopy was declined in 13 (5%) patients while 9 (4%) were on waiting lists for endoscopy at the study hospital at the time of the study. In the remaining 74 patients (29%), no data were obtainable in determining if endoscopy was intended or undertaken.

The use of GI endoscopy in groups A and B combined differed significantly according to the specialty of the treating clinical team (Table 3). The frequency of omission of any form of endoscopy varied from 6% for gastroenterology to 72% for renal medicine, with intermediate values of 58%, 48% and 50% for haematology/oncology, general medicine and rheumatology/immunology respectively (\( P < 0.001 \) for all comparisons relative to gastroenterology). There was no significant difference between the proportion of inpatients or outpatients undergoing endoscopy (46% vs 53% respectively).

**Lesions identified on endoscopy and histological results**

The endoscopic and histological results for 272 patients who underwent OGD endoscopy are listed in Table 4. Endoscopy was normal in 78 (29%) of all patients, 29

---

**Table 1** Baseline patient characteristics

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. patients (%)</th>
<th>Age (years) (Mean ± SD)</th>
<th>Sex, M/F (%)</th>
<th>Hb (g/L) (Mean ± SD)</th>
<th>MCV</th>
<th>Serum ferritin (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>621 59/308 (50%/50%)</td>
<td>59 ± 18</td>
<td>308/313 (50%/50%)</td>
<td>104 ± 16</td>
<td>88 ± 10</td>
<td>22.9 ± 13.6</td>
</tr>
<tr>
<td>Group A</td>
<td>180 (29%)</td>
<td>63 ± 16</td>
<td>100/80 (50%/50%)</td>
<td>100 ± 18</td>
<td>82 ± 10</td>
<td>9.0 ± 3.8</td>
</tr>
<tr>
<td>All male and female ≥45 and ferritin ≤15</td>
<td>253 (57%)</td>
<td>64 ± 16</td>
<td>128/145 (59%/41%)</td>
<td>106 ± 15</td>
<td>91 ± 7</td>
<td>31.3 ± 10.1</td>
</tr>
<tr>
<td>Group B</td>
<td>88 (14%)</td>
<td>34 ± 8</td>
<td>–</td>
<td>101 ± 12</td>
<td>85 ± 10</td>
<td>17.6 ± 12.8</td>
</tr>
<tr>
<td>All female &lt;45 and ferritin ≥50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F, female; Hb, haemoglobin; M, male; MCV, mean corpuscular volume; SD, standard deviation.

**Table 2** Rates of endoscopy

<table>
<thead>
<tr>
<th>All patients</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGD endoscopy</td>
<td>272/621</td>
<td>109/180</td>
<td>137/353</td>
</tr>
<tr>
<td>(44%)</td>
<td>(61%)</td>
<td>(39%)</td>
<td>(30%)</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>257/621</td>
<td>100/180</td>
<td>130/353</td>
</tr>
<tr>
<td>(41%)</td>
<td>(56%)</td>
<td>(37%)</td>
<td>(31%)</td>
</tr>
<tr>
<td>Both</td>
<td>218/621</td>
<td>89/180</td>
<td>108/353</td>
</tr>
<tr>
<td>(35%)</td>
<td>(49%)</td>
<td>(31%)</td>
<td>(25%)</td>
</tr>
</tbody>
</table>

OGD, oesophagogastroduodenal.
(27%) in group A, 37 (27%) in group B and 12 (46%) in group C. Significant lesions were detected in 89 patients (33%) with oesophageal or gastric malignancy occurring in 12 (4%). The frequencies of abnormal findings and of significant lesions in patients undergoing endoscopy were similar in group A (80/109, 74% and 36/109, 33% respectively) and group B (101/137, 74% and 43/137, 31%) but lower in group C (14/26, 54% and 10/26, 38%), although these differences were not significant.

Similar yields were seen for colonoscopy (Table 5), which was normal in 83 (32%) of all patients, 27 (27%) group A, 40 (31%) group B and 12 (44%) group C. Significant lesions were seen in 137 (53%), with cancer and high-risk adenomas detected in 51 patients (20%), intermediate in group B (23/130, 18%) and lowest in group C (1/27, 4%, \( P = 0.02 \) for comparisons to group A). Of the 23 cases of colon cancer detected among all patients undergoing colonoscopy, 14 (61%) were located in the caecum and ascending colon, 4 (17%) in the descending colon and 5 (22%) in the sigmoid colon and rectum. Surgery was performed on 20 patients (87%), with hemicolectomy occurring in 11 (58%). Mean interval from blood tests to surgery was 113 days (range: 11–764).

**Faecal occult blood testing**

Among all 621 patients, FOBT was performed in 112 patients (18%), among whom immunoassays (FOBI) were undertaken in all patients (100%), and both FOBI and guaiac acid-based tests (FOBG) in 98 (88%). In the 275 patients who underwent colonoscopy, the prevalence of colon cancer and high-risk adenomas was not significantly different regardless of whether FOBG and FOBI were both positive (6/27, 22%), either one was positive (8/42, 19%), both were negative (4/17, 24%) or no FOBT had been performed (37/189, 20%). Of the 254 patients in groups A and B combined who did not

<table>
<thead>
<tr>
<th>Findings</th>
<th>All patients, no. (%)</th>
<th>Group A, no. (%)</th>
<th>Group B, no. (%)</th>
<th>Group C, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>272/621 (44%)</td>
<td>109/180 (61%)</td>
<td>137/353 (39%)</td>
<td>26/88 (30%)</td>
</tr>
<tr>
<td>Normal</td>
<td>78 (29%)</td>
<td>29 (27%)</td>
<td>37 (27%)</td>
<td>12 (46%)</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>25 (9%)</td>
<td>9 (8%)</td>
<td>11 (8%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>12 (4%)</td>
<td>7 (6%)</td>
<td>5 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>27 (10%)</td>
<td>10 (9%)</td>
<td>14 (10%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>19 (7%)</td>
<td>7 (6%)</td>
<td>11 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Gastritis/oesophagitis</td>
<td>55 (20%)</td>
<td>18 (17%)</td>
<td>33 (24%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>GORD/HH</td>
<td>16 (6%)</td>
<td>7 (6%)</td>
<td>9 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Polyp/other tumour</td>
<td>11 (4%)</td>
<td>5 (5%)</td>
<td>7 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>6 (2%)</td>
<td>3 (3%)</td>
<td>2 (1%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Barrett’s oesophagus</td>
<td>11 (4%)</td>
<td>7 (6%)</td>
<td>4 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>12 (4%)</td>
<td>7 (6%)</td>
<td>5 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Total lesions in all patients</td>
<td>194 (31%)</td>
<td>80 (44%)</td>
<td>101 (29%)</td>
<td>14 (16%)</td>
</tr>
<tr>
<td>Total lesions in those tested</td>
<td>71%</td>
<td>73%</td>
<td>74%</td>
<td>54%</td>
</tr>
<tr>
<td>Significant lesions in those tested†</td>
<td>89 (33%)</td>
<td>36 (33%)</td>
<td>43 (31%)</td>
<td>10 (38%)</td>
</tr>
</tbody>
</table>

†Peptic ulcers, malignancy, coeliac disease, portal hypertension, vascular malformation. GORD, gastro-oesophageal reflux disease; HH, hiatus hernia.
undergo endoscopy, 241 (95%) either did not have FOBT checked or returned negative results.

**Iron supplementation**

Excluding patients for whom no data were obtainable ($n = 90$), iron supplementation was prescribed to 317 of 531 (60%) patients overall, with higher prescribing rates in group A (116/156, 74%) than in group B (155/296, 52%) or group C (46/79, 58%, $P \leq 0.01$ for all comparisons). Among the entire cohort, red cell transfusions were administered in 18 (3%) patients.

**Discussion**

To our knowledge, this is the largest contemporary audit of evaluation of IDA in an Australian tertiary hospital setting. Our audit revealed that only one in two patients was documented to have undergone any form of endoscopy, and just over one in three patients underwent dual endoscopy. While higher than reported in past studies involving younger patients and smaller samples,$^2$ these rates are still far from optimal according to current guidelines.

Endoscopy rates were highest among patients attending gastroenterologists and lowest in those attending nephrologists. In patients with CKD, clinicians may be more likely to ascribe iron deficiency to poor iron absorption and occult GI loss secondary to gastritis/duodenitis in the absence of guidelines that state explicit indications for GI evaluation in such patients.$^3$ We could find no study that investigated the frequency and yield of GI endoscopy in non-dialysis patients with CKD and IDA. In a single centre study of 2417 patients with end-stage renal failure treated with dialysis/transplantation over 30 years (1967–2000),$^4$ of the 14 patients who developed colorectal cancer, 9 patients were transplant patients and 5 patients were undergoing dialysis, with 6 of the 7 transplant patients presenting at an advanced stage of disease, and all 7 dying within 9 months, suggesting delays in diagnosis.

Patients $>$45 years of age with definite IDA underwent either OGD endoscopy or colonoscopy or both more frequently than those with probable IDA who, in turn, underwent these procedures more frequently than young female patients with either definite or probable IDA. We theorise that this was driven by the higher risk of malignancy in older patients, and the greater likelihood of menorrhagia and inadequate dietary iron intake as causes of IDA in younger females.

Our results confirmed detection rates of malignant and pre-malignant lesions combined that were significantly different between groups, averaging more than 1 in 4 patients $>$45 years of age with definite IDA, almost 1 in 5 patients $>$45 years of age with probable IDA, but less than 1 in 20 females $<$45 years of age with definite or probable IDA. Not surprisingly, these lesions were more commonly detected in the lower than in the upper GI tract (20% vs 4%). Importantly, the majority of lower GI cancers were found in the ascending colon and caecum, which are only accessible by colonoscopy, confirming this as procedure of first choice over flexible sigmoidoscopy. Nevertheless, significant GI lesions were seen in 38% and 37% of premenopausal patients who underwent OGD endoscopy and colonoscopy, respectively, highlighting the need, noted by others,$^5$ for close monitoring of patients in whom IDA persists despite treatment of non-GI causes.

---

**Table 5** Gross endoscopic findings and histology of biopsied lesions in patients undergoing colonoscopy

<table>
<thead>
<tr>
<th>Findings</th>
<th>All patients, no. (%)</th>
<th>Group A, no. (%)</th>
<th>Group B, no. (%)</th>
<th>Group C, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n = 257/621 (41%)$</td>
<td>$n = 100/180 (56%)$</td>
<td>$n = 130/353 (37%)$</td>
<td>$n = 27/88 (31%)$</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>83 (32%)</td>
<td>27 (27%)</td>
<td>40 (31%)</td>
<td>12 (44%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>23 (9%)</td>
<td>11 (11%)</td>
<td>11 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>High-risk adenoma</td>
<td>28 (11%)</td>
<td>16 (16%)</td>
<td>12 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Other adenoma</td>
<td>42 (16%)</td>
<td>14 (14%)</td>
<td>28 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>IBD</td>
<td>30 (12%)</td>
<td>9 (9%)</td>
<td>13 (10%)</td>
<td>8 (30%)</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>12 (5%)</td>
<td>4 (4%)</td>
<td>8 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperplastic polyp</td>
<td>15 (6%)</td>
<td>6 (6%)</td>
<td>8 (6%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Haemorrhoids</td>
<td>14 (5%)</td>
<td>7 (7%)</td>
<td>6 (5%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Ulcers</td>
<td>2 (&lt;1%)</td>
<td>4 (4%)</td>
<td>1 (&lt;1%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Others</td>
<td>8 (3%)</td>
<td>2 (2%)</td>
<td>3 (2%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Total lesions in all patients</td>
<td>174 (28%)</td>
<td>73 (41%)</td>
<td>90 (25%)</td>
<td>15 (17%)</td>
</tr>
<tr>
<td>Total lesions in those tested</td>
<td>68%</td>
<td>73%</td>
<td>69%</td>
<td>56%</td>
</tr>
<tr>
<td>Significant lesions† in those tested</td>
<td>137 (53%)</td>
<td>58 (58%)</td>
<td>56%</td>
<td>37%</td>
</tr>
</tbody>
</table>

†Cancer, adenoma, inflammatory bowel disease, vascular malformation, ulcers. IBD, inflammatory bowel disease.
The yield of colon cancer and high-risk adenomas at colonoscopy demonstrated no relation with the results of FOBT and was approximately the same – about one in five patients – irrespective of whether FOBT was positive or negative or even performed. This replicates results of other studies and confirms the uselessness of such testing in deciding whether patients should undergo endoscopy. In addition, three of four patients with IDA were normocytic, which underlines the importance of requesting iron studies in all patients with anaemia regardless of the MCV value.

Finally, 40% of evaluable patients received iron supplementation, with patients >45 years of age with definite IDA about 40% more likely to receive supplements than premenopausal females with IDA despite the greater likelihood of easily remediable dietary deficiency in the latter group. The rates of red cell transfusions were appropriately low in the presence of Hb levels that were at or above 85 g/L for more than 95% of patients.

Study limitations

Limitations of our study include the use of a cut-point for serum ferritin of 50 ug/L to identify patients with IDA which, compared with a cut-point of 100 ug/L, may underestimate IDA prevalence. However, our cut-point accords with current guidelines and defines patients with IDA at highest risk. Retrospective review of case notes may have prevented ascertainment of legitimate reasons for omission of endoscopy, which a prospective study with real-time clinician contact may have achieved.

However, such a study may engender Hawthorne effects and generate a distorted view of routine practice. Finally, long-term follow up was not possible in assessing and comparing outcomes of endoscoped versus non-endoscoped patients. Such a study would require a large patient cohort monitored over several years in order to show significant differences in mortality or serious morbidity.

Conclusion

This study reveals that almost one in two patients with IDA and no obvious cause attending a tertiary hospital were not documented as undergoing any form of GI endoscopy, despite a one in five prevalence of colon cancer and high-risk adenomas in patients older than 45 years undergoing colonoscopy, and one in three prevalence of significant GI lesions in similar patients undergoing OGD endoscopy. While considerable attention is currently being given to community-based FOBT screening for colorectal cancer, our results suggest a need for more complete GI evaluation in high-risk patients with known IDA attending hospitals. More intense promulgation of guidelines for evaluating patients with IDA, more expeditious access to endoscopy and repeat audits similar to ours are required to improve suboptimal rates of endoscopy.

Acknowledgement

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Oral drug challenges in non-steroidal anti-inflammatory drug-induced urticaria, angioedema and anaphylaxis

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Key words
NSAID, allergy, urticaria, angioedema, anaphylaxis, challenge.

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Abstract

Background: Urticaria, angioedema and anaphylaxis are common adverse reactions to non-steroidal anti-inflammatory drugs (NSAIDs).

Aim: To investigate the clinical characteristics of NSAID-induced acute hypersensitivity reactions with structured oral drug challenges.

Methods: Patients with NSAID-induced urticaria, angioedema or anaphylaxis were challenged with either the homologous NSAID to confirm diagnosis or a heterologous NSAID to investigate cross-reactivity. Data were analysed retrospectively and supplemented by a telephone questionnaire.

Results: Sixty-eight patients (mean age 48.3, 53 females) reported a total of 75 instances of NSAID-induced reactions of which 64% were purely cutaneous and 36% were systemic anaphylaxis. Ibuprofen was the most frequent cause of reactions (35%), however, diclofenac was the most frequent cause of anaphylaxis (48%). Seventeen out of 40 (43%) homologous NSAID challenges were positive; presentation with anaphylaxis or reaction to diclofenac predicted a positive challenge. Only 7 of 28 (25%) of heterologous NSAID challenges were positive. Structured challenges enabled us to identify 23 (34%) patients with selective reactivity to a single NSAID, 19 (28%) patients with cross-reactivity to multiple NSAIDs and 23 (34%) patients in whom NSAID hypersensitivity was not reproduced. Selective reactors presented most often with anaphylaxis and some had a background of beta-lactam antibiotic allergy. Cross-reactive patients often had a background of chronic urticaria and presented with milder reactions.

Conclusion: In the absence of a reliable in vitro test, structured drug challenges allow identification of selective and cross-reactive NSAID hypersensitivity syndromes. NSAID-induced anaphylaxis is often associated with selective hypersensitivity and patients may not need to avoid other NSAIDs.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are cyclo-oxygenase inhibitors with analgesic, anti-inflammatory, antipyretic and antithrombotic effects. They are the most commonly prescribed class of drugs in the world,1 are implicated in 20–25% of all adverse drug reactions2 and hypersensitivity reactions have a population prevalence of 0.3–2.5%.

Acute NSAID hypersensitivity reactions may take several forms that are not mutually exclusive.3 These reaction types may have differing pathogenesis and genetic predisposition,4 and can be grouped into the following categories:5

- respiratory (rhinoconjuctivitis and/or bronchospasm)
- cutaneous (urticaria and/or angioedema)
- systemic (anaphylaxis)
- mixed

Respiratory reactions usually occur in the context of a background of chronic asthma and polypoid rhinosinusitis (aspirin-exacerbated respiratory disease (AERD) or ‘Samter’s triad’). Patients with chronic urticaria (CU) may suffer exacerbations from aspirin or NSAIDs.3 However, discrete reactions to NSAIDs may occur in the absence of these conditions, and these are the focus of this paper.

NSAID hypersensitivity may be isolated to a single NSAID, or a syndrome of cross-reactive (CR) intolerance to multiple NSAIDs. Selective NSAID hypersensitivity has many features resembling Type 1 hypersensitivity,6 although the mechanism is unknown. The syndrome of CR NSAID hypersensitivity does not have an immunological basis, but is the result of pharmacological inhibition of COX1, and is therefore a class effect; most but not all of these patients tolerate COX2-specific NSAIDs.7

In the absence of a reliable in vitro test, the accurate diagnosis of NSAID hypersensitivity depends on a careful
history and oral drug challenge (ODC). Previous studies describing ODCs have largely relied on the use of specific COX2 inhibitors in NSAID intolerant patients, irrespective of the clinical history. Although this approach enables identification of a safe alternative, it does not differentiate between selective and CR NSAID hypersensitivity, and may lead to unnecessary avoidance of potentially useful NSAIDs. We devised a structured protocol for assessment of patients with suspected or confirmed NSAID hypersensitivity and retrospectively examined the results of this approach as a tool for defining and differentiating selective and CR NSAID hypersensitivity syndromes.

Materials and methods

Patient selection

Patients who presented to the Royal Adelaide Hospital (RAH) Clinical Immunology and Allergy Department between February 2006 and June 2010 with a history of acute cutaneous or anaphylactic reaction to one or more NSAIDs (the index reaction(s)) and subsequently underwent a controlled oral challenge were retrospectively identified from our database. Patients with known AERD, current CU (ongoing spontaneous urticaria on most days of the week for more than 6 weeks) or aspirin-dependent exercise-induced anaphylaxis were excluded. Anaphylaxis was defined as a rapidly evolving multisystem reaction with any of the features of a grade 2 or grade 3 generalised hypersensitivity reaction according to the Brown classification, occurring acutely after NSAID ingestion.

ODC

Unblinded graded-dose ODCs were performed with informed consent as day procedures in the hospital ambulatory day centre where resuscitation facilities were available. The dosing schedule is summarised in Table 1. Antihistamines, montelukast, cromolyn and inhaled sympathomimetics were withheld at least 48 h prior to the challenge. The clinical characteristics of each ODC (NSAID involved, symptom pattern, time of onset of reaction) were recorded. A challenge was considered positive if characterised by the development of objective symptoms and signs including urticaria, angioedema, rhinoconjunctivitis or bronchospasm (FEV1 reduced by >15% from baseline). No patient in our cohort had hypotension, laryngeal oedema or required treatment with adrenaline.

The structured protocol is depicted as a flow chart in Figure 1. Patients were assigned to undergo one of two different types of ODC:

- Homologous ODC: challenge with the same drug involved in the index reaction. This was primarily to confirm diagnosis when it could not be confidently established from the history. A homologous ODC was sometimes avoided when the patient’s index reaction was severe anaphylaxis.

- Heterologous ODC: challenge with a different COX1 inhibitory NSAID (usually aspirin). This was done when NSAID hypersensitivity was already confidently established on clinical history (or when the primary homologous ODC was positive) in order to investigate cross-reactivity. Some patients with a positive heterologous ODC underwent a further challenge with a COX2 selective NSAID.

Not all patients were evaluated strictly in accordance with the final protocol (Fig. 1), which evolved and was refined over the 5 years of data collection. In some instances intermediate steps were omitted as dictated by clinical circumstances.

A patient was designated a selective reactor (SR) if the reaction was limited to a single NSAID and tolerance was demonstrated to at least one other potent COX1 inhibitor (usually aspirin) in full dosage. Aspirin is an irreversible inhibitor of COX and displays approximately fourfold selectivity towards COX1. As oral challenges with 30–150 mg aspirin typically induce COX1 mediated hypersensitivity reactions in susceptible individuals, absence of reaction to 600 mg aspirin was deemed to exclude CR NSAID hypersensitivity.

CR NSAID hypersensitivity was defined as a primary reaction to aspirin or reactions to at least two separate NSAIDs, usually one suspected from history plus a positive ODC to aspirin. Our review of the literature did not identify any reports where aspirin caused selective hypersensitivity, so an index reaction to aspirin was deemed to signify CR hypersensitivity. This group could be further divided into those in whom the cross-reactivity was limited to the classical COX1-inhibiting NSAIDs with tolerance to the COX2 selective NSAIDs, and those with hypersensitivity to all NSAIDs including COX2 selective agents.

Table 1: Non-steroidal anti-inflammatory drug doses used for oral drug challenge

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Dose (mg)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potent, non-selective COX1/COX2 inhibitor</td>
<td>Aspirin</td>
<td>20, 75, 150, 600</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>40, 120, 400</td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
<td>5, 15, 50</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td>50, 150, 500</td>
</tr>
<tr>
<td>Weak non-selective COX1/COX2 inhibitor</td>
<td>Paracetamol</td>
<td>150, 500, 1500</td>
</tr>
<tr>
<td>Preferential COX2 inhibitor</td>
<td>Meloxicam</td>
<td>1.5, 5, 15</td>
</tr>
<tr>
<td>Selective COX2 inhibitor</td>
<td>Celecoxib</td>
<td>50, 100, 200</td>
</tr>
</tbody>
</table>

†All doses 120 min apart.
Telephone questionnaire

Clinical information obtained from review of referral and discharge letters was further supplemented with data gained from a telephone questionnaire (approved by the RAH ethics committee). The following data were collected: age, sex, concomitant diseases, characteristics of adverse reactions (NSAID involved, dose, time elapsed between administration of drug and onset of reaction, symptoms experienced and treatment given), number of episodes to the same or different NSAIDs, and NSAID use and tolerance after classification. Atopy was determined by a history of doctor-confirmed hay fever, asthma or eczema. Patient-reported history of allergy to other drugs was not confirmed by further testing or challenge.

Statistical analysis

Statistical analysis was conducted with PASW Version 18.0. Comparison between two groups of continuous variables was performed with an unpaired t-test. Differences in the frequency of nominal variables were detected with a 2 ¥ 2 Fisher exact test and a type I error rate of <0.05 was considered significant. Differences in the frequency of ordinal variables was calculated using a likelihood ratio, with a type I error rate of <0.05 considered significant. Where two variables were shown to be predictive of an outcome, the contribution of each variable to the outcome was determined by addition to a logistic regression model. The second variable was then added to determine the correlation coefficient, and if this increased, each variable was determined to be an independent predictor of the outcome.

Results

Patients

Sixty-eight patients (53 females) were included in the study. Mean age was 48.5 (range 16 to 73) years. These
patients reported a total of 75 acute NSAID hypersensitivity reactions of which 27 (36%) were systemic anaphylaxis and 48 (64%) pure cutaneous reactions (urticaria and/or angioedema). Five patients had reacted to two and one patient to three different NSAIDs. The NSAIDs involved are presented in Table 2. In order of frequency, these include ibuprofen (n = 26 reactions, 35%), diclofenac (n = 14, 19%), aspirin (n = 11, 15%) and paracetamol (n = 11, 15%). Naproxen, celecoxib, lumiracoxib, meloxicam and indomethacin were responsible for the remaining 13 reactions (17%). In the anaphylaxis subgroup, diclofenac was the most commonly incriminated drug (n = 13, 48%) followed by celecoxib (n = 5, 18%). No cases of anaphylaxis were seen with aspirin. Except for one patient (topical), all NSAIDs were taken orally for acute (63%) or chronic (37%) pain. Systemic anaphylaxis was associated with NSAID use for acute pain (duration <7 days) in 25 of 27 patients (92%). Time intervals between drug intake and reaction onset were less than 1 h in 60%, between 1 and 6 h in 32% and >6 h in 8% of patients. Forty-four (64%) of all patients were successfully contacted by telephone. Supplementing this information with case records, a personal history of atopy was found in 19 (27%), family history of atopy in 14 (20%) and a patient-reported history of beta-lactam antibiotic allergy in 23 (33%) patients.

### Homologous ODC

Forty patients (33 females, mean age 43.8 years) were subjected to a homologous ODC because of diagnostic uncertainty. Seventeen had a positive challenge. Challenges were more frequently positive when the index reaction was anaphylaxis (10/15, 66%) compared with urticaria and/or angioedema (7/18, 39%) (P = 0.024). Challenge with diclofenac was most commonly associated with a positive outcome (8/11, 73%) compared with other NSAIDs combined (9/29, 30%) (P = 0.031). Logistic regression analysis indicated that anaphylaxis as the index reaction and diclofenac as the index drug independently predicted the ODC outcome. There was a trend towards increased likelihood of a positive challenge when there was a shorter index reaction to challenge interval: <6 months (10/21, 48%); ≥6 months (7/19, 37%) (P = 0.54). Fourteen patients who had a positive homologous ODC subsequently underwent a secondary heterologous ODC with an alternative NSAID. Three patients declined a secondary ODC and preferred to avoid all NSAIDs. Five of the six (83%) diclofenac-intolerant patients subsequently tolerated aspirin in a secondary ODC, suggesting that they had selective diclofenac hypersensitivity. For ibuprofen, reproducibility of the index reaction was lower (4/13 positive, 30%) and most of the positively identified intolerant patients (3/4, 75%) were also intolerant to aspirin, indicating a cross-reactor status.

### Heterologous ODC

Twenty-eight patients (20 females, 8 males, mean age 53.3 years) had reliable evidence on clinical grounds to satisfy a diagnosis of acute hypersensitivity to the index NSAID and hence underwent an ODC with a heterologous NSAID. These patients were considered in two subgroups. **Sub-group 1** comprised 21 patients who had previously reacted to a single NSAID and were therefore challenged with aspirin to determine cross-reactivity. Seven of these reacted, whereas 14 tolerated the aspirin ODC and were thus designated cross-reactors (CR) and SRS respectively. **Sub-group 2** comprised of 7 patients in which cross-reactivity was already apparent on history by virtue of reactions to two or more different NSAIDs and further aspirin ODC was therefore not required.

A total of 19 confirmed CR (including some who started with a primary homologous challenge) underwent a further challenge with a COX2 selective NSAID. Tolerance was 72% (8 of 11) for meloxicam, 100% (4/4) for celecoxib and 75% (3/4) for paracetamol. Three patients declined a secondary NSAID challenge and could not be classified.

Overall, by means of homologous and heterologous ODC, in our cohort of 68 patients we identified 23 (34%) SR, 19 (28%) CR and 23 (34%) NSAID-tolerant individuals.

SR (mean age 38.7, 53% females) presented almost exclusively with anaphylaxis (20/23, 87%, compared with 5/19 (26.3%) for CR (P = 0.001). All but one of the 23 SR had prior history of intake of the same NSAID (without reaction). SR more commonly had a self-reported history of allergy to beta-lactam antibiotics (9/23 (39%) versus 1/19 (5.3%); P = 0.013). CR were...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reactions</th>
<th>SA</th>
<th>PA</th>
<th>U &amp; A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>11</td>
<td>0</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>26</td>
<td>7</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>11</td>
<td>1</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>14</td>
<td>13</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Naproxen</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>27</td>
<td>27</td>
<td>21</td>
</tr>
</tbody>
</table>

PA, isolated periorbital angioedema; SA, systemic anaphylaxis; U & A, urticaria and angioedema.
older (mean age 62.1) \( (P < 0.001) \), mostly females (74%) and the predominant presentation was angioedema (14/19, 73%). CR had a significant association with a history of CU (10/19 (52.6%), compared with 1/23 (4.3%) for SR \( (P < 0.001) \). Although patients with AERD were excluded, 1/23 SR patients had a history of asthma compared with 3/19 CR patients (not significant). Many CR gave a history of reaction on first exposure to a NSAID.

The NSAID-tolerant group was contacted by telephone to confirm out of hospital tolerance. Eighteen patients responded of which seven confirmed tolerance. Eleven, however, continued to avoid NSAID despite a negative ODC.

**Discussion**

This study addresses the optimal diagnostic procedure to define NSAID hypersensitivity reactions. The main limitation of the study is the retrospective design. However, the importance of ODCs in the diagnosis of NSAID hypersensitivity is highlighted by the observation that less than 50% of patients in our series with a history of suspected NSAID hypersensitivity demonstrated reactivity in the controlled ODC. Reasons for this might include temporary hypersensitivity, cofactors no longer present or misattribution to the NSAID when it was a different trigger such as another drug, a food or a viral illness. These patients would have unnecessarily continued to avoid NSAIDs. The clinical parameters that significantly predicted a positive challenge outcome in this series were anaphylaxis as the index reaction and diclofenac as the index NSAID, whereas the reaction-to-challenge duration of less than 6 months appeared to be predictive but did not reach statistical significance.

**Selective NSAID hypersensitivity**

This is defined by reactivity to a single, specific NSAID with good tolerance to other NSAIDs. SRs were distinguished from cross-reactors (CR) in our patient group by presentation with more severe reactions (anaphylaxis) (Fig. 2) and a higher rate of a self-reported history of allergy to beta-lactam antibiotics (Fig. 3). Most SR had a history of prior exposure to the same drug, especially when used intermittently for acute pain. SR was most commonly associated with reactions to diclofenac and celecoxib; selective hypersensitivity was uncommon to ibuprofen and not seen with aspirin.

The mechanism for selective NSAID hypersensitivity appears to relate to the molecular structure of the drug rather than its pharmacological activity. Studies\(^{12,13}\) have validated this concept in patients with anaphylaxis to a single NSAID, using multiple challenges that showed tolerance to a number of structurally unrelated NSAIDs. Cross-reactivity between structurally similar NSAIDs does occur (e.g. aceclofenac/diclofenac, dipyrone/propyphenazone) but these are not used in Australia. NSAID currently available in Australia are structurally diverse and there is no evidence that any two are sufficiently similar to cross-react on the basis of structure.\(^3\)

Several features of the clinical pattern of selective NSAID hypersensitivity are consistent with a type-1 (immunoglobulin E (IgE)-mediated) hypersensitivity model: the dependence on molecule structure rather than function, the history of prior exposure and intermittent use (consistent with immunological sensitisation), reproducibility in challenge (anamnestic response) and diminution of response over time (waning of immunological memory). The delayed and variable timing of anaphylaxis following NSAID ingestion may argue against an IgE mechanism. Specific IgE to the pyrazolone class of NSAIDs (not used in Australia) was identified \textit{in vitro} more than...
20 years ago, however, there have been no convincing demonstrations of specific IgE to other NSAIDs. Despite the relatively common association of diclofenac with anaphylaxis, only a single case report claims to identify in vitro evidence for specific IgE. A recent comprehensive investigation of 41 individuals with a history of anaphylaxis to diclofenac failed to identify specific IgE to the drug or its phase 1 metabolites despite four different assay systems; indeed given the well-controlled experimental systems used, the authors concluded that drug-specific IgE is excluded as a mechanism. Therefore, despite circumstantial indications, there is no evidence of a role for IgE in most cases of selective NSAID anaphylaxis and the mechanism remains unknown.

Selective NSAID hypersensitivity is more common than often recognised. In a recent study, 75% of patients with history of allergy to a single (non-aspirin) NSAID were able to tolerate aspirin in an oral challenge test.

**CR NSAID hypersensitivity**

The syndrome of CR NSAID hypersensitivity is characterised by intolerance to multiple COX1-inhibiting NSAIDs, which may extend to the selective COX2 inhibitors. AERD and chronic urticaria (CU) are commonly associated with CR NSAID hypersensitivity.

Statistically significant clinical observations regarding CR from our study include greater mean age, presentation with angioedema and/or urticaria more commonly than anaphylaxis and history of chronic urticaria. There were trends to female predominance, index reaction to aspirin or ibuprofen and reactions on the first exposure to a NSAID.

The likely explanation for CR NSAID hypersensitivity is the inhibition of COX1 by NSAIDs, which makes the protective prostaglandin E2 unavailable to prevent 5-lipoxygenase mediated biosynthesis of sulfidoleukotrienes from arachidonic acid and the release of histamine and PGD2 from mast cells and basophils. Hence the balance between the anti- and pro-inflammatory arachidonic acid metabolites is acutely disturbed by the NSAID. Observations from other studies that lend support to this hypothesis include a relationship between the potential to cause reactions and the COX1 inhibitory potency of the drug, tolerance to selective COX2 inhibitors, elevation of basal leukotriene E4 levels in patients with NSAID-intolerant asthma or urticaria, and the ability of leukotriene receptor antagonist drugs to suppress reactions to NSAIDs.

In our cohort of CR NSAID intolerant patients, 72% were able to tolerate meloxicam, 75% paracetamol and 100% celecoxib. Although numbers are small, this parallels the degree of COX2 selectivity of these drugs.

**Diagnostic approach to patients with NSAID-induced reactions**

ODC is the primary tool available to the clinician for diagnosis and management of NSAID hypersensitivity. Diagnostic drug challenges must be carried out under close supervision by experienced medical and nursing staff in a centre with facilities to treat anaphylaxis. The history is crucial; the presence of current or recent asthma, nasal polyposis or chronic urticaria (not discussed in this paper) suggest CR NSAID intolerance and investigation generally commences with aspirin challenge for diagnosis if required, and if positive, subsequent challenge with a COX2-selective agent, which will be tolerated in most but not all cases. In the absence of these conditions, in patients with discrete NSAID reactions, our experience led us to devise a structured approach, as shown in Figure 1, resulting in a high diagnostic yield and acceptable patient safety. If the diagnosis is not clinically certain then a homologous challenge will confirm or refute hypersensitivity to the index NSAID. However, if this is reliably evident on the history, one may directly proceed to the second step of heterologous challenge with another COX1 inhibitor such as aspirin to allow distinction between SR and CR. Those who tolerate aspirin can be considered SR (to the index drug) and should tolerate any other NSAID. A positive aspirin challenge indicates CR. The options for CR are to avoid NSAIDs altogether and use alternative analgesics or to consider further challenge with a COX2-specific NSAID. Avoiding all COX1 inhibitors in patients with a reaction to one NSAID without first defining their status as SR or CR significantly limits the NSAID repertoire.

We have found that certain features of the history or presentation are associated with challenge positivity and with SR or CR status; however, we advise against any assumptions on the basis of history alone in the absence of challenge confirmation. When the diagnosis has been established, a MedicAlert® should be considered to guard against inadvertent NSAID administration, such as during emergency surgery in injectable or suppository form.

**Conclusion**

Hypersensitivity reactions to NSAIDs are commonly encountered adverse drug reactions. In the absence of a reliable in vitro test, a structured approach based on history and standardised ODCs is essential for diagnosis and subsequent management of selective and CR NSAID hypersensitivity syndromes. Patients who suffer acute hypersensitivity reactions to a NSAID must initially avoid all NSAIDs but with appropriate investigation as outlined the majority can resume tailored NSAID therapy.
References

Anti-glomerular basement membrane disease in Auckland

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Key words
anti-glomerular basement disease, crescentic glomerulonephritis, Goodpastures disease.

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Introduction

Anti-glomerular basement membrane (GBM) antibody disease is a disorder in which circulating antibodies are directed against the non-collagenous domain of type IV collagen in the GBM, thereby resulting in acute or rapidly progressive glomerulonephritis that is typically associated with crescent formation.1 Goodpastures disease is used synonymously to refer to anti-GBM antibody-mediated disease, which typically presents with the syndrome of glomerulonephritis and pulmonary haemorrhage, but may present with glomerulonephritis alone. However, some use the term Goodpastures syndrome for the clinical constellation of glomerulonephritis and pulmonary haemorrhage, irrespective of the underlying pathogenesis.

There are little data on the population incidence and prevalence of anti-GBM disease.2 It is recognised that anti-GBM disease may develop post-transplant in 3–5% of patients with Alport’s disease.3 In the general population acute glomerulonephritis caused by anti-GBM antibody disease is considered rare, and generally estimated to occur in fewer than one case per million population. In case series published before the 1980s, anti-GBM antibody disease accounted for fewer than 20% of cases of rapidly progressive glomerulonephritis.4 However, anti-GBM disease may be present in up to 50% of patients presenting with concomitant severe pulmonary involvement.5 A study from New Zealand in the 1970s identified 29 cases of Goodpastures syndrome occurring during a 13-year period, with frequent pulmonary involvement a prominent feature.6 That study noted a male preponderance, a disproportionate frequency among Maori, the indigenous people of New Zealand, and a high mortality rate of 55% within 2 years of presentation. All patients had a renal biopsy showing linear immunoglobulin G (IgG) staining on immunofluorescence.

The aim of this study was to determine the incidence, clinical features, management and outcomes of anti-GBM disease in the Greater Auckland region between 1998 and 2008.
This study was approved by the New Zealand Health and Disability Northern X Regional Ethics Committee (NTX/10/EXP/094).

Subjects and methods
Testing for anti-GBM antibodies is performed in a single, central laboratory in the greater Auckland region, LabPlus. Serum is screened by indirect immunofluorescence for GBM antibodies. All renal biopsies performed in the greater Auckland region are processed and interpreted in LabPlus. When adequate tissue is obtained at renal biopsy, immunofluorescence is routinely performed on samples. There are three district health boards in the greater Auckland region with universal publicly funded healthcare.

All positive results for anti-GBM antibody at LabPlus, between 01 January 1998 and 01 January 2008, were determined. An electronic search of all renal biopsy reports on procedures performed between 01 January 1998 and 01 January 2008 was performed using the terms ‘anti-GBM’ or ‘Goodpastures’ to identify potential subjects. In-hospital admissions between 01 January 1998 and 01 January 2008 were evaluated by clinical decision support at all three district health boards searching International Classification of Diseases 9 and 10 codes that included the specific diagnoses plus non-specific diagnostic codes that may be used to describe important clinical features of anti-GBM disease.

A retrospective case notes review was performed with clinical and demographic data obtained, with data censored for 31 December 2010. Patients who had tests sent to LabPlus for processing from outside the greater Auckland region were excluded from this report. Patients referred from other regions for in-patient tertiary care were also excluded. The clinical records of all potential patients within the region were able to be obtained from hospitals. Additional data from primary practice or private specialist care were obtained if necessary.

Patients were included if a diagnosis of anti-GBM antibody disease was made. In the majority (all but two), this was made solely on renal histology. In the other two cases, a combination of biopsy, clinical and serological evidence was used. Those patients with concurrent positive ANCA serology, so-called ‘double positive’ disease, were excluded.

Population estimates were obtained from Statistics New Zealand and data from the 1996, 2001 and 2006 New Zealand censuses. Population estimates were obtained from Statistics New Zealand and data from the 1996, 2001 and 2006 New Zealand censuses. Data were entered directly into a prepared Microsoft Access database, and statistical analysis was performed using Microsoft Excel. Where not stated, P-values reflect a chi-square test.

Results

Demographics
Twenty three cases of anti-GBM disease were identified, 12 men and 11 women. The median age at the time of presentation was 45 years with a range of 12 to 74 years.

It is estimated that over the 10-year study period, for the Auckland region there were 12 791 880 patient-years with 11.1% of the population identifying themselves as New Zealand Māori and 14.3% as Pacific peoples. The rate of proven anti-GBM disease is therefore 1.79 cases per million person-years. Sixteen patients were Europeans, three Pacific peoples, three Māori and one Chinese. Using Fisher’s exact test there is no difference noted in the risk of developing anti-GBM disease between European, Māori and Pacific peoples.

Date of presentation
We determined the date and the season that each case presented. Four cases presented in spring, six cases in summer, six cases in autumn and seven in winter. A chi-square test did not reveal any clustering of cases by month of presentation ($P = 0.5437$) or season ($P = 0.8206$)

Smoking
Eleven patients were smokers at presentation, eight were ex-smokers and four patients had never smoked. Using a chi-squared significance test, these statistics were compared with population rates from the 2006 census. The proportions of both current ($P < 0.001$) and ex-smokers ($P < 0.001$) are significantly higher than the general population (Table 1).

One patient who presented with a pulmonary renal syndrome had worked as a spray painter, and one patient who had a pure pulmonary syndrome had inhaled methamphetamine exposure.

Table 1 Smoking history in the Auckland region and in subjects

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Auckland population 2006†</th>
<th>Anti-glomerular basement membrane study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular smoker (%)</td>
<td>172 506 (17%)</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Ex-smoker (%)</td>
<td>178 557 (17%)</td>
<td>8 (36%)</td>
</tr>
<tr>
<td>Never smoked regularly (%)</td>
<td>577 638 (56%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Total</td>
<td>1 026 558</td>
<td>22</td>
</tr>
</tbody>
</table>

†These data exclude those under the age of 15 years, so the one patient in our series who was 12 years of age at presentation, and had never smoked, is excluded from the analysis.
Those who were smokers at presentation were significantly more likely to have respiratory involvement than ex-smokers or those who had never smoked ($P = 0.03$).

**Clinical features**

The majority of patients, 22 of 23, presented with renal disease as defined by new renal impairment, haematuria and/or proteinuria. Pulmonary disease was defined as bilateral infiltrates on chest radiograph, haemoptysis or frank pulmonary haemorrhage. One patient had pulmonary features alone with no sign of renal disease. Eight had the pulmonary renal syndrome and 14 had lone renal disease.

One patient had normal renal function, no haematuria or proteinuria. Two patients were anuric at presentation and urinalysis was not possible. Twenty patients had haematuria and proteinuria. Four patients had macroscopic haematuria as a presenting feature; six were oligoanuric, as defined by a urine output of less than 300 mL/day, at presentation.

The mean serum creatinine at presentation was $474 \mu\text{mol/L}$, range $69–1460 \mu\text{mol/L}$. The mean peak serum creatinine in the first 6 months was $657 \mu\text{mol/L}$, range $69–1460 \mu\text{mol/L}$. Laboratory data were not available for one patient. Eighteen out of 23 patients (78%) were anaemic at presentation ($\text{Hb} < 120 \text{g/L}$) and five were lymphopaenic ($\text{lymphocytes} < 0.9 \times 10^9/L$). Other laboratory indices at presentation are listed in Table 2.

Nine patients had respiratory involvement. All had cough as a presenting complaint. Six had significant dyspnoea and five frank haemoptysis. Six had features of pulmonary haemorrhage on chest radiograph, typically with bilateral opacities. Two patients developed respiratory failure; one was treated with non-invasive ventilation, the other was not ventilated and care was withdrawn. None was treated with invasive ventilation.

**Diagnostic tests**

Twelve patients had positive anti-GBM antibodies by the indirect immunofluorescence method. All patients underwent a percutaneous renal biopsy under ultrasound guidance. One patient developed a symptomatic, post-biopsy perinephric haematoma that did not require surgical or endoluminal intervention. There were no other recorded complications from the renal biopsy.

Twenty patients had crescentic glomerulonephritis. Seven were reported as having diffuse disease. Twenty-one of 23 had marked linear IgG deposition on immunofluorescence, clearly diagnostic of anti-GBM disease. In the other two patients, one had weak IgG deposition and one had inadequate tissue for immunofluorescence testing. In these, diagnosis was made based on positive serology and their clinical evidence of Goodpastures syndrome.

During the data collection process, 26 patients were found to have positive serology, but did not have biopsy or clinical evidence of anti-GBM disease and thus were considered to have false positive results and were excluded.

**Therapy**

One patient maintained normal renal function without treatment. The remaining 22 received immunosuppression with cyclophosphamide and corticosteroids (Fig. 1).

The mean duration of therapy with cyclophosphamide was 1.5 months, range 2 days to 12 months, the mean total dose was approximately 7210 mg, range 200 to 22 800 mg.

Seventeen patients were treated with plasmapheresis, with a median of eight exchanges (range 5–16). The indication for treatment was renal disease alone in 14, pulmonary disease alone in two, and combined renal and pulmonary disease in one.
Three patients developed neutropenic sepsis, one requiring critical care admission. One person died of respiratory failure, caused by pulmonary haemorrhage, during the same admission after her neutrophil count recovered. The patient was not treated with plasma exchange as she was felt to be too frail by the treating clinicians. There were three other episodes of neutropenia without sepsis and one of lymphopenia, requiring cessation of immunosuppression. There were three other non-neutropenic infections requiring hospital admission. Two patients developed haematuria thought secondary to cyclophosphamide.

Ten patients (43%) were treated with haemodialysis within 1 month of presentation. Nine remained dialysis dependent, one recovered renal function after 56 days of dialysis. One patient progressed to end-stage renal disease (ESRD) requiring dialysis 7 months after their initial presentation.

**Outcomes**

Patient outcomes are summarised in Figure 2. One patient died acutely of alveolar haemorrhage. Eight (35%) recovered normal renal function of whom one died later of cancer. Ten survived the acute illness but developed ESRD, two of whom have died (one with peritoneal dialysis related peritonitis, and one with peritonitis from a perforated sigmoid diverticulum). Thirteen (56%) received renal replacement therapy at any time. At the time of censoring 19 (83%) were alive, after an average follow-up time of 77 months (range 19–155 months).

**Predictors of outcome**

NZ Maori or Pacific peoples were significantly more likely to reach ESRD than Europeans ($P = 0.003$). A creatinine level greater than 400 µmol/L at presentation was predictive of the development of ESRD ($P = 0.01$), but not of death ($P = 0.1$). The need for haemodialysis within the first month was a predictor of ESRD ($P = 0.0001$). The presence of pulmonary disease at presentation was not a predictor of progression to ESRD ($P = 0.054$).

**Discussion**

Significant advances have been made in the understanding of Goodpastures disease. It is recognised that there are changes to the structure of the $\alpha345$ non-collagenous-1 hexamer of collagen IV that cause conformational changes in the $\alpha3$ and $\alpha5$ non-collagenous 1 subunit, which elicit an autoimmune response. Anti-GBM disease is a rare disease with an incidence typically quoted at 0.5 to 1.0 cases per million patient-years. We confirmed that anti-GBM disease is rare, and estimated the rate of confirmed cases in our series at 1.79 per million patients. It is unclear whether this modest increase is a reflection of an ageing population, better recognition of a rare disease or a true change in incidence.

We note an equal prevalence in men and women, across all age groups. An equal prevalence has been noted in some reports, whereas others have reported a male preponderance. Although ESRD is more common in NZ Maori and Pacific peoples, most of this risk is attributed to diabetic nephropathy and hypertensive nephrosclerosis. It had been previously suggested that Goodpastures syndrome may be more common among Maori. However, we did not find any difference in incidence of Goodpastures disease based on ethnicity.

Respiratory tract infections, tobacco and exposure to hydrocarbons are environmental factors that have been linked with the development of anti-GBM disease. We did not see any seasonal variation in anti-GBM disease.
However, smokers and ex-smokers were overrepresented in our case series. Smoking was associated with the development of respiratory disease and we noted two cases of possible toxic substance exposure, both of whom had respiratory disease. It is possible that these environmental exposures may lead to either a direct autoimmune response or may uncover an epitope that induces an autoimmune response.

The incidence of pulmonary involvement was almost 40% (9/23) in our series, similar to rates reported in some modern series, but much less than that seen in the historic New Zealand cohort. One explanation is that pulmonary involvement may represent a later step in the natural history of the disease, or a more severe form, and that advances in immunosuppressive therapy now prevent pulmonary disease from developing.

Immunosuppressive therapy has improved outcomes in the disease. In our series the mortality rate of anti-GBM disease was 17%. This compares favourably with some modern series, but much less than that seen in the previous New Zealand study, 55% of patients died within 2 years. Urgency of diagnosis and rapid initiation of treatments, including plasmapheresis, are recommended.

The use of the indirect immunofluorescence method for detecting anti-GBM antibodies was analysed in our study. We found that only half of the patients with clinically significant anti-GBM disease had a positive test by this method. There was also a large number of patients found to have positive antibodies, who were not found to have clinically significant disease. False negative tests have been described with both indirect immunofluorescence and some enzyme linked immunosassays. In our study, the diagnosis of anti-GBM antibody disease was made on biopsy evidence alone in the majority. Thus renal biopsy remains imperative in patients even in the presence of a positive or negative result.

**Conclusion**

We report a series of anti-GBM disease. This condition is rare, with no ethnic predisposition noted. The mortality and morbidity remain high, but has improved with aggressive therapy.

**Acknowledgements**

The authors would like to thank Dr Logan Carpenter, Pathologist at LabPlus, Auckland, for searching the renal biopsy database and Dr Janeen Milner, General Practitioner, Auckland, for reviewing and commenting on the paper.

**References**

Risk factors for 30-day readmission in general medical patients admitted from the emergency department: a single centre study

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Key words
age, emergency department, hospital readmission, risk factor.

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Abstract

Background: Overcrowding in emergency departments (ED) around the world is an increasingly serious problem with an adverse impact on both patient flow and patient outcomes. A significant contributing factor to ED overcrowding is possibly due to readmission. Risk factors for readmission in patients admitted from ED are rarely studied, particularly in Asian countries where the length of stay is reportedly longer.

Methods: A retrospective study of patients admitted to general medical wards from the ED of a referral centre in northern Taiwan from November 2009 to April 2010 was conducted. The primary outcome was 30-day hospital readmission and clinical characteristics were analysed for predictors of readmission.

Results: Of the recruited 2698 patients, 451 (16.7%) were readmitted within 30 days after discharge. Age, gender, marital status and the activities of daily living (Barthel’s score) were not associated with 30-day readmission. Higher Charlson score ((score 2–4) hazard ratio (HR): 1.42, 95% confidence interval (CI): 1.07–1.89; (score >4) HR: 1.93, 95% CI: 1.37–2.73), longer hospital stay ((8–14 days) HR: 1.51, 95% CI: 1.17–1.95; (15–28 days) HR: 1.64, 95% CI: 1.22–2.19; (>28 days) HR: 1.97, 95% CI: 1.43–2.71), and presence of underlying active malignancy (HR: 1.66, 95% CI: 1.27–2.16) and anaemia (HR: 1.26, 95% CI: 1.02–1.55) were independently associated with readmission.

Conclusion: Medical patients admitted from the ED of a referral centre have a 30-day readmission rate of 16.7%. Post-discharge care should focus on patients with higher Charlson score, longer hospitalisation, anaemia and underlying active malignancy, which are independent predictive factors for 30-day readmission.

Introduction
Post-discharge care after hospitalisation remains challenging, especially for the elderly and those with underlying comorbidity.1,2 More than 10% of discharged patients have new or worsening symptoms within days to weeks.3 The reported readmission rate is as high as 19.6%.2 In order to improve post-discharge care, follow up by telephone, telehealth communication/monitoring and home visits have been implemented with the goal of lowering readmission.4–8

Before implementing post-discharge care, having a better understanding of risk factors for readmission might allow for the more efficient allocation of resources of post-discharge care. Although reports on hospital readmission are quite common and well researched,1,2 the studies have rarely focused on patients admitted from the emergency department (ED). Overcrowding of the ED is a constant problem,9 and a significant contributing factor to ED overcrowding is possibly readmission, which at times is as high as 20% within 30 days after discharge. There are potential avenues for improving both patient flow and patient outcomes if readmission can be reduced by improving post-discharge care. Investigating ED patients is important as they may require more detailed post-discharge attention compared to the general population. Moreover, previous studies have been rare in Asian countries; therefore, this study was conducted in a Taiwan tertiary referral centre aiming to document a retrospective study of general medical patients admitted from the ED and we attempted to determine possible risk factors for readmission within 30 days after discharge.

Methods
This retrospective study was conducted at the National Taiwan University Hospital, a 2200-bed tertiary-care referral centre in Taipei metropolitan of northern Taiwan,
in which 6.5 million people live. In 2010, 103,923 patients were served in our ED, of whom 20,506 (19.7%) were admitted. The ED patients were classified to have a diagnosis in internal medicine (73%), surgical department (19%), paediatrics (7%) and others (1%). From November 2009 to April 2010, all patients older than 16 years of age and admitted to the general medical ward from the ED were selected. The general medical wards did not include specialty wards like oncology, cardiology, neurology and so on. The ED physicians were responsible for determining who needed hospitalisation and for classifying the diagnosis category. Patients who died in the hospital or went home to palliative care after discharge were excluded. The Institutional Review Board of the hospital’s Research Ethics Committee approved the study.

The patients’ clinical characteristics, laboratory data and hospital course were recorded by research assistants blinded to the study purpose. The outcome of readmission was recorded by one other assistant blinded to the detailed clinical features. The two research assistants were board certified nurses. They were trained to do the recording by a physician and another senior assistant. In addition, we trained our assistants with 50 practice cases under careful supervision (kappa agreement of 0.77 ± 0.14) before they performed chart review. We used a unified case report form, which contained a default option for selection in order to avoid ambiguous data coding. The clinical characteristics included age, gender, activities of daily living by Barthel’s score and underlying comorbidities by Charlson score.\textsuperscript{10,11} The Charlson score, which has been widely used in patients with cancer and acute illness, is reportedly accurate in readmission prediction and has excellent interrater reliability.\textsuperscript{12–15} Because a high 30-day readmission rate was reported,\textsuperscript{2} we defined it as the primary outcome and patients were categorised as readmitted and non-readmitted for comparison. Patients were retrospectively tracked for 30 days after discharge until readmission or being lost to follow up.

For the definitions of underlying diseases, liver cirrhosis was defined as typical ultrasound or computed tomography characteristics of cirrhosis plus at least one of the following: splenomegaly, ascites formation, oesophageal or gastric varices or hepatorenal syndrome.\textsuperscript{16} Congestive heart failure was based on clinical signs of heart failure and echocardiogram.\textsuperscript{17} Chronic obstructive pulmonary disease was defined by pulmonary function test or clinical presentation plus treatment response.\textsuperscript{18} Diabetes was diagnosed by referring to the guidelines of the American Diabetes Association.\textsuperscript{19} Estimated glomerular filtration rate was obtained by using the Modification of Diet in Renal Disease Study equation.\textsuperscript{20} Severe chronic kidney disease was defined as an estimated glomerular filtration rate of ≤30 mL/min/1.73 m\(^2\). Active malignancy was defined as the cancer being still active without mention of cure or remission. We defined anaemia as haemoglobin <110 g/L in men and <120 g/L in women according to our laboratory references.

**Statistical analysis**

Inter-group differences were compared using the independent Student’s \(t\)-test for numerical variables and Chi-squared test for categorical variables. Curves of probability of being readmission-free within 30 days were generated using the Kaplan–Meier method and compared using the log–rank test. Multivariate analysis for possible significant factors (\(P < 0.15\)) in the univariate analysis was performed by the Cox proportional regression model using the backward conditional method. All statistical analyses were performed using the SPSS software version 13.0 (SPSS, Chicago, IL, USA).

**Results**

From November 2009 to April 2010, 2932 of 3454 patients in the general medical wards of the hospital were admitted from the ED. Among them, 451 patients were readmitted within 30 days after discharge and 2247 were considered as the non-readmission group. The remaining 234 patients died in hospital or were discharged with a life expectancy <30 days. The average age was 68 years for the readmission group, which was 2 years older than the non-readmission group albeit not statistically significant (\(P = 0.069\), Table 1). Patients aged <65 years had less underlying chronic illnesses except for liver cirrhosis (10% vs 6%, \(P < 0.001\)) and active malignancy (29% vs 23%, \(P < 0.001\)). Male gender, education status and Barthel’s score were comparable in both groups.

There were more patients with cirrhosis or active malignancy in the readmission group than non-readmission group that had a lower Charlson score. There were more currently married patients in the readmission group. The unmarried patients were younger than the married ones (63.7 vs 71.1 years, \(P < 0.001\)) and had lower Charlson score (2.4 vs 3.2, \(P < 0.001\)).

The laboratory results on initial admission were similar in both groups except for haemoglobin level, which was lower in the readmission group (110.0 vs 118.0 g/L, \(P < 0.001\)). Those hospitalised <7 days were more likely to be the non-readmission group (40 vs 27%, \(P < 0.001\)). The readmission group had longer hospital stay (17.3 vs 14.2 days, \(P = 0.002\)).
By univariate analysis, higher Charlson score, longer length of hospital stay, currently married status and presence of anaemia were associated with a higher 30-day readmission (Fig. 1). Among patients hospitalised for ≤1 week, those with ≤3 days had similar 30-day readmission rate as those with 4–7 days (P = 0.819 by log–rank test). In contrast, age and Barthel’s score were not associated with 30-day readmission (<65 vs ≥65 years, P = 0.395 by log–rank test and <60 vs ≥60, P = 0.425 respectively).

Factors with significance of <0.15 in the univariate analysis were selected for multivariate analysis. The Cox proportional regression revealed four independent factors for 30-day readmission, including underlying active malignancy (hazard ratio (HR): 1.66, 95% confidence interval (CI): 1.27–2.16), Charlson score ((score 2–4) HR: 1.42, 95% CI: 1.07–1.89; (score >4) HR: 1.93, 95% CI: 1.37–2.73), length of hospital stay ((8–14 days) HR: 1.51, 95% CI: 1.17–1.95; (15–28 days) HR: 1.64, 95% CI: 1.22–2.19; (>28 days) HR: 1.97, 95% CI: 1.43–2.71) and anaemia (HR: 1.26, 95% CI: 1.02–1.55) (Table 2). The haemoglobin level was still significant in this model if we used it as a continuous variable (HR: 0.94, 95% CI: 0.90–0.98, by an increase of per 10.0 g/L haemoglobin.

Discussion

The 30-day hospital readmission rate is as high as 16.7% in patients admitted to the general medical wards from the ED of a tertiary referral centre. The independent factors for readmission include Charlson score, underlying active malignancy, anaemia and length of hospital stay.

Although age has previously been reported to be a risk factor for early readmission in some studies,2,21,22 this has
not been clearly the case in this and some other studies. There are two possible explanations worth mentioning. First, other significant risk factors, like the Charlson score which does correlate with readmission already incorporates age into their score. In particular, those with underlying chronic illnesses account for almost half of the population. Second, although increasing age correlates with many underlying comorbidities, liver cirrhosis is prevalent in the middle age group in Taiwan, thereby disrupting the effect of age on readmission.

Moreover, the current study shows underlying active malignancy predominantly in patients aged <65 years. In patients with neither malignancy nor chronic liver disease, age becomes significantly associated with readmission. Therefore, underlying diseases instead of age should be the basis for prioritising patients requiring post-discharge care, especially for those admitted from the ED in a referral hospital where underlying diseases are highly prevalent.

Charlson score, representing the complexity of the underlying disease, is an independent risk factor for readmission. Because chronic health status is an important factor to react to an acute stress, it is widely used in many aspects, such as cancer, acute illness and readmission as well as ED revisits. The Charlson score is reportedly valid in post-discharge outcome and has excellent interrater reliability. However, current literature regarding hospital readmission mostly discuss general medical patients with lower Charlson scores. This study demonstrates that predicted risk is still high in those with Charlson scores of 2–4 and >4.

In this study, the activities of daily living (measured by the Barthel’s score) are not associated with early readmission, in contrast to other reports. Possible reasons

| Table 2 The 30-day readmission by multivariate Cox proportional hazard regression |
|---------------------------------|----------------|----------------|----------------|
| Characteristics                | No. | Readmitted no. (%) | P-value | HR [95% CI] |
| Age, years                     |     |                  |         |             |
| <65                            | 1636| 281 (17)         | 0.858  |             |
| ≥65                            | 1062| 170 (16)         |         |             |
| Marital status                 |     |                  |         |             |
| Currently unmarried            | 1001| 148 (15)         |         |             |
| Currently married              | 1416| 285 (20)         |         |             |
| Education status               |     |                  |         |             |
| None                           | 324 | 46 (14)          |         |             |
| Elementary                     | 707 | 112 (16)         |         |             |
| High school                    | 765 | 150 (20)         |         |             |
| College                        | 631 | 102 (16)         |         |             |
| Charlson score                 |     |                  |         |             |
| <2                             | 1262| 122 (10)         |         |             |
| 2–4                            | 887 | 167 (19)         | 0.014  | 1.07–1.89   |
| >4                             | 549 | 162 (30)         | 0.001  | 1.37–2.73   |
| Underlying active malignancy   |     |                  |         |             |
| Absence                        | 2020| 252 (13)         | <0.001 | 1.27–2.16   |
| Presence                       | 678 | 199 (29)         |         |             |
| Liver cirrhosis                |     |                  |         |             |
| Absence                        | 2498| 397 (16)         |         |             |
| Presence                       | 200 | 54 (27)          | 0.107  |             |
| Barthel’s score                |     |                  |         |             |
| ≥60                            | 1739| 283 (16)         |         |             |
| <60                            | 957 | 168 (18)         | 0.406  |             |
| Length of hospital stay, days  |     |                  |         |             |
| ≤7                             | 1014| 120 (12)         | 1.0 (Reference) |         |
| 8–14                           | 901 | 162 (18)         | 0.002  | 1.17–1.95   |
| 15–28                          | 481 | 100 (21)         | 0.001  | 1.22–2.19   |
| >28                            | 302 | 69 (23)          | <0.001 | 1.43–2.71   |
| Anaemia†                       |     |                  |         |             |
| No                             | 1658| 225 (14)         | 1.0 (Reference) |         |
| Yes                            | 1022| 223 (22)         | 0.029  | 1.02–1.55   |

†Haemoglobin <110 g/L in male and <120 g/L in female. Data were lacked in 281 patients for marital status, 271 for education, two for Barthel’s score and 18 for haemoglobin. CI, confidence interval; HR, hazard ratio.
are that the Barthel’s score on admission may change with time because daily activities can improve after discharge. In addition, the care skills of the caregiver will be more important than the Barthel’s score. Third, many underlying diseases have complications that may not be predicted by daily living activities. For instance, the complications of cirrhosis like variceal bleeding lead to acute changes that are not correlated with daily activities. In addition, the fact that Barthel’s score is not associated is probably because of interdependence with Charlson score.

The role of marital status with regards to readmission is unclear, but may be associated with care after discharge. Currently married patients have higher rates of readmission; however, current married status also correlates with older age and higher Charlson scores. Marital status is not significant in the Cox regression model. It is speculated that the spouse will bring the patient home even if his or her care skills are not adequate, or even if some of the patients are presumably cared for in a subacute care facility. A better assessment of ability to deal with patients may be necessary to apply before discharge.

Length of hospital stay has been reported to be an important factor for readmission, and in this study, hospitalisation longer than 7 days is associated with higher readmission. Western literature shows that overall hospitalisation longer than 7 days is associated with higher readmission, especially during the first week of hospitalisation. The longer hospital stay might also be due to social and culture characteristics of hospital dependency and relatively low admission cost under the nationwide health insurance programme in Taiwan.

This study has several limitations that are worth noting. First, because this study was performed in a tertiary referral centre in Taiwan, patients were more severely ill. The results of this study may therefore not be so relevant to smaller regional or district hospitals and moreover, it also deserves further investigation for the generalisation outside Taiwan or South-East Asia. Furthermore, it was a retrospective study, and as such the definition of covariates was based on chart review and therefore dependent on data extraction and doctors entering the correct data. The inter-observer variation in coding may exist, although we used a unified case report form and excellent kappa agreement in 50 practice cases was achieved in the initial training. Third, death after discharge, which could bias the results, was not recorded even though the rate was only approximately 1% within 30 days after discharge in the same hospital (C. C. Shu et al., unpublished, 2010).

Conclusion

In conclusion, 16.7% patients who were admitted from the ED in a referral centre were readmitted within 30 days after discharge. Patients with a higher Charlson score, longer hospital stay, anaemia and underlying active malignancy are associated with higher 30-day readmission and may benefit from post-discharge care.

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Anaemia is highly prevalent among unselected internal medicine inpatients and is associated with increased mortality, earlier readmission and more prolonged hospital stay: an observational retrospective cohort study

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Key words
anaemia, inpatient, mortality, length of stay, hospital readmission.

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Abstract

Background: Anaemia is associated with adverse outcomes in elderly community-dwelling individuals, but this problem is less well characterised in the inpatient setting.

Aims: To determine the prevalence of anaemia and its associations in a well-defined cohort of internal medicine inpatients.

Methods: A retrospective cohort study of non-elective admissions under internal medicine at Palmerston North Hospital, New Zealand, was conducted for 4 months of 2008 with outcome analysis on 1 March 2010.

Results: At admission, 497 of 1491 (33.3%) patients were anaemic by World Health Organization criteria (haemoglobin <130 g/L for males; <120 g/L for females). Anaemia was more prevalent in males (38.1%) than females (28.2%), P < 0.001, in patients aged 65 years or older (41%) than in those under 65 (21.3%), P < 0.001, in New Zealand Europeans (34.3%) than in Māori and people from the Pacific Islands (26.4%), P = 0.04, and in patients admitted primarily because of malignancy, endocrine/metabolic disease, infection, and acute coronary syndrome/congestive heart failure (P < 0.001). Anaemia was independently associated with increased length of hospital stay (7.3 days vs 5.1 days in non-anaemic patients; P < 0.001), with mortality (P < 0.001) and unplanned hospital readmission (P < 0.001) during the follow-up period. Anaemia was infrequently acknowledged or investigated. Secondary analysis using a haemoglobin threshold of 110 g/L showed similar results.

Conclusions: Anaemia is highly prevalent among medical inpatients with variation because of gender, age, race and reason for admission. Anaemia independently predicts for prolonged hospital stay, increased mortality and shorter time to readmission, but is usually not documented or investigated in this setting.

Introduction

Anaemia in the elderly has been highlighted as a ‘public health crisis’ following publication of the third National Health and Nutrition Examination Survey.2 A prevalence of approximately 12%3 and an annual incidence of 22.5 per 1000 person-years4 have been demonstrated in studies of elderly community-dwelling individuals in developed countries.

Anaemia in the elderly is associated with reduced physical performance,5,6 executive function7 and quality of life8 as well as an increased risk of fracture9 and poorer outcomes following myocardial infarction,10 and in heart failure.11 Anaemic individuals have an increased risk of hospitalisation and death.12,13 While it is biologically plausible that anaemia is responsible for these adverse outcomes, the benefit of correcting anaemia in this group of patients has yet to be proven.14,15 Nevertheless, this is worthy of further study because optimal recognition and appropriate treatment of anaemia could lead to improved outcomes, at least in a subset of these patients.

Few previous studies have focussed on hospitalised patients, but several small studies have demonstrated a high prevalence of anaemia,16–19 and one large study20 has reported an anaemia prevalence of 38.6%, although the main purpose of that study was to determine the...
The impact of anaemia on cognitive function and this population included patients admitted to geriatric services. The prevalence of anaemia in hospitalised internal medicine patients and its impact on clinical outcomes is, therefore, unclear. While the primary focus during admission is management of the primary illness, hospitalisation also represents an opportunity for recognition and appropriate treatment of underlying problems, including anaemia.

In this retrospective study of a large cohort of unselected medical inpatients we have sought to measure the prevalence of anaemia and to determine associations with age, gender, race, primary reason for admission and month of admission. We have also analysed whether anaemia in this setting predicts for length of stay, subsequent unplanned readmission and mortality.

Materials and methods

Study population

Palmerston North Hospital is a 350-bed secondary-care hospital, serving a population of approximately 160,000. In this region, all adults requiring acute internal medicine admission are admitted to this hospital under general medicine, with subspecialty referral (including to specialist geriatric services) occurring subsequently, if required.

The study population comprised patients aged over 14 requiring unplanned admission to this hospital under the Internal Medicine Services, who were discharged from or died in hospital during the months of January, April, July and October 2008. Patients were excluded if they did not have the haemoglobin recorded during admission or if the primary reason for admission was gastrointestinal bleeding. For patients admitted more than once during the study period, only the first admission was analysed.

Study design

This was a retrospective observational cohort study to determine the prevalence of anaemia in this population and to investigate associations between anaemia and age, gender, race, month of admission, primary reason for admission, mortality, time to non-elective readmission and length of hospital stay. Analysis for mortality and readmission includes all events up to 1 March 2010, allowing a minimum of 16 months’ follow up.

The study proposal was submitted to the Central Regional Ethics Committee and was approved under the provisions of the Ethical Guidelines for Observational Studies: Observational Research and Related Activities.

Data collection

Patient demographic, admission and mortality data were electronically collated from the hospital information system. Laboratory results were extracted from the laboratory database. Discharge summaries, written by hospital medical staff to the patients’ primary care physicians, were reviewed by qualified medical practitioners, with at least 1 year of postgraduate experience, to assign a primary reason for each admission from 10 pre-specified diagnostic categories: (i) acute coronary syndrome (ACS)/congestive heart failure, (ii) cerebrovascular accident/transient ischaemic attack, (iii) other cardiac conditions, (iv) infection, (v) respiratory conditions, (vi) gastrointestinal conditions, (vii) metabolic conditions, (viii) malignancy, (ix) other neurological conditions and (x) other conditions. The discharge summary was also screened for evidence that anaemia was noted as a clinical problem during admission.

Definitions of anaemia

The first haemoglobin measured during the index admission was used for all analyses. Anaemia was defined by the World Health Organization (WHO) criteria as a haemoglobin concentration < 130 g/L in men and < 120 g/L in women. A secondary analysis was also performed in patients with more severe anaemia, defined as a haemoglobin concentration of < 110 g/L.

Laboratory methods

In anaemic patients, details of five investigations that might clarify the cause of anaemia were recorded: serum levels of: (i) ferritin, (ii) vitamin B12, (iii) folate, (iv) creatinine and (v) C-reactive protein (CRP). Where more than one measurement of creatinine or CRP was obtained during admission, the lowest value was recorded on the assumption that this most closely reflected the baseline level of renal function or inflammation. Full blood counts were performed by a Sysmex XE-2100 counter (Sysmex Corporation, Kobe, Japan). Assays for serum ferritin, creatinine, B12, folate and CRP were analysed according to the manufacturer’s recommendations using an Abbott Architect ci8200 analyser (Abbott, Chicago, IL, USA). The limits of the laboratory’s reference ranges were used to determine the percentage of abnormal tests: < 30 µg/L for ferritin, < 138 pmol/L for B12, < 8 nmol/L for folate, > 100 µmol/L in men and > 120 µmol/L in women for creatinine, and ≥ 5 mg/L for CRP.
Statistical analysis
The association between anaemia on admission and age, gender, race, primary reason for admission and month of admission was explored using Chi-square tests. The relationships between anaemia and subsequent survival and readmission were summarised as Kaplan–Meier curves and compared between anaemic and non-anaemic patients using log-rank tests. The independent effects of anaemia on mortality and readmission, correcting for age, gender, race and reason for admission, were tested using Cox proportional hazards regression models. The mean length of stay was compared between anaemic and non-anaemic patients using ANOVA. The independent effect of anaemia on length of stay correcting for age, gender, race and reason for admission was also tested using ANOVA, which included the presence of anaemia and these confounding variables as main effects. A two-tailed P-value of less than 0.05 was taken to indicate statistical significance.

Results
Of the total 1742 admissions, 13 had no haemoglobin measurement, 71 were for gastrointestinal bleeding and 167 involved a subsequent admission of the same patient. After excluding these, the final study population comprised 1491 patients. Their ages ranged from 15 to 100 (median 71) years and there were slightly more males (n = 774, 51.9%) than females (n = 717, 48.1%). The median duration of follow up for analysis of mortality and unplanned readmission was 613 (range 485–868) days.

Of 1491 admissions, 497 (33.3%) patients met the WHO criteria for anaemia at the time of admission and 204 (13.7%) had a first haemoglobin recording of less than 110 g/L. The results of our analyses of the association between the prevalence of anaemia and demographic variables, reason for admission and month of admission are reported in Table 1.

WHO-defined anaemia was more prevalent in males than females, but this gender difference was not apparent when the same haemoglobin threshold of 110 g/L was used for both sexes (Table 1).

Anaemia prevalence rose with increasing age (Fig. 1). Anaemia by either definition was approximately twice as prevalent in those aged ≥65 as it was in those aged <65 (Table 1).

Anaemia was significantly more prevalent in Europeans than in Māori and people from the Pacific, who were numerically the only other significant racial group. This trend persisted, although more weakly, using the lower haemoglobin threshold of 110 g/L (Table 1).

There was no significant variation in the prevalence of anaemia for admissions in the different months studied (Table 1).

A primary reason for admission could be determined for 1436 of the 1491 patients. Anaemia by both definitions was more prevalent in admissions for malignancy, endocrine/metabolic disorders, infection and ACS/congestive heart failure than it was in the study population as a whole (Table 1).

During the follow-up period 397 of 1491 (26.6%) patients died. Mortality was significantly increased in anaemic patients (hazard ratio = 2.34, 95% CI 1.92–2.86, P < 0.001, Fig. 2a), this association persisting when corrected for age, gender, race and reason for admission (hazard ratio = 1.78, 95% CI 1.44–2.19, P < 0.001). Anaemia defined by haemoglobin <110 g/L was also significantly associated with mortality (hazard ratio = 3.30, 95% CI 2.65–4.10, P < 0.001, Fig. 2b) and this also remained significant when corrected for these variables (hazard ratio = 2.54, 95% CI 2.01–3.22, P < 0.001).

Unplanned readmission was recorded following 798 of 1491 (53.5%) admissions. Anaemic patients had a significantly shorter time until readmission compared with non-anaemic patients (median 216 vs 517 days, P < 0.001, Fig. 3a) and this association also persisted when corrected for age, gender, race and primary reason for admission (P < 0.001). In patients with haemoglobin <110 g/L, the association shown with time to readmission (median 161 days vs 428 days, P < 0.001, Fig. 3b) also remained significant when corrected for these variables (P < 0.001).

Anaemic patients had significantly longer hospital stays during the index admission (mean 7.3 days; 95% CI 6.6–7.9) than non-anaemic patients by WHO criteria (mean 5.1 days; 95% CI 4.6–5.6, Fig. 4a). This association remained significant (P < 0.001) when corrected for gender, race, age and reason for admission. Patients with haemoglobin <110 g/L also spent significantly longer in hospital (mean 8.4 days; 95% CI 7.4–9.5) than those with haemoglobin ≥110 g/L (mean 5.4 days; 95% CI 5.0–5.8, Fig. 4b) and this also remained significant (P < 0.001) when corrected for these potentially confounding variables.

Of 477 admissions involving patients anaemic by WHO criteria for which a discharge summary was available, anaemia was mentioned as a clinical problem for 45 of 193 women (23.3%) and 51 of 284 men (18.0%). More severe anaemia was also poorly acknowledged, being mentioned for only 28 of 95 women (29.5%) and 29 of 97 men (30.0%) with haemoglobin levels <110 g/L.

Few of the 497 patients anaemic by WHO criteria had serum ferritin (19.5%), vitamin B12 (15.1%) or folate (14.7%) assays during admission. Ferritin was below...
Table 1  Association of anaemia defined by WHO criteria (haemoglobin <130 g/L for males and <120 g/L for females) and by haemoglobin <110 g/L with demographic variables, reason for admission and month of admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of admissions</th>
<th>Number Anaemic by WHO, n (%)</th>
<th>(P)-value (Chi-square)</th>
<th>Number with haemoglobin &lt;110 g/L, n (%)</th>
<th>(P)-value (Chi-square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) by decade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–19</td>
<td>33</td>
<td>5 (15.2)</td>
<td>&lt;0.001</td>
<td>2 (6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20–29</td>
<td>47</td>
<td>3 (6.4)</td>
<td>7 (8.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>79</td>
<td>15 (19.0)</td>
<td>12 (9.1)</td>
<td>10 (6.6)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>132</td>
<td>39 (29.5)</td>
<td>33 (25.4)</td>
<td>33 (25.4)</td>
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<tr>
<td>50–59</td>
<td>152</td>
<td>25 (16.4)</td>
<td>23 (15.1)</td>
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<tr>
<td>60–69</td>
<td>264</td>
<td>75 (28.4)</td>
<td>61 (17.4)</td>
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<tr>
<td>70–79</td>
<td>359</td>
<td>140 (39.0)</td>
<td>56 (15.6)</td>
<td>56 (15.6)</td>
<td></td>
</tr>
<tr>
<td>80–89</td>
<td>350</td>
<td>155 (44.3)</td>
<td>61 (17.4)</td>
<td>61 (17.4)</td>
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</tr>
<tr>
<td>90–99</td>
<td>73</td>
<td>39 (53.4)</td>
<td>23 (31.5)</td>
<td>23 (31.5)</td>
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</tr>
<tr>
<td>100+</td>
<td>2</td>
<td>1 (50.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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</tr>
<tr>
<td>Age (years) using cut point 65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;65</td>
<td>578</td>
<td>123 (21.3)</td>
<td>&lt;0.001</td>
<td>45 (7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥65</td>
<td>913</td>
<td>374 (41.0)</td>
<td>159 (17.4)</td>
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<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>774</td>
<td>295 (38.1)</td>
<td>&lt;0.001</td>
<td>102 (13.2)</td>
<td>0.560</td>
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<tr>
<td>Female</td>
<td>717</td>
<td>202 (28.2)</td>
<td>102 (14.2)</td>
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<td>Ethnicity</td>
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<tr>
<td>New Zealand–European</td>
<td>1291</td>
<td>443 (34.3)</td>
<td>0.040</td>
<td>179 (13.9)</td>
<td>0.290</td>
</tr>
<tr>
<td>Māori/Pacific</td>
<td>174</td>
<td>46 (26.4)</td>
<td>19 (10.9)</td>
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<tr>
<td>Primary diagnosis</td>
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<td></td>
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<tr>
<td>ACS/CHF</td>
<td>248</td>
<td>85 (34.3)</td>
<td>&lt;0.001</td>
<td>43 (17.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV/TIA</td>
<td>85</td>
<td>28 (32.9)</td>
<td>9 (10.6)</td>
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<tr>
<td>Other cardiac</td>
<td>164</td>
<td>45 (27.4)</td>
<td>15 (9.1)</td>
<td></td>
<td></td>
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<tr>
<td>Infection</td>
<td>396</td>
<td>160 (40.4)</td>
<td>60 (15.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-infective respiratory</td>
<td>69</td>
<td>13 (18.8)</td>
<td>3 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-infective gastroenterology</td>
<td>47</td>
<td>13 (31.9)</td>
<td>4 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine/metabolic</td>
<td>63</td>
<td>27 (42.9)</td>
<td>17 (27.0)</td>
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<tr>
<td>Malignancy</td>
<td>37</td>
<td>18 (48.6)</td>
<td>12 (32.4)</td>
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<td></td>
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<tr>
<td>Other neurology</td>
<td>77</td>
<td>14 (18.2)</td>
<td>4 (5.2)</td>
<td></td>
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</tr>
<tr>
<td>Other</td>
<td>250</td>
<td>72 (28.8)</td>
<td>25 (10.0)</td>
<td></td>
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<tr>
<td>Month of admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>378</td>
<td>131 (34.7)</td>
<td>0.610</td>
<td>51 (13.5)</td>
<td>0.750</td>
</tr>
<tr>
<td>April</td>
<td>367</td>
<td>124 (33.8)</td>
<td>45 (12.3)</td>
<td></td>
<td></td>
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<tr>
<td>July</td>
<td>393</td>
<td>127 (32.3)</td>
<td>55 (14.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>October</td>
<td>353</td>
<td>115 (32.6)</td>
<td>33 (15.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total admissions \(n = 1491\); anaemic on admission by WHO criteria \(n = 497\); anaemic with haemoglobin <110 g/L \(n = 204\). ACS, acute coronary syndrome; CHF, congestive heart failure; CVA, cerebrovascular accident; TIA, transient ischaemic attack; WHO, World Health Organization.
30 µg/L in 11 of the 97 tests (11.3%); vitamin B12 levels were below 138 pmol/L in three of the 75 tests (4.0%); and folate levels were below 8 nmol/L in 10 of the 75 tests (13.3%). CRP was recorded for 387 (77.9%) of 497 anaemic patients and the lowest recording was 5 mg/L in 335 (86.5%) of them. Creatinine was measured in 494 of 497 anaemic patients and the lowest level recorded was above the laboratory reference range in 153 (30.1%) of them.

Discussion

This retrospective study has demonstrated that anaemia is highly prevalent in patients requiring acute medical admission. This is not surprising since previous studies have shown that anaemia is much more common in hospitalised geriatric patients and nursing home residents than in community-dwelling individuals. Moreover, anaemia in community-dwelling older adults predicts for hospitalisation and anaemia has been associated with several conditions that predispose to hospital admission.

Predictably, elderly patients predominate in this cohort and we have demonstrated a marked difference in anaemia prevalence between patients aged ≥65 years and younger inpatients, with approximately twice the prevalence of anaemia in the older group (Table 1). The difference in anaemia prevalence between men and women depended on the definition of anaemia used, with no difference when a single haemoglobin threshold was used for both sexes.

The different anaemia prevalence in the two main racial groups was unexpected. Race was determined from the patient management information system, which records self-assessed ethnicity. While this has potential inaccuracies, it is the same basis for determining ethnicity used in the third National Health and Nutrition...
Examination Survey and Kaiser Permanente studies in the USA, which have demonstrated lower rates of anaemia in non-Hispanic white people than in other racial groups. The prevalence of anaemia in adult Māori and people from the Pacific Islands in our community is unknown although α-thalassaemia trait is common in this group. The difference observed in our study could reflect different comorbidities and admission patterns in this group of hospitalised patients. Several conditions that can result in chronic hypoxia and increased haemoglobin levels are more prevalent in Māori, most notably smoking, chronic obstructive pulmonary disease and obstructive sleep apnoea. We were unable to account for variables, such as these in our study, and this observation requires further investigation.

Previous studies have highlighted an increased rate of cardiovascular-specific hospitalisation (due to myocardial infarction/ACS or CVS/transient ischaemic attack) in anaemic community-dwelling subjects, prompting us to examine the association between anaemia and primary reason for admission in our cohort. Our assigning a single reason for admission in patients who often have multiple comorbidities has numerous potential flaws. Nevertheless, there was a significant difference in the prevalence of anaemia between groups determined in this way. While it can be hypothesised that anaemia in community-dwelling individuals may exacerbate conditions, such as cardiovascular disease, leading to hospitalisation, it is likely that the increased prevalence of anaemia seen in our patients admitted for infection or malignancy was at least partly a consequence of the underlying disease.

Hospital stay was approximately 2 days longer for admissions characterised by WHO-defined anaemia at the time of admission (Fig. 4a). This increased admission duration was even more striking for patients with a haemoglobin <110 g/L (Fig. 4b) and these differences remained significant after accounting for potentially confounding variables. The majority of patients included in this study required unplanned readmission to hospital during follow up, but the median time to readmission in anaemic patients was significantly shorter than in non-anaemic patients, whether WHO criteria or a haemoglobin threshold of 110 g/L was used to define anaemia (Fig. 3). Approximately a third of patients in our study died during the follow-up period and survival was significantly reduced in the anaemic patients compared to their non-anaemic counterparts. The survival difference was particularly striking when a threshold of 110 g/L was used to define anaemia with a median survival of only 447 days in those anaemic by this criterion. Although hospitalised patients often have multiple comorbidities and acute illnesses that have resulted in admission, our study confirms that anaemia at the time of an index medical admission independently predicts for poor outcomes. Apart from the obvious clinical consequences, these observations have important social and financial implications, given the considerable cost of hospitalisation and the increasingly aged population in developed countries.
As with other studies, we were unable to determine whether anaemia is a cause of these adverse effects or a marker of other factors. Nevertheless, a significant proportion of elderly individuals who are anaemic have potentially modifiable causes and hospitalisation represents an ideal opportunity for recognising and investigating anaemia. Although our analysis may have underestimated the degree to which anaemia was recognised, it was acknowledged in the discharge summaries in only a small minority of anaemic patients, even in those with haemoglobin levels \(<110\) g/L. There was a high prevalence of renal impairment and inflammatory disease in the anaemic patients and anaemia may have been attributed to these causes in many cases, without recording this in the discharge summary. This probably contributed to the infrequent performance of simple investigations into correctable causes of anaemia.

Despite this, about a third of anaemic patients who underwent testing had some evidence of vitamin B12, folate or iron deficiency. This represents a potentially important area for education and improved practice. While it remains to be proven that correcting mild anaemia in this population can improve outcomes, deficiencies of these haematinics often have important clinical implications apart from their causal relationship with anaemia.

Our study suffers from a number of limitations. It is a retrospective survey, for which much of the information was generated from electronic databases. However, all patients accessing public hospital services in New Zealand are assigned a unique ‘hospital number’ which allows robust linking of information about individual patients from different data sources and hospital mortality records are correlated monthly with national death records. The readmission data are subject to greater potential error because we could not account for patients who might have been admitted to other hospitals during the follow-up period. However, there are no other providers of acute inpatient services in this geographical region and the number of patients admitted acutely to other hospitals is likely to have been very small.

Our study was conducted in a single hospital, raising questions about the relevance of our conclusions to other institutions. Nevertheless, our study population has considerable advantages. We are the sole provider of non-elective internal medicine services for a well-defined geographic region, whose inhabitants comprise a mixture of urban and rural dwellers, with predominantly European racial origins. Thus, our referral population is typical of many developed countries and our cohort includes patients admitted for a wide variety of reasons, with minimal selection.
For our primary analyses we used the WHO definition of anaemia, because this has been most frequently used in previous studies, although alternative definitions have been suggested. We also performed a secondary analysis on the subgroup of patients with more significant anaemia (haemoglobin < 110 g/L) because outcomes have been shown to correlate with anaemia of this severity in community-based populations. Many patients in this cohort had more than one haemoglobin measured during admission and we chose to use the first haemoglobin recorded for our analysis. This approach is likely to have underestimated the number of patients who reached an anaemia threshold at any time during the admission and may have contributed to the low rate of acknowledging anaemia as a problem at the time of discharge.

**Conclusion**

Despite these limitations, our study is one of the largest detailed assessments of anaemia in acutely hospitalised patients reported to date. Hospitalisation represents an excellent opportunity for investigation and treatment of this problem, which has a high prevalence and is associated with poor clinical outcomes in this setting. Although the cause of anaemia in this population is often multifactorial, routine testing for and treatment of potentially correctable causes, including haematinic deficiency, has the potential to improve outcomes in a significant proportion of medical inpatients.

**Acknowledgements**

The authors would like to thank Mr Greg Bolton, Mid-Central District Health Board, Palmerston North, New Zealand, for retrieving data from the hospital information system, Dr Jane Foley, Internal Medicine Service, Palmerston North Hospital, New Zealand, for checking the accuracy of the data entry and our colleagues and their patients, whose data are presented here.
Temporal trend of cadmium exposure in the United States population suggests gender specificities

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Key words
cadmium, environmental pollution, mortality, nutrition survey, trend.

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Abstract

Background: Over the years, environmental cadmium exposure has been linked to increased mortality. Over the years, the use of cadmium has generally decreased.

Aims: Although even relatively low levels of cadmium have been associated with increased mortality in the general population, whether this applies to blood cadmium is not well understood.

Methods: The authors analysed data of the National Health and Nutrition Examination Survey to study the temporal trend of cadmium exposure in the period 1988–2006 and the risk of all-cause, cancer and cardiovascular mortality associated with blood cadmium levels.

Results: Urinary cadmium decreased significantly over time in males (0.58 (0.01) mcg/g to 0.41 (0.01) mcg/g; \( P < 0.001 \)) but not in females (0.71 (0.09) mcg/g to 0.63 (0.08) mcg/g; \( P = 0.66 \)). All-cause mortality was significantly higher in the highest quartiles compared with the lowest quartile of blood cadmium in both males (hazard ratio 1.89, 95% confidence interval 1.22, 2.89; \( P = 0.005 \)) and females (hazard ratio 2.03, 95% confidence interval 1.06, 3.89; \( P = 0.035 \)) after adjustment for age, race/ethnicity, smoking status, alcohol intake, annual household income and body mass index. There was also a significant association with cardiovascular mortality in females (\( P = 0.025 \)).

Conclusions: Our data show that elevated blood cadmium levels are associated with elevated mortality, that there seem to be gender differences in temporal trends of cadmium exposure and that blood cadmium is a proxy of chronic cadmium exposure.
Introduction

Cadmium is a toxic metal whose toxicity has been well characterised in occupational studies, some of which linked cadmium exposure to cancer mortality.1–4 Furthermore, population-based studies conducted in highly polluted areas showed a higher risk of death for cancer and cardiovascular events for subjects exposed to high levels of cadmium.5–8

Less is known about the effects of a lower exposure as it occurs in general populations, although in June 2010, concern about cadmium toxicity prompted McDonald’s to recall voluntarily more than 12 million ‘Shrek Forever After 3D’ Collectable Drinking Glasses because of alarm over cadmium levels in paint pigments used on the glassware. In 2006, cadmium was one of six substances banned by the European Union’s Restriction on Hazardous Substances directive, which bans certain hazardous substances in electrical and electronic equipment.9 One recently published research article has focused on the issue of cadmium toxicity in the general population, analysing the relatively older data from the Third National Health and Nutrition Examination Survey (NHANES) in 1988–1994.10 This study disclosed that environmental cadmium exposure as evidenced by certain higher levels of urinary cadmium was associated with an increased risk of all-cause, cancer and cardiovascular disease mortality among men, but not among women. Over the years, there have been major concerns over the public health effects of cadmium, and with the introduction of competing technologies, the use of cadmium has generally decreased with the exception of its use in nickel–cadmium batteries and cadmium telluride solar panels. Therefore, it is reasonable to expect that environmental cadmium exposure of the general population has decreased.

We aimed to determine whether cadmium exposure in the general population, as reflected by levels of urinary cadmium, changed through time by comparing the levels of urinary cadmium in subjects participating in the NHANES 1988–1994 with subjects participating in the NHANES 1999–2006.

Furthermore, as the blood level of cadmium is generally considered to undergo wide fluctuations following the acute exposure to cadmium, it is commonly assumed to be a weak surrogate of chronic exposure, despite the recent finding of an association between blood cadmium and history of stroke and heart failure in the general population11 and the association with chronic kidney disease.12,13 Hence, we analysed the effects of blood cadmium levels on mortality in subjects participating in the NHANES 1999–2004 to support the idea that it also is a reliable marker of chronic exposure. Finally, as it has been noted that gender differences exist with regard to the effects of cadmium exposure,14 we further investigated possible differences between genders with regard to cadmium toxicity and exposure.

Materials and methods

Subjects and measurements

The NHANES is a stratified multistage probability survey representing a sample of the civilian non-institutionalised US population. It consists of a questionnaire followed by a detailed physical examination and blood and urine samples drawn in a Mobile Examination Center.15

Adults participating in the surveys from 1988 to 2004 were followed for mortality through 31 December 2006, using 12 identifiers to match NHANES participants to the National Death Index. The International Classification of Diseases, Tenth Revision (ICD-10) was used to identify deaths due to malignant neoplasm (ICD-10 codes C00–C97) and major cardiovascular disease (ICD-10 codes I00–I78). Persons who were not matched to a death record were considered alive through the follow-up period and administratively censored.

Laboratory procedures used to determine the analytes of interest are detailed in the website.15 Specifically, cadmium was measured on a PerkinElmer model SIMAA 6000 (PerkinElmer, Norwalk, CT, USA) simultaneous multielement atomic absorption spectrometer, with Zeeman background correction. Cadmium was determined at the Environmental Health Sciences Laboratory of the Centers for Disease Control and Prevention (CDC) National Center for Environmental Health after confirmation of no background contamination and using extensive quality-control procedures.

Urinary cadmium was expressed as cadmium/creatinine ratio to account for urinary concentration.

Subjects were classified as smokers if they smoked at least 100 cigarettes in their life and further classified as current or former smokers. Furthermore, pack years (computed as packs/day smoked × years of smoking) were included in the analysis together with the number of smokers living inside the respondent’s home, to account for passive smoking.

Body mass index (BMI) was calculated as weight (kg)/height (m)².

As race/ethnicity was coded differently in the NHANES 1988–1994 and 1999–2006, this variable was recoded for

Funding: None.
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subjects in the 1999–2006 survey by merging the ‘Other Hispanic’ and ‘Mexican American’ categories.

Statistical analysis

The data are reported as means and standard errors for continuous variables and as percentages and standard errors for categorical variables.

All the multivariate models were adjusted for potential confounders, defined as variables that (i) are related to both exposure and outcome; (ii) are not an effect of exposure and (iii) are not in the causal pathway between the exposure and the outcome.16

For the time-trend analysis of urinary cadmium levels, a linear model was built with urinary cadmium as dependent variable and survey period, age and race as independent variables.

For the association between blood cadmium and mortality, blood cadmium levels were categorised in quartiles, and a Cox regression analysis was used to calculate hazard ratios (HR) and 95% confidence interval for all-cause mortality associated with each quartile of blood cadmium compared with the lowest quartile, adjusting for age, race/ethnicity, smoking status, alcohol intake, annual household income and BMI.

Trend analyses were carried out by treating the quartiles of blood cadmium as a continuous variable.

All the analyses were carried out separately for males and females. Two-sided P-values < 0.05 were regarded as statistically significant.

To make the results generalisable to the US general population, data were analysed using the Complex Samples procedures of PASW 17.0 (SPSS Inc., Chicago, IL, USA) to account for the complex NHANES sampling design, including unequal probabilities of selection, over-sampling and non-response.

Results

Time-trend analysis of urinary cadmium


The age and race/ethnicity-adjusted mean values of blood cadmium were slightly but significantly higher for females (0.62 (0.01) mcg/L) compared with males (0.59 (0.01) mcg/L; P = 0.02). There was indeed a significant correlation between these items and urinary cadmium in females.

Blood cadmium and mortality

The analysis was performed only in the 1999–2004 survey, as in the 1988–1994 survey blood cadmium was not determined. Of the 15 332 subjects, ≥20 years, who participated, 11 124 (72.6%) had all the data available for analysis. As a whole, subjects had a mean follow up of 57.0 (1.2) months.

Age and race/ethnicity-adjusted mean values of blood cadmium were slightly but significantly higher for females (0.62 (0.01) mcg/L) compared with males (0.59 (0.01) mcg/L; P = 0.02).

The adjusted HR for mortality by quartiles of blood cadmium is reported in Table 1. Both males and females in the highest blood cadmium quartile had a significantly higher risk of all-cause death compared with individuals in the lowest quartile, after adjustment for age, race/ethnicity, smoking status, alcohol intake, annual household income and BMI. Trend analysis was significant for cardiovascular mortality in females (P trend = 0.025), while there was no association between cancer mortality and blood cadmium levels.
We investigated a large sample of the US general population to determine whether exposure to cadmium, determined by levels of urinary cadmium, changed from the period 1988–1994 to the period 1999–2006. We found that while in males there was a significant reduction in urinary cadmium, the same was not true for females.

In an attempt to understand the reasons of these findings, we speculated that the possible causes for the lack of reduction of urinary cadmium in women could be due to (i) the effect of pregnancies, as iron deficiency during pregnancy leads to increased cadmium absorption and body burden;\(^1\) (ii) a higher prevalence of iron deficiency in women, which could be responsible for a higher intestinal absorption of cadmium together with iron;\(^1\) (iii) a possible reduction of smoking attitude in males but not in females and (iv) differences in dietary behaviour, as polluted food has been showed to be one of the main sources of cadmium exposure in the general population, with bread, potatoes and cereals being particularly rich in cadmium.\(^2\)

Table 1  Hazard ratio for all-cause, cardiovascular and cancer mortality by quartiles of blood cadmium, National Health and Nutrition Examination Survey 1999–2004

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First quartile (0.10–0.20 mcg/L)</td>
<td>Second quartile (0.30–0.40 mcg/L)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>No. events                                                         39</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)                                                     1.19 (0.74, 1.92)</td>
<td>1.59 (1.01, 2.49)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>No. events                                                         15</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)                                                     0.70 (0.32, 1.54)</td>
<td>1.08 (0.50, 2.30)</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>No. events                                                         8</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)                                                     0.90 (0.32, 2.57)</td>
<td>1.53 (0.57, 4.08)</td>
</tr>
</tbody>
</table>

Model adjusted for age, race/ethnicity, smoke status, pack years, number of in-house smokers, alcohol intake, annual household income and body mass index. CI, confidence interval; HR, hazard ratio.
adjusted mean urinary cadmium was significantly higher in females who had had at least one pregnancy compared with nulliparous women; (ii) women who had had three or more pregnancies had a 29% higher odd of being in the higher quartile of urinary cadmium \( (P = 0.007) \) and (iii) in the survey 1999–2006, 68% of females had more than two pregnancies versus 64% in the 1988–1994 survey \( (P = 0.01) \). On the other hand, regarding the second hypothesis, none of the markers of body iron status correlated significantly with urinary cadmium in women.

With regard to the third hypothesis, the age and race/ethnicity-adjusted proportion of smokers significantly decreased from 54.4 (1.2)% in the 1988–1994 period to 51.4 (1.7)% in the 1999–2006 period for males \( (P < 0.001) \), while for females, it did not vary over time: 36.3 (1.3)% and 35.8 (1.9)% \( (P = 0.19) \) respectively. Furthermore, the gender differences in urinary cadmium are only significant for smokers (males: 0.59 (0.02) mcg/g; females: 0.80 (0.02) mcg/g; \( P < 0.001 \)) but not for non-smokers (males: 0.28 (0.10) mcg/g; females: 0.62 (0.07) mcg/g; \( P = 0.054 \)), even if such a borderline \( P \)-value could just be due to the smaller sample size in this subgroup. On the other hand, however, limiting the time-trend analysis to only non-smokers, the reduction in urinary cadmium is still significant in males but not in females (data not shown), suggesting that there should be modifiable factors other than smoking practice to explain the observed differences for males and females with regard to the temporal trend of urinary cadmium, that is, nutritional factors. And, hence, regarding the fourth hypothesis, we analysed the reported frequency of consumption of certain dietary items, namely cereals, bread and potatoes, among males and females and found that, compared with males, females consumed significantly higher monthly amounts of cooked cereals and dark bread, and the frequency of consumption of both these items was significantly associated with levels of urinary cadmium. These data as a whole suggest that pregnancies and nutritional habits may explain, at least in part, differences between genders in cadmiumuria.

Regarding the analysis of the association between blood cadmium and mortality, levels of blood cadmium were associated with increased HR for all-cause mortality for both males and females after adjustment for age, race/ethnicity, smoke status, alcohol intake, annual household income and BMI.

Although blood cadmium increases promptly following exposure, the blood cadmium concentration is considered to be a less reliable marker of health effects than the urinary excretion.

After pulmonary and/or gastrointestinal absorption, cadmium binds to serum albumin and accumulates in the liver, where it is complexed to a metal-binding protein with a high affinity for cadmium, metallothionein-1.\(^{20}\) The cadmium-metallothionein-1 complex reaches the kidney where it is filtered and accumulates indefinitely in the proximal tubule, whose cells possess transporters for free and bound forms of cadmium\(^{21}\) and interferes with the tubular function. As urinary cadmium is considered to mirror its renal deposits, it is assumed to be the most reliable marker of chronic risk from cadmium. Indeed, the association between urinary cadmium and mortality\(^{10}\) and other chronic disorders has been studied in previous works. However, a Japanese study, carried out on over 600 women, has clearly shown a close correlation between cadmium levels in the blood and urine and concluded that blood cadmium can be employed as a biomarker of environmental cadmium exposure.\(^{22}\)

In reference to blood cadmium, until now, the association with mortality was only investigated in particular settings, such as heavy environmental exposures\(^{23}\) or uraemic patients on haemodialysis.\(^{24}\)

Our analysis extends these findings to the general population showing that blood cadmium appears an independent predictor of mortality in the general population akin to urinary cadmium.

Furthermore, our data confirm that even low blood levels of cadmium, an order of magnitude lower than those historically considered as toxic in industrial medicine, are clinically and epidemiologically relevant.

This was already shown in reference to the risk of having chronic kidney disease\(^{12,13,25}\) and hypertension.\(^{26}\) Blood values greater than 0.089 mcmol/L (10 mcg/L) are considered evidence of excessive exposure.\(^{27}\) Very few Americans are exposed to such high levels of cadmium: in fact, no one among the investigated subjects in the 1999–2004 NHANES surveys exceeded this threshold in blood. The blood cadmium levels associated with an increased mortality risk in the general population are \( \geq 0.71 \) mcg/L, that is, at least 10 times lower than those considered at risk in industrial medicine. In the 1999–2004 NHANES surveys, 20.7 (0.7)% of the participants (corresponding to over 33 millions Americans) had these blood cadmium levels, a huge number of subjects in comparison with none exposed to the ‘traditional’ threshold of occupational medicine. On the basis of our findings, these subjects might have a higher risk of dying in the following 2–7 years than matched people with lower blood cadmium, a risk comparable with the one associated with chronic kidney disease, a well-known condition characterised by an excess of mortality.\(^{28}\)

The strong points of this study include the well-typified NHANES datasets, on a large sample of the US population.
for which mortality data after a sufficiently long follow up are available.

As several potential confounders were collected as part of the NHANES, we were able to examine the association between cadmium exposure and mortality after adjustment for potential confounders. Limitations include the fact that blood cadmium levels were low, relatively close to the detection limit of the instrument (0.3 mcg/L for the 1999–2002 survey and 0.2 mcg/L for the 2003–2004 survey) with 20.1% of participants falling below such a limit. However, National Institute of Standards and Technology whole-blood standard reference materials were used for external calibration, with the interassay coefficients of variation ranging from 4.1% to 9.4% making it very unlikely that individuals in the highest blood cadmium quartile fall well below the detection limit and on the contrary that those 20% of undetectable values indeed belong to the upper quartile.

Conclusion
This study shows that cadmium exposure decreased over time for males but not for females. There are still significant sources of cadmium in everyday life, which, in females, have been only partly modified in the last decades or which cannot be modified. The blood levels that we have shown to be associated with increased mortality are much lower than those considered by industrial hygienists as indicators of pathological exposure to cadmium. Thus, health authorities should reconsider the actual toxicological thresholds for cadmium and implement measures to further reduce the general population’s environmental exposure to cadmium, which perhaps is the only or best strategy available to reduce cadmium levels in women. Finally, the study supports the idea that blood cadmium is a proxy of chronic cadmium exposure.

Acknowledgements
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POSITION PAPER

Prevention of venous thromboembolism in patients admitted to Australian hospitals: summary of National Health and Medical Research Council clinical practice guideline

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Key words
venous thromboembolism, clinical practice guideline, risk assessment.

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*Members of the entire committee are listed in Box 1.

Abstract
Each year in Australia, about 1 in 1000 people develop a first episode of venous thromboembolism (VTE), which approximates to about 20,000 cases. More than half of these episodes occur during or soon after a hospital admission, which makes them potentially preventable. This paper summarises recommendations from the National Health and Medical Research Council’s ‘Clinical Practice Guideline for the Prevention of Venous Thromboembolism in Patients Admitted to Australian Hospitals’ and describes the way these recommendations were developed. The guideline has two aims: to provide advice on VTE prevention to Australian clinicians and to support implementation of effective programmes for VTE prevention in Australian hospitals by offering evidence-based recommendations which local hospital guidelines can be based on. Methods for preventing VTE are pharmacological and/or mechanical, and they require appropriate timing, dosing and duration and also need to be accompanied by good clinical care, such as promoting mobility and hydration whilst in hospital. With some procedures or injuries, the risk of VTE is sufficiently high to require that all patients receive an effective form of prophylaxis unless this is contraindicated; in other clinical settings, the need for prophylaxis requires individual assessment. For optimal VTE prevention, all patients admitted to hospital should have early and formal assessments of: (i) their intrinsic VTE risk and the risks related to their medical conditions; (ii) the added VTE risks resulting from surgery or trauma; (iii) bleeding risks that would contraindicate pharmacological prophylaxis; (iv) any contraindications to mechanical prophylaxis, culminating in (v) a decision about prophylaxis (pharmacological and/or mechanical, or none). The most appropriate form of prophylaxis will depend on the type of surgery, medical condition and patient characteristics. Recommendations for various clinical circumstances are provided as summary tables with relevance to orthopaedic surgical procedures, other types of surgery and medical inpatients. In addition, the tables indicate the grades of supporting evidence for the recommendations (these range from Grade A which can be trusted to guide practice, to Grade D where there is more uncertainty; Good Practice Points are consensus-based expert opinions).

Introduction
Each year in Australia, as in other Western countries, about 1 in 1000 people develop a first episode of venous thromboembolism (VTE), which approximates to about 20,000 cases across the nation.1,2 Approximately half of these patients present as pulmonary embolism (PE).3 In almost 80% of patients, VTE occurs during or soon after

Funding: The development of the 2009 NHMRC Clinical Practice Guideline for the Prevention of Venous Thromboembolism in Patients Admitted to Australian Hospitals was funded by the NHMRC.

Conflict of interest: As with all working committees established under Section 39 of the NHMRC Act 1992, some members are eligible for remuneration by way of sitting fees and travel (arranged by NHMRC to attend meetings relating to the business of NHMRC). In this capacity the following committee members were entitled to sitting fees and travel arranged by the NHMRC to produce the guideline: N. Wickham, A.S Gallus and B.N.J. Walters. The following committee member received consultancy fees from the following organisations: A.S. Gallus – BMS/Pfizer, Bayer, Daiichi-Sankyo, Astellas, Progen and Boehringer Ingelheim.
admission to hospital. One important finding in autopsy studies done before the systematic application of prophylaxis for VTE was that PE had caused or contributed to death in about 10% of patients who died in hospital.1,4 Another was that most people who died with an embolism after surgery had been operated on for a benign disease.3 These statistics make VTE a major patient safety issue for hospitals.5–7 As prophylaxis is known to reduce the rate of VTE,8–10 the National Institute of Clinical Studies, an institute of the National Health and Medical Research Council (NHMRC), identified the need to address the underuse of preventive measures for VTE in Australian hospitals as a clinical priority.11 This paper presents the latest recommendations contained within the NHMRC’s Clinical Practice Guideline for the prevention of VTE in patients admitted to Australian hospitals, as one part of the strategy to increase appropriate VTE prophylaxis.

**Background**

VTE can manifest as deep-vein thrombosis (DVT) and PE, and early consequences can include pain and swelling of the leg with DVT, or dyspnoea, hypoxia and even death from PE. Subsequent recurrent events affect approximately 30% of patients, and severe post-thrombotic syndrome affects 5% of patients during the 10 years after DVT.12–14 The population incidence of VTE is between 1 and 2 per 1000 per annum and increases with age.15,16

Surveys of clinical practice in hospitals consistently find that VTE prophylaxis remains poorly implemented.3–17 A good example is a recent large and multinational, prospective, cross-sectional survey of VTE risk and prophylaxis that included Australian hospitals.18 The survey examined inpatient charts from a randomly selected sample of hospitals to estimate VTE risk, bleeding risk and the use of VTE prophylaxis. About 50% of patients were judged to carry a VTE risk that was sufficient to justify prophylaxis; only half of these received prophylaxis as recommended by evidence-based guidelines (40% in medical and 59% in surgical wards), while many at low risk of VTE received prophylaxis they did not need (29% of medical and 34% of surgical admissions); pharmacological prophylaxis was contraindicated in 10%.18 The implementation of prophylaxis for medical inpatients in this and other surveys was low.18,19 despite evidence that about 75% of hospital deaths from PE occur in medical wards and that preventive methods are effective.20,21 During 2005–2008, NHMRC implemented a national programme to improve VTE prevention in public and private hospitals which resulted in improvements in best practice VTE prevention.22

In December 2009, the NHMRC issued an Australian evidence-based clinical practice guideline for the prevention of VTE in hospitalised patients.21 The first aim of this guideline was to provide advice on VTE prophylaxis appropriate for the Australian healthcare setting, developed using a consistent and rigorous evidence assessment methodology endorsed by the NHMRC. The second aim was to assist the implementation of effective VTE prevention programmes in our hospitals by providing consistent advice relevant to the Australian healthcare setting on which local guidelines can be based. This summary is intended to support that strategy. The full guideline and summary versions of the guideline developed for clinicians and patients are available from the NHMRC website at: http://www.nhmrc.gov.au/nics/nics-programs/vte-prevention-guideline

Clinical circumstances determine the best choice from several prophylactic options, and this can vary depending on the patient, type of surgery and medical condition. To be fully effective, pharmacological and/or mechanical preventive measures require appropriate timing, dosing and duration, applied in a context of good hospital care with attention to patient mobilisation, hydration and other basic aspects. The pharmacological options considered in this guideline include unfractionated heparin, low molecular-weight heparins, fondaparinux, danaparoid (a heparinoid), aspirin, warfarin and two relatively new oral anticoagulants (rivaroxaban and dabigatran etexilate) – all with marketing approval in Australia. The mechanical options include graduated compression stockings, intermittent pneumatic leg compression devices and foot pumps.

**Methods**

The methods used to develop this guideline are briefly described here but are available in detail in Appendix B of the full guideline.23 This guideline was developed in accordance with NHMRC standards for guideline development24–27 with guidance from a multidisciplinary expert committee (Box 1) and with public consultation undertaken before the guideline was released.

The process began with an attempt to minimise duplication by using existing high-quality evidence-based international guidelines for VTE prevention, with the intent of adapting these to the Australian context by applying a structured guideline development methodology known as ADAPTE.28,29 After reviewing several international VTE prevention guidelines,25–27 this committee found that it was unable to use the ADAPTE methodology to take directly evidence and/or recommendations from existing VTE prevention guidelines because of uncertainty surrounding the methods used to assess the supporting evidence or to formulate the recommendations, or both. The UK’s 2007 National Institute for
### Box 1 Membership of the NHMRC VTE Prevention Guideline Development Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Area of expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Michael Frommer (Chair)</td>
<td>Chair, Sydney Medical Program, Associate Dean (Learning and Teaching), Sydney Medical School, The University of Sydney.</td>
<td>Clinical epidemiology</td>
</tr>
<tr>
<td>Professor A. B. (Barry) Baker</td>
<td>Emeritus Professor, The University of Sydney and Director of Professional Affairs, Australian and New Zealand College of Anaesthetists. Nominee of the Australian and New Zealand College of Anaesthetists.</td>
<td>Anaesthesia</td>
</tr>
<tr>
<td>Kay Currie</td>
<td>Former Director of the Guidelines Research Program, NICS, NHMRC.</td>
<td>Guideline research and development</td>
</tr>
<tr>
<td>Professor John Fletcher</td>
<td>Professor of Surgery, The University of Sydney and Westmead Hospital Sydney. Representative of the Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism (Chairman).</td>
<td>Vascular surgery</td>
</tr>
<tr>
<td>Professor Alex Gallus</td>
<td>Department of Haematology, SA Pathology at Flinders Medical Centre, and Flinders University, SA. Representative of the Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism (Member).</td>
<td>Physician/pathologist</td>
</tr>
<tr>
<td>Sharon Goldsworthy</td>
<td>Clinical Pharmacy Team Leader, The Queen Elizabeth Hospital, SA. Nominee of the Society for Hospital Pharmacists Australia.</td>
<td>Pharmacy</td>
</tr>
<tr>
<td>Christine Griffiths</td>
<td>Patient Representative. The committee was saddened to learn of the death of Ms Griffiths in March 2009.</td>
<td>Patient experience</td>
</tr>
<tr>
<td>Jeannette Kamar</td>
<td>Nurse (Injury Prevention), The Northern Hospital, VIC. Nominee of the Royal College of Nursing Australia.</td>
<td>Nursing</td>
</tr>
<tr>
<td>Philippa Middleton</td>
<td>Research Leader with the Australian Centre for Health of Women and Babies (ARCH), The University of Adelaide, SA. Contracted Methodologist.</td>
<td>Systematic reviews and guideline development</td>
</tr>
<tr>
<td>Dr Sue Phillips</td>
<td>Former Executive Director, NICS, NHMRC. Dr Sue Phillips was represented by Dr Sonja Hood from August 2008 (for the duration of the guideline development process).</td>
<td>Guideline development, adaptation and guideline implementation</td>
</tr>
<tr>
<td>Dr Rebecca Tooher</td>
<td>Research Fellow with the Australian Centre for Health of Women and Babies (ARCH), The University of Adelaide, SA. Contracted Methodologist.</td>
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</tr>
<tr>
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<td>Clinical Associate Professor, Obstetrics and Internal Medicine, Royal Perth Hospital and King Edward Memorial Hospital for Women, WA. Nominee of the Royal Australian and New Zealand College of Obstetrics and Gynaecology.</td>
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</tr>
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<td>Physician</td>
</tr>
<tr>
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<td>Oncology</td>
</tr>
<tr>
<td>Mr Simon Williams</td>
<td>Orthopaedic Surgeon, VMO, Geelong Hospital, St John of God Hospital and Geelong Private Hospital, VIC. Nominee of the Royal Australasian College of Surgeons.</td>
<td>Orthopaedic surgery</td>
</tr>
<tr>
<td>Dr Agnes Wilson</td>
<td>Research Scientist, NICS, NHMRC.</td>
<td>Guideline development, adaptation and guideline implementation</td>
</tr>
</tbody>
</table>

Note: Declarations of interest of all committee members are detailed within the full guideline.
Health and Clinical Excellence’s (NICE) VTE prevention guideline, although limited to surgical patients, provided the only systematic review of available evidence; however, the structure of the clinical questions and cost-effectiveness modelling used in developing the recommendations were unsuitable for direct translation of recommendations for use in the Australian healthcare context. This was because the NICE guideline grouped all surgical procedures together, and this committee considered that this would not be meaningful in the Australian context. In addition, this committee considered that the evidence for individual surgical procedures needed to be examined separately, as the risk profile of patients undergoing different procedures differed, and that the overall recommendations provided in the NICE guideline were not expected to be clinically relevant to practitioners from different surgical and medical specialties. Therefore, in developing its recommendations, this committee ‘unpicked’ the evidence tables from the existing 2007 NICE VTE prevention guideline, and brought them up to date with top-up searches of the literature to January 2009 (to ensure currency and completeness). Separate searches for evidence about medical patients were undertaken as the 2007 NICE guideline only covered surgical patients.

Clinical questions were agreed at the outset of the guideline development process (for the full list, see Appendix C of the guideline). These determined the surgical procedures and medical conditions of interest, and guided the review of evidence and the scope of recommendations. Recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context (as required by NHMRC). Where the quality of evidence was not sufficient to allocate a grade (e.g. for VTE prevention in pregnancy or patients with active cancer), the committee offered consensus advice, distinguished as a Good Practice Point – GPP (Box 2). Consensus recommendations were reached in an equitable manner with a vote by show of hands by all committee members. Agreement of the full committee was required in order to proceed with making the recommendation.

Credible guidelines are based on systematic reviews of relevant evidence, using accepted methodology to weigh the evidence and minimise bias when developing recommendations. For this guideline, predetermined clinical questions guided systematic evidence reviews where each study was allocated a ‘level of evidence’ from the intervention component of the evidence hierarchy; rising from the lowest level of IV (case series), through to level II (randomised controlled trials (RCT)) and level I (systematic reviews of randomised trials). Consistent with the principles of ADAPTE, only systematic reviews and evidence from RCT were considered for inclusion for this guideline (level I or level II evidence for intervention studies). In order to reflect the strength or weakness of supporting evidence and its balance of effectiveness with hazards, recommendations are graded from A (the strongest, where evidence can be trusted to guide clinical practice) to D (the weakest, where definitive evidence is uncertain or lacking), again according to NHMRC standards for guideline development. Full details on grading of recommendations can be found in the methods section of the guideline.

Like most other guideline groups, when considering effectiveness of prophylaxis, this committee chose to accept evidence that reported outcomes from across the full spectrum of VTE, asymptomatic or symptomatic. This decision acknowledges that asymptomatic and symptomatic VTE are stages in one process that often starts as asymptomatic calf vein thrombosis before progressing to symptomatic thrombosis and ending, potentially, as fatal PE. Furthermore, large studies and overviews find that various forms of prophylaxis have similar relative effects in reducing asymptomatic and symptomatic adverse outcomes. Nevertheless, this committee gave more weight to evidence relating to symptomatic VTE and based no recommendation on reductions in asymptomatic outcomes alone.

The guideline development committee consisted of guideline methodologists and experts from a wide range of affected clinical disciplines (internal medicine, general,

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**Box 2 Grades of guideline recommendations, using NHMRC standards (2008–2010)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Body of evidence can be trusted to guide practice</td>
</tr>
<tr>
<td>B</td>
<td>Body of evidence can be trusted to guide practice in most situations</td>
</tr>
<tr>
<td>C</td>
<td>Body of evidence provides some support for recommendation(s) but care should be taken in its application</td>
</tr>
<tr>
<td>D</td>
<td>Body of evidence is weak and recommendation must be applied with caution</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable – unable to grade body of evidence</td>
</tr>
<tr>
<td>GPP</td>
<td>Good Practice Point – consensus-based recommendation</td>
</tr>
</tbody>
</table>
vascular and orthopaedic surgery, anaesthesia, obstetrics and gynaecology, oncology, haematology, nursing and pharmacy) who were nominated by professional associations, as well as two invited experts on VTE, two NHMRC representatives and a patient representative. The chair was a senior and experienced academic clinical epidemiologist. Potential conflicts of interest were declared and recorded at each committee meeting with committee members excluded from discussion and development of recommendations if conflict of interest was noted. Funding to develop this guideline and the associated summaries for clinicians and patients was provided by the Australian NHMRC.

**Risk assessment, recommendations and GPPs**

On hospital admission, there should be an early and formal assessment of the need for VTE prophylaxis. This should record: (i) the VTE risk attributable to patients and their medical condition and (ii) the added VTE risk resulting from surgery or trauma; (iii) bleeding risks that would contraindicate pharmacological prophylaxis; (iv) any contraindications to mechanical prophylaxis and (v) the decision about prophylaxis (pharmacological and/or mechanical, or none). The risk of VTE is sufficient after some procedures or injuries for all patients to receive some form of effective prophylaxis; in others, the need for prophylaxis depends on individual assessment of patient characteristics (Table 1). As both the VTE risk without prophylaxis and the bleeding risk with pharmacological prophylaxis increase with age, application of recommendations in the elderly requires careful consideration of all factors.

The guideline’s recommendations for orthopaedic procedures are summarised in Table 2, and in Table 3 for other surgery, including Caesarean section. In addition, a Grade A recommendation was made that surgery under central neural blockade is less likely to provoke VTE than similar surgery done under general anaesthesia. However, central neural blockade brings the need to plan the timing of anticoagulant prophylaxis, because the very small chance of epidural haematoma may increase (GPP). Table 4 summarises the recommendations for medical inpatients. Pregnant women are advised to minimise immobility and ensure adequate hydration throughout pregnancy, labour and the puerperium (GPP). The NHMRC has produced a two-page clinician summary of all the recommendations which can be downloaded from http://www.nhmrc.gov.au/nics/nics-programs/vte-prevention-guideline. The differing content and grade of the recommendations for various surgical and medical indications reflect the degree of confidence able to be placed in the relative effectiveness and safety of available preventive methods in each clinical setting.

The choice of a method for VTE prevention will depend on a judgement of the treating clinician and the preference expressed by the informed patient. The NHMRC has also developed a patient information brochure based on this guideline that aims to assist patients in understanding VTE and the benefits and risks associated with prophylaxis. This brochure can be downloaded from http://www.nhmrc.gov.au/nics/nics-programs/vte-prevention-guideline.

**Discussion**

Guidelines for clinical practice provide evidence-based advice for clinicians about the relative effectiveness and safety of different aspects of disease management, and they play an important role in system-wide clinical practice improvement.

Patient safety analysis consistently ranks effective thromboprophylaxis among the top 10 targets for clinical practice improvement in hospitals. Almost 60% of VTE events in western communities are potentially preventable because they are provoked by surgery or a medical illness and develop during or soon after admission to hospital. The key to reducing the morbidity and mortality of VTE is effective prophylaxis, because death from embolism is often rapid and most large emboli discovered at autopsy were clinically unsuspected during life. These aspects of natural history severely restrict the possible impact of treatment after embolism on mortality from this disease.

It is widely accepted that good clinical care, early mobilisation, the use of graduated compression stockings or other mechanical devices to prevent venous stasis, and low doses of anticoagulant all reduce the likelihood of DVT and PE in hospital patients. As preventive methods differ in their efficacy and bleeding risk, it is essential to balance benefit against risk in each situation. This NHMRC guideline was developed to assist Australian clinicians with that choice.

A concern about the use of antithrombotic drugs for prophylaxis is their potential influence on bleeding risk. In this guideline, Grade A recommendations are based on reliable evidence that benefit exceeds hazard for that form of prophylaxis in the specified clinical context. Also, the words ‘recommended’ or ‘use’ mean that benefit is clearly greater than harm and that the evidence supporting the recommendation was trusted to guide practice. Where the word ‘consider’ is used in recommendations, the advice is weaker because the relevant studies were underpowered, demonstrated little advantage or left unclear the balance of benefit to harm. ‘Not
Table 1: Steps in selecting thromboprophylaxis

**STEP 1: If the patient is admitted for any of the following surgical procedures or injury, the procedures carry a high risk of VTE and some form of thromboprophylaxis is warranted (as per Table 2 or 3):**

- Any surgical procedure, but especially abdominal, pelvic, thoracic or orthopaedic surgery. Major joint surgery and curative surgery for cancer carry very high VTE risk
- Leg injury requiring surgery or prolonged immobilisation
- Prolonged surgery and/or prolonged immobilisation.

Prior to selecting an appropriate method, consider other VTE risk factors (STEP 2), patient preference and possible pharmacological (STEP 3) or mechanical (STEP 4) contraindications and then refer to Table 2 or 3 for advice on recommended VTE prophylactic options based on the type of surgery or injury.

**STEP 2: Assess other VTE risk factors (patient and condition based).**

Presence of any of these risk factors or conditions may warrant VTE prophylaxis for any hospital admission.

VTE risk is increased with:

- Previous VTE
- Active cancer
- Age (incidence of VTE rises with each decade over age 40)
- Prolonged severe immobility (prolonged bed rest, immobilisation in a plaster cast/brace, or prolonged travel with limited movement and venous stasis)
- Pregnancy and the puerperium
- Marked obesity
- Oestrogen-containing hormone replacement therapy (HRT) or oral contraceptive
- Certain types of thrombophilia
- General anaesthesia (vs regional anaesthesia).

VTE risk is increased with the following medical conditions:

- Acute/acute-on-chronic chest infection
- Heart failure
- Myocardial infarction
- Ischaemic stroke with immobility
- Some forms of cancer chemotherapy
- Acute inflammatory bowel disease.

**STEP 3: Assess the risk of bleeding/contraindications to pharmacological prophylaxis.** Presence of any of the following factors may contraindicate pharmacological prophylaxis. If pharmacological prophylaxis is contraindicated, consider mechanical prophylaxis, if appropriate (STEP 4).

Consider:

- Significant renal impairment (reduced creatinine clearance for renally excreted anticoagulants)
- Current active major bleeding (i.e. at least 2 units of blood/blood products transfused in 24 hours)
- Current chronic, clinically significant and measurable bleeding over 48 hours
- Inherited or acquired bleeding disorders, for example haemophilia or other coagulation factor abnormality, coagulopathy or disseminated intravascular coagulation (DIC)
- Severe platelet function disorder or thrombocytopenia (pharmacological prophylaxis not recommended with platelet count <50 000/μL)
- Recent central nervous system (CNS) bleeding
- Intracranial or spinal lesion
- Recent major surgical procedure of high bleeding risk
- Active peptic ulcer or active ulcerative gastrointestinal disease
- Liver failure or prolonged obstructive jaundice
- Concomitant use of medications that may affect clotting (e.g. anticoagulants, antiplatelet agents, selective/non-selective non-steroidal anti-inflammatory drugs – NSAIDs)
- Neuraxial block or recent lumbar puncture.

**STEP 4: Assess any contraindications to mechanical prophylaxis.**

Graduated compression stockings may cause reduced blood flow, pressure ulcers or increase the risk of falls, so are contraindicated with:

- Any factor that prevents correct fitting of stockings (e.g. morbid obesity)
- Inflammatory conditions of the lower leg
- Severe peripheral arterial disease
- Diabetic neuropathy
- Severe oedema of the legs
- Severe lower limb deformity or inability to correctly fit stockings.

Intermittent pneumatic compression (IPC) or foot pumps can exacerbate peripheral arterial disease or arterial ulcers.

**STEP 5: Select appropriate thromboprophylaxis.**

Consult with patient to ensure support for, and adherence to, VTE prophylaxis measures.
recommended' indicates a lack of appropriate evidence or that harms are likely to outweigh benefits; GPP is expert, consensus-based advice developed in the absence of good evidence. As with other recent guidelines, the differences in recommendations for various surgical or medical settings reflect available evidence about effectiveness and potential for harm.

In developing its recommendations, the committee faced several methodological challenges – and especially the question of how to reconcile the variety of outcomes reported in different studies of thromboprophylaxis. These range from asymptomatic deep-vein thrombosis (affecting mostly the calf but also the popliteal or thigh veins), through symptomatic DVT and PE, to fatal embolism and death. There is some lack of agreement among clinicians and in the literature as to which of these outcomes provide a valid basis for developing clinical practice recommendations. Some would restrict analysis to studies using only symptomatic VTE (or PE alone), but this approach discards much of the potentially relevant evidence and has its own methodological flaws. An early decision of this committee was to accept studies that included any outcome from within the spectrum of VTE, asymptomatic and symptomatic, but to base no firm recommendation on a reduction in asymptomatic outcomes alone. This recognises that both asymptomatic and symptomatic VTE are stages of one disease that starts as subclinical calf vein thrombosis before progressing to overt thrombosis and embolism; and that various forms of prophylaxis are likely to be similarly beneficial in preventing both asymptomatic and symptomatic outcomes. In this regard, the committee concurred with most panels that have developed guidelines for preventing VTE but differed from the American Academy of Orthopaedic Surgeons which restricted its considerations to evidence about PE as the only outcome worth preventing.

Other challenges include the relative lack of large RCT of thromboprophylaxis, because most of the large studies dealt only with elective major joint replacement. Very few studies have had enough statistical power to consider effects on the incidence of clinical DVT or PE, as most have focused on the much more frequent outcome of subclinical DVT. Estimating an impact of thromboprophylaxis on clinical outcomes, including PE and fatal PE, therefore required meta-analysis. Limited study size also means that small but potentially important effects on surgical bleeding, an infrequent complication, may not be apparent. There have been very few RCT of mechanical

Table 2: Recommendations for orthopaedic surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Need for effective prophylaxis</th>
<th>Recommended pharmacological prophylaxis</th>
<th>Recommended mechanical options (grade of recommendation)</th>
<th>Duration of prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip replacement</td>
<td>All admissions</td>
<td>Use either:</td>
<td>Use GCS or IPC or foot pump (B), whether or not pharmacological prophylaxis is used</td>
<td>For up to 35 days for pharmacological options and until fully mobile for mechanical options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LMWH (A) or</td>
<td>If pharmacological prophylaxis is contraindicated, use GCS and foot pump (B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fondaparinux (B) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rivaroxaban (B) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dabigatran etexilate (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td>All admissions</td>
<td>Use either:</td>
<td>If pharmacological prophylaxis is contraindicated, use foot pump or IPC (C)</td>
<td>For up to 35 days for pharmacological options and until fully mobile for mechanical options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fondaparinux (B) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LMWH (B). If using LMWH, consider adding low-dose aspirin (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>All admissions</td>
<td>Use either:</td>
<td>Use foot pump or IPC (C), whether or not pharmacological prophylaxis is used</td>
<td>For up to 14 days for pharmacological options and until fully mobile for mechanical options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LMWH (A) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fondaparinux (B) or</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Rivaroxaban (B) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dabigatran etexilate (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee arthroscopy</td>
<td>Consider prophylaxis if added VTE risk factors (Table 1, STEP 2)</td>
<td>Routine thromboprophylaxis is not recommended (C)</td>
<td>Routine thromboprophylaxis is not recommended (C)</td>
<td>NA</td>
</tr>
<tr>
<td>Lower leg fracture or injury with immobilisation in a brace or plaster cast</td>
<td>All admissions</td>
<td>Use LMWH (A)</td>
<td>Insufficient evidence; unable to make a recommendation on mechanical prophylaxis</td>
<td>For the entire period of immobilisation</td>
</tr>
</tbody>
</table>

GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LMWH, low molecular weight heparin; NA, not applicable; VTE, venous thromboembolism.
Table 3 Recommendations for other surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Need for effective prophylaxis</th>
<th>Recommended pharmacological prophylaxis (grade of recommendation)</th>
<th>Recommended mechanical options (grade of recommendation)</th>
<th>Duration of prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td>All admissions</td>
<td>Use either:</td>
<td>Use GCS, whether or not pharmacological prophylaxis is used (B)</td>
<td>For up to 7 days or until fully mobile after major surgery for pharmacological options and until fully mobile for mechanical options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LMWH (B) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• UFH (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>All admissions if major</td>
<td>Use LMWH (B)</td>
<td>Use GCS whether or not pharmacological prophylaxis is used (B)</td>
<td>For 5–9 days for LMWH and until fully mobile for GCS</td>
</tr>
<tr>
<td>Urological surgery</td>
<td>Consider prophylaxis</td>
<td>Consider use of thromboprophylaxis based on assessing patient’s risk of VTE &amp; bleeding (GPP)</td>
<td>Inconclusive evidence. Unable to make a recommendation on mechanical prophylaxis.</td>
<td>NA</td>
</tr>
<tr>
<td>Gynaecological surgery</td>
<td>All admissions if major</td>
<td>Use either:</td>
<td>Consider using GCS or other mechanical options, especially if pharmacological prophylaxis is contraindicated (GPP)</td>
<td>For up to 7 days or until fully mobile for pharmacological options and until fully mobile for mechanical options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LMWH (B) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• UFH (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac, thoracic and vascular surgery</td>
<td>All admissions</td>
<td>Use either:</td>
<td>Use GCS (C) or IPC (C) whether or not pharmacological prophylaxis is used</td>
<td>For up to 7 days or until fully mobile for pharmacological options and until fully mobile for mechanical options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LMWH (B) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• UFH (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Use pharmacological prophylaxis with extreme caution due to high surgical bleeding risk (GPP).</td>
<td>Use either:</td>
<td>Use IPC (A) whether or not pharmacological prophylaxis is used</td>
<td>Until fully mobile for IPC or GCS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LMWH or</td>
<td>Consider using GCS (alone or with anticoagulant use) (C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• UFH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If appropriate and not contraindicated (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma surgery and spinal surgery</td>
<td>All admissions</td>
<td>Do not commence anticoagulant prophylaxis until primary haemostasis has been established (GPP)</td>
<td>Use a foot pump from admission (and in addition to any pharmacological prophylaxis) (C)</td>
<td>Until fully mobile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use LMWH starting 5 days after admission (C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery in patients with active cancer</td>
<td>All admissions</td>
<td>Use either:</td>
<td>Use GCS if pharmacological prophylaxis is contraindicated (GPP)</td>
<td>Use for at least 7–10 days post surgery</td>
</tr>
<tr>
<td>(includes general, abdominal, pelvic or</td>
<td></td>
<td>• LMWH (GPP) or</td>
<td></td>
<td>Consider extending the duration of LMWH use for up to 28 days after major abdominal or pelvic surgery for cancer, especially if added VTE risks</td>
</tr>
<tr>
<td>neurosurgery)</td>
<td></td>
<td>• UFH (GPP) in major surgery. In particular, consider risk of bleeding</td>
<td></td>
<td>Use GCS until fully mobile. Use LMWH for 5–7 days or until fully mobile (GPP).</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>Consider in all admissions</td>
<td>Use LMWH (GPP) if appropriate and not contraindicated</td>
<td>Mobilise promptly post caesarean (GPP)</td>
<td>For women with additional VTE risk factors (Table 1, STEP 2), consider extending LMWH or adjusted therapeutic dose warfarin to 6 weeks (GPP)</td>
</tr>
</tbody>
</table>

GPP, Good Practice Point; IPC, intermittent pneumatic compression; LMWH, low molecular weight heparin; NA, not applicable; UFH, unfractionated heparin; VTE, venous thromboembolism.
Table 4 Recommendations for medical inpatients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Need for effective prophylaxis</th>
<th>Recommended pharmacological prophylaxis (grade of recommendation)</th>
<th>Recommended mechanical options (grade of recommendation)</th>
<th>Duration of prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>General medical patients†</td>
<td>Consider based on estimated VTE risk and bleeding risk (GPP)</td>
<td>Use either:</td>
<td>Insufficient evidence; unable to make a recommendation</td>
<td>Unable to advise on duration</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>Consider for all patients, based on degree of immobility and risk of bleeding (GPP)</td>
<td>Consider LMWH (B) if appropriate and not contraindicated</td>
<td>Inconclusive evidence; unable to make a recommendation</td>
<td>Unable to advise on duration</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>Do not use pharmacological prophylaxis in haemorrhagic stroke patients, due to risk of bleeding (GPP)</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>All patients not receiving full-dose anticoagulant (GPP)</td>
<td>Use UFH (C) only when full anticoagulation is not in use</td>
<td>Insufficient evidence; unable to make a recommendation</td>
<td>Unable to advise on duration</td>
</tr>
<tr>
<td>Medical inpatients with active cancer</td>
<td>All</td>
<td>Use either:</td>
<td></td>
<td>From admission until discharge</td>
</tr>
<tr>
<td>Pregnancy and childbirth (not Caesarean, see surgical recommendations)</td>
<td>Consider if added VTE risk factors</td>
<td>Use either:</td>
<td></td>
<td>For 6 weeks post delivery if added</td>
</tr>
</tbody>
</table>

†General medical patients include: acute/acute-on-chronic chest infection, heart failure, myocardial infarction, stroke with immobility, some forms of cancer chemotherapy, acute inflammatory bowel disease. GPP, Good Practice Point; LMWH, low molecular weight heparin; NA, not applicable; UFH, unfractionated heparin; VTE, venous thromboembolism.

Implementation

This guideline emphasises the need for clinicians to record formally their decision about thrombosis prophylaxis when patients are first admitted to hospital. That requires clinicians to estimate intrinsic risk of VTE, add risks attributed to hospitalisation, assess contraindications to a pharmacological or mechanical prevention method, balance benefits with risks and record a decision about prophylaxis (anticoagulant, mechanical or none). With some procedures, the thrombosis risk is sufficiently high that all patients should receive effective prophylaxis, often for some time after discharge from hospital. Examples include major joint surgery and surgery for cancer. In others, like medical inpatients, thrombosis risk is not determined by a procedure but mainly by patient characteristics like age, previous thrombosis and immobility. At all times, the choice of preventive method depends on the likely balance of effectiveness to risk.

Hospital-based surveys of clinical practice have reported a suboptimal use of thromboprophylaxis, in that it was prescribed for too few patients with a high risk of VTE or too many patients where the risk was very low,17-19 or used schedules where choice, timing or duration of preventive method was inappropriate.48,49
This NHMRC guideline seeks to assist the nationwide task of stimulating and encouraging the implementation of evidence-based and effective VTE prevention programmes in Australian hospitals by providing a nationally consistent basis for local guideline development in hospitals. Addressing the gaps between clinical evidence and clinical practice is a complex challenge that guidelines alone cannot satisfy. Clinical practice improvement requires that clinical units establish local guidelines and policy that are formulated and accepted by staff, embedded into routine practice using multiple strategies, such as use of real-time electronic reminders, ongoing audit and feedback, engagement of hospital executive and clinical leaders and regular guideline review.2,20,51

We are optimistic that this NHMRC guideline will contribute to the important goal of improving the application of appropriate thromboprophylaxis in Australian hospitals in order to reduce rates of harm to patients from VTE.

References


7 Cosomers B. Venous thromboembolism caused 25,000 deaths a year, say MPs. BMJ 2005; 330: 559.


Successful catheter ablation of incessant atrial tachycardia in pregnancy using three-dimensional electroanatomical mapping with minimal radiation

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Key words
incessant atrial tachycardia, catheter ablation, pregnancy.

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Abstract
Arrhythmias during pregnancy are not an infrequent problem and present a difficult therapeutic challenge to physicians. Anti-arrhythmic medication is used with some trepidation given concerns for the unborn foetus. Catheter ablation is typically avoided due to concerns regarding foetal exposure to radiation and delayed until the post-partum period. With the availability of three-dimensional mapping systems, catheter ablation may be performed with minimal radiation. We report a pregnant woman who underwent successful ablation of focal atrial tachycardia using three-dimensional electroanatomical mapping with minimal radiation exposure.

A 32-year-old woman, at 14 weeks gestation (gravida 2, para 1), presented with 2 weeks of palpitations and exertional dyspnoea. An incessant atrial tachycardia with ventricular rates up to 220 beats per minute (bpm) was confirmed on electrocardiogram. Her first pregnancy had proceeded without complication. Although there were no clinical signs of heart failure, a transthoracic echocardiogram demonstrated global left ventricular dysfunction with an ejection fraction of 40%. Haematological studies, urea, electrolytes, cardiac enzymes, liver and thyroid function tests were within normal limits. Foetal ultrasound confirmed a viable foetus. Initial medical management using labetalol and digoxin was compromised by hypotension. Labetalol was replaced with metoprolol at up to 50 mg bd and flecainide titrated up to 100 mg bd; however, atrial tachycardia remained incessant, although ventricular rate improved to 150 bpm over the next 7 days.

After a multidisciplinary meeting with the electrophysiologist, obstetrician and medical physicist, the patient elected to undergo catheter ablation using 3D mapping systems with minimal fluoroscopy and lead pelvic shielding. Written informed consent was obtained before the procedure.

The electrophysiological study was performed without sedation. The P wave morphology (Fig. 1) demonstrated...
The findings at electrophysiological study were an incessant atrial tachycardia with variable cycle length between 400 and 480 ms. Catheter navigation was guided by NAVX (a 3D mapping system utilising electrical impedance to give real-time assessment of catheter positions in 3D space), with the earliest endocardial activation located within the body of the right atrial appendage 45 ms ahead of P wave onset (Fig. 2). Ablation using an irrigated catheter (30 w at 17 mL/min) was applied accelerating tachycardia before abrupt termination (Fig. 3). Twenty minutes following apparently successful ablation, tachycardia recurred and was remapped to a location just distal to the original application with success achieved. The procedure time was 90 min, with a total fluoroscopy time of 55 s. A medical physicist at our institution calculated the effective radiation dose at <0.1 mSv to the foetus, which is equivalent to a chest X-ray. There were no procedural complications.

Supraventricular tachycardia (SVT) is the most common sustained arrhythmia during pregnancy.6 The incidence of SVT complicating pregnancy has been estimated to be between 13 and 24 in 100 000.6,7 Focal atrial tachycardia accounts for approximately 10% of all SVT, with the more common causes being atrioventricular nodal re-entry and atrioventricular reciprocating tachycardia. Incessant focal atrial tachycardia is particularly challenging, as anti-arrhythmic drugs are relatively ineffective and up to 30% of patients with incessant atrial tachycardia have an associated cardiomyopathy. In general, the initial management of arrhythmias in pregnancy is similar to that in the non-pregnant state, which

![Figure 1](image1.png)

**Figure 1** P wave morphology – there is a change in the P wave with the onset of tachycardia in leads V2 and three in keeping with an origin from the right atrial appendage or superior tricuspid annulus. AT, atrial tachycardia; SR, sinus rhythm.

![Figure 2](image2.png)

**Figure 2** Activation mapping during tachycardia using the NAVX system (a three-dimensional (3D) mapping system utilising electrical impedance to give real-time assessment of catheter positions in 3D space) with white/red representing earliest activation and purple latest in left anterior oblique (LAO) and right anterior oblique (RAO) views. The earliest site was located within the body of the right atrial appendage. ABL, ablation; RAA, right atrial appendage; SVC, superior vena cava; TA, tricuspid annulus.
is guided by symptoms, the presence or absence of haemodynamic compromise and associated comorbidities. However, the categorisation of risk of anti-arrhythmic drug use in pregnancy affects selection.

Historically, catheter ablation had been avoided during pregnancy because of the requirement for fluoroscopy. Studies have shown a typical electrophysiological study results in an effective radiation dose of 8.3 mSv/h of fluoroscopy.8 Significant foetal complications are known to occur when exposure rates exceed 50 Sv.9 Some of the potential detrimental consequences of ionising radiation to the foetus include teratogenesis, structural malformation, growth retardation, organ dysfunction and intrauterine death.9–11 Low-level radiation exposure in utero may increase the risk of childhood cancers, such as leukaemia, twofold.10 Animal studies suggest that exposure to ionising radiation during organogenesis in the first trimester is the most concerning for carcinogenesis.11 In the present case, the effective radiation dose to the foetus was <0.1 mSv equivalent to a chest X-ray.

With the advent of 3D mapping systems, the need for fluoroscopy during catheter ablation has been substantially reduced. 3D mapping provides a recreation of the geometry of the cardiac chamber of interest generally by tracing the mapping catheter around the chamber. Additional information regarding the ‘health’ of the cardiac tissue is obtained from the voltage, with areas of low voltage or scar being potential sites for arrhythmia. The activation or pattern of electrical conduction during the arrhythmia provides the necessary information to identify the responsible focus for the tachycardia and target ablation to this location. As such, catheter ablation may be performed with minimal fluoroscopy and is an important consideration in patients with incessant tachycardia, such as the present case. The P wave morphology is particularly useful in determining the likely location9 and as such whether transeptal access will be required and often longer fluoroscopy times. There is limited published experience evaluating the safety of catheter ablation during pregnancy. To date, there have been two other reports of successful catheter ablation of incessant atrial tachycardia during pregnancy.12,13 Previous ablations were similarly delayed until after the first trimester. Fluoroscopy time varied from 0 s to 36 min, with all procedures completed without complications to the mother or foetus.12,13 Szumowski et al. published a series of nine women who underwent successful catheter ablation for supraventricular arrhythmias during pregnancy.13 Wolf–Parkinson–White syndrome was present in three, atrioventricular nodal re-entrant tachycardia in one, incessant atrial tachycardia in two and permanent junctional reciprocating tachycardia in three. 3D mapping alone was used in three patients, with minimal fluoroscopy in six patients. After a mean follow-up of 43 months, all patients were free of arrhythmia, and no long-term maternal and foetal complications were reported.

Catheter ablation may be safely and successfully completed with minimal radiation exposure in pregnancy with the guidance of 3D mapping systems. Catheter ablation should be considered in pregnancy in patients with arrhythmia refractory to medical therapy.

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**Figure 3** (A) Electrogram (ABLd) at earliest location within body of the right atrial appendage 41 ms ahead of P wave onset. (B) Acceleration or ‘speeding’ of tachycardia during ablation with termination. ABL, ablation; CS, coronary sinus; HISd, HIS bundle distal; HISp, HIS bundle proximal; SR, sinus rhythm.

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Severe refractory hypoxaemia in submassive pulmonary embolism: a surrogate marker of severe right ventricular dysfunction and indication for thrombolysis

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Key words
hypoxaemia in pulmonary embolism, thrombolysis in pulmonary embolism.

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Brief Communication

Severe refractory hypoxaemia in submassive pulmonary embolism: a surrogate marker of severe right ventricular dysfunction and indication for thrombolysis

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Abstract

The role of thrombolysis in pulmonary thromboembolism is controversial. We describe a case of life-threatening acute pulmonary embolism where thrombolysis was successfully administered because of extreme refractory hypoxaemia. We suggest that profound refractory hypoxaemia in this clinical setting was due to the combination of severe right ventricular dysfunction and shunting from pulmonary infarction. The shunt was not likely to have resolved in the short term, but right ventricular function and hypoxaemia improved with clot lysis. Similar clinical presentations should prompt active consideration of thrombolysis.
A 72-year-old man presented with a 4-day history of progressive dyspnoea and pleuritic chest pain 25 days post lumbar laminectomy. Co-morbidities included ischaemic heart disease (coronary artery bypass grafting 1992), thrombotic cerebrovascular accident without residual disability (2003), hypertension and type 2 diabetes mellitus.

Physical examination revealed the patient to be afebrile, tachypnoeic (respiratory rate 32 breaths per minute), tachycardic (heart rate 120 beats per minute), with a blood pressure of 130/80 mm/Hg. He required high-flow oxygen through a non-rebreather mask (15 L/minute) to achieve oxygen saturation of 90%. The chest was clear to auscultation, and there were no clinical signs of frank right heart failure.

Initial investigation included a clear chest X-ray (CXR), although subsequent CXRs showed consolidation in the left upper lobe. Arterial blood gas analysis on high-flow oxygen revealed pH 7.42, partial pressure of oxygen in arterial blood (PaO2) 61 mm/Hg and partial pressure of carbon dioxide in arterial blood (PaCO2) 39 mm/Hg. An electrocardiogram showed sinus tachycardia with inverted T-waves in V1–V4. Complete blood count, coagulation profile and biochemistry were unremarkable, and initial and subsequent troponin levels were normal.

Computed tomography pulmonary angiogram showed significant filling defects in the right and left main pulmonary arteries and in all lobar branches, bilaterally confirming the diagnosis of acute pulmonary embolism (PE) (Fig. 1). Airspace consolidation was noted in the left upper lobe, consistent with pulmonary infarction or over-perfusion (Fig. 2). Transthoracic echocardiography revealed abnormal septal motion in keeping with right ventricular (RV) pressure overload. The RV was dilated and hypokinetic and estimated pulmonary artery systolic pressure was approximately 80 mm/Hg.

Conventional anticoagulation with heparin by infusion was commenced. Thrombolysis was considered but initially rejected in view of adequate haemodynamic parameters and recent surgical intervention. The patient was admitted to the high-dependency unit where he rapidly became increasingly dyspnoeic and required bi-level non-invasive ventilatory support with inspired fraction of oxygen of 0.9 to 1.0 to maintain oxygen saturation greater than 92%. He remained tachycardic but normotensive. On day 2, however, it was clear that there had been no objective improvement in key cardiorespiratory variables. The patient exhibited evidence of fatigue, and thrombolysis was actively reconsidered.

With the agreement of the patient’s neurosurgeon, we proceeded to thrombolysis (tenecteplase, recombinant tissue plasminogen activator) on the basis of the severity and refractory nature of the hypoxaemia and the likelihood that the patient would imminently require intubation and mechanical ventilatory support.

Figure 1 Computed tomography pulmonary angiogram demonstrating significant filling defects in the right and left main pulmonary artery.

Figure 2 Airspace consolidation within the left upper lobe, consistent with pulmonary infarction.
Over the hours following thrombolysis, the patient progressively improved. At 12 h postinfusion, the tachycardia had resolved and arterial blood gas analysis (venturi mask, inspired fraction of oxygen 0.40) showed pH 7.40 m, PaO₂ 74 mm/Hg and PaCO₂ 43 mm/Hg. Repeat transthoracic echocardiography on day 3 of admission, 16 h after thrombolysis, revealed marked improvement in RV function with estimated pulmonary artery systolic pressure of 50 mm/Hg. Anticoagulation with heparin was continued, and the patient was discharged from the high-dependency unit on day 5.

The role of thrombolysis in acute PE remains controversial, more than 40 years after it was first suggested that it may offer greater benefit than standard anticoagulation with heparin. Although there has been some subsequent evidence to support the notion of greater efficacy with heparin,1–3 the data have significant limitations. There are still no convincing, adequately powered trials of future randomised controlled trials, assessing thrombolysis. This is based on a series of major reviews of thrombolysis in acute PE have mentioned severe hypoxaemia as a potential indication for thrombolysis.5 There are, however, no guidelines of the extent of hypoxaemia that would warrant this therapy, nor has its pathophysiological rationale been elucidated. The patient discussed in this case report had severe RV dysfunction, prompted the decision to proceed with thrombolysis.

The pathophysiology of the patient’s profound hypoxaemia is of considerable interest. He exhibited two striking abnormalities. There was significant left upper lobe airspace consolidation, which in the clinical context, almost certainly represented pulmonary infarction; this would create a significant shunt. In addition, he had severe RV dysfunction with associated inadequate cardiac output. As a consequence of this, the mixed venous oxygen saturation would be severely reduced. The relevant key physiological principle as expressed in the shunt equation12 is that for a fixed degree of shunt, the lower the cardiac output and therefore mixed venous oxygen saturation, the worse the ultimate arterial oxygenation. Thus, in this patient, it was the combination of these two potentiating pathophysiological derangements that resulted in the observed severity of hypoxaemia.

Clinical improvement after thrombolysis was prompt and impressive. There was dramatic improvement in oxygenation, as described earlier, and repeat echocardiography showed marked improvement in RV function. Left upper lobe consolidation was, however, radiographically persistent. It is likely, therefore, that the significant resolution of hypoxaemia was attributable to clot lysis, improvement in RV function and subsequent improvement in mixed venous oxygen saturation. Given the stability of imaging appearances, the degree of shunt almost certainly remained constant. Thus, the improvement in oxygenation gives further credence to the postulate of why this patient was so profoundly hypoxic clinically. It focuses our attention on the key role of RV dysfunction in causing severe oxygenation deficit when associated with significant shunt.

In summary, the clinical response of this patient to thrombolysis is prompt and imperative. There was dramatic improvement in oxygenation, as described earlier, and repeat echocardiography showed marked improvement in RV function. Left upper lobe consolidation was, however, radiographically persistent. It is likely, therefore, that the significant resolution of hypoxaemia was attributable to clot lysis, improvement in RV function and subsequent improvement in mixed venous oxygen saturation. Given the stability of imaging appearances, the degree of shunt almost certainly remained constant. Thus, the improvement in oxygenation gives further credence to the postulate of why this patient was so profoundly hypoxemic clinically. It focuses our attention on the key role of RV dysfunction in causing severe oxygenation deficit when associated with significant shunt.

In summary, the clinical response of this patient to thrombolysis is important, as it may identify a subgroup of patients with submassive PE who warrant this intervention. We propose that extreme refractory hypoxaemia in patients with acute PE is an indicator of the severity of RV dysfunction and should therefore prompt clinicians to consider thrombolysis. Available guidelines4 are non-specific in terms of the degree of hypoxaemia that would warrant thrombolysis. We would suggest that a requirement for either high-flow oxygen to maintain oxygen saturation greater than 92% (with no improvement after 24-h therapeutic anticoagulation) or non-invasive ventilatory support to maintain that degree of oxygenation should prompt serious consideration of thrombolysis. We further suggest that oxygenation status should be a component of future randomised controlled trials, assessing thrombolysis in acute PE.
References

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Implementation of standardised surveillance for *Clostridium difficile* infections in Australia: initial report from the Victorian Healthcare Associated Infection Surveillance System

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Key words

*Clostridium difficile*, healthcare associated infection, surveillance

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*Clostridium difficile* is the most common pathogen causing healthcare-associated diarrhoea. Australian infectious disease physicians and microbiologists have anxiously anticipated a local increase in incidence and severity of *C. difficile* diarrhoea since the emergence of hypervirulent strains internationally. These strains have been associated with hospital outbreaks of severe infection, high mortality, and more frequent relapses. The epidemic strain of *C. difficile* polymerase chain reaction (PCR) ribotype 027 first identified in Quebec in 2005 has caused outbreaks across North America, Europe, Asia and Central America. The
first Australian patient in 2009 was believed to have acquired infection in North America, but more recently, local acquisition of this ribotype causing severe disease has been reported. Other ribotypes associated with severe disease have also been described.

Understanding this threat, the Australian Commission for Safety and Quality in Healthcare (ACSQH) proposed national surveillance for *C. difficile* infection. Routine surveillance for *C. difficile* in Victorian public hospitals commenced in 2010. This report describes the first 6 months of collated data, enabling an understanding of the extent and severity of this infection in Victorian public hospitals.

**Development of surveillance module.** Routine surveillance for hospital identified *C. difficile* commenced on 1 October 2010 in accordance with recommendations from the ACSQH and in consultation with the Department of Health Victoria. All cases of laboratory-confirmed *C. difficile* infection identified in Victorian healthcare facilities were reported to the Victorian Healthcare Associated Infection Surveillance System (VICNISS) Coordinating Centre by infection control consultants.

**Application of standardised definitions.** A nationally decided case definition for *C. difficile* infection was applied. Potentially infected patients with diarrhoea must have yielded a positive result for *C. difficile* toxin A or B or had the presence of a toxin-producing *C. difficile* organism in a diarrhoeal specimen. Infants under 2 years of age were excluded due to frequent asymptomatic carriage of *C. difficile* in this population.

Markers of illness severity were also collected. ‘Severe’ disease was defined as either admission to intensive care unit (ICU), surgery for *C. difficile*-related complications or death attributed to *C. difficile* infection within 30 days of symptom onset. Strain typing (PCR ribotype) was performed at the discretion of the treating clinician, and testing for hypervirulence was according to practices of laboratories associated with individual healthcare facilities.

Cases were reported using the following criteria for time/place of onset:
1. Healthcare associated, healthcare facility (HCF) onset – more than 48 h after admission,
2. Healthcare associated, community onset – within 48 h of admission and within 4 weeks of discharge from a HCF,
3. Community associated – symptom onset in the community or within 48 h of admission where symptom onset was more than 12 weeks after discharge from a HCF,
4. Indeterminate exposure – onset in the community between 4 and 12 weeks of discharge from a HCF,
5. Unknown exposure – unable to be determined.

**Data collection and reporting.** Data were submitted to the VICNISS Coordinating Centre using a web-based data collection form, including non-identifying demographic data, specimen collection date, whether the organism was cultured, identification of hypervirulence, strain type and where the infection was thought to have originated.

Data were reported back to participating hospitals on a quarterly basis. For reporting of surveillance data, rates of infection were calculated using the denominator ‘per 10 000 occupied bed days (OBD)’, sourced from the Victorian Admitted Episodes Dataset.

Between 1 October 2010 and 31 March 2011, 477 cases of *C. difficile* infection were reported from 52 separate Victorian healthcare facilities. Three hundred and seventy cases were reported as healthcare associated (criteria 1 or 2), corresponding to a rate of 1.7 cases per 10 000 occupied bed days (OBD), sourced from the Victorian Admitted Episodes Dataset.

Eleven cases (2.3%) were reported as secondary to a hypervirulent strain of *C. difficile*. Ten isolates were PCR ribotype 027, and one was PCR ribotype 078. Nine of the eleven hypervirulent strains were reported as healthcare associated.

The median age of patients with *C. difficile* infection was 74 years (range 2 to 101). Three hundred and seventy-seven cases (74.6%) occurred in patients aged 60 years or
over. One hundred and twenty one cases and two of the 11 hypervirulent strains occurred in patients aged less than 60 years.

Monthly numbers of cases (October 2010–March 2011) are summarised in Table 1.

Six of the hypervirulent strains identified in October/November 2010 were associated with a single outbreak at an aged-care facility. All were identified during a 4-week period (October 27–November 25).

During the reported surveillance period, seven cases fulfilled the definition for severe disease (Table 2). Of these, two were patients aged less than 60 with a confirmed hypervirulent strain. All three Clostridium difficile infection–attributed deaths occurred in patients aged over 80 years.

Victoria now has a well-established surveillance system for reporting of Clostridium difficile infection in public hospitals. This report outlines the initial surveillance findings. The observed rate of 1.7 per 10 000 occupied bed days is comparable to rates published from other Australian states, although standardised surveillance for Clostridium difficile infection is not currently practised across all Australian jurisdictions. Rates in other states have sometimes been obtained using laboratory data only, and the definition has not included clinical signs or symptoms. Using laboratory-based data, the incidence in Victoria has not included clinical signs or symptoms. Using laboratory data only, and the definition for reporting of Clostridium difficile infection cases have recently been reported as community onset. Hypervirulent strains of Clostridium difficile infection have been reported across the United States and Europe, and from 40 US states and all Canadian provinces. A study including five geographically diverse academic medical centres across the United States reported statistically significant rate increases over a 6-year period from 7.0 to 8.5 cases per 10 000 patient days. In Europe, the first reports were from the United Kingdom, where two separate outbreaks resulted in 334 cases and mortality rates of 12% and 11%, respectively. Until recently, no hypervirulent Clostridium difficile infection cases were reported in Australia. Findings from the reported surveillance period suggest a rate of 2.3% among all Clostridium difficile infection cases, and that hypervirulent Clostridium difficile infection cases were predominantly healthcare associated. This is significant in terms of the potential for severe disease in this subpopulation. However, our findings suggest that nonhypervirulent Clostridium difficile strains may also be responsible for severe Clostridium difficile infection, including Clostridium difficile infection-related death (Table 2). The finding of 38.1% cases being community onset or community associated (Fig. 1) is comparable to US centres, where approximately 35% of Clostridium difficile infection cases have recently been reported as community onset.

A limitation of the reported surveillance strategy is that validity of data has not been independently assessed. The strategy employed for surveillance of Clostridium difficile infection in Victoria was based primarily upon laboratory notifications of Clostridium difficile infection. Epidemiological and clinical data were also collected, and this was regarded as a necessary and appropriate use of resources, given the imminence of changing Clostridium difficile infection disease patterns. Our experience is that the surveillance tool was well-accepted, and definitions readily applied by participating infection control staff. State-wide strain-typing may also be

<table>
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<tr>
<th>Month/year of surveillance</th>
<th>Total number of Clostridium difficile infection cases</th>
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<th>Number of hypervirulent Clostridium difficile infection cases</th>
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<th>Age/sex</th>
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<th>Surgery</th>
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<td>yes</td>
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</table>

†Testing for hypervirulence not performed by treating centre. F, female; ICU, intensive care unit; M, male.
necessary, and we suggest that periodic reporting by laboratories be used in tandem with other surveillance data to provide insights into changing strain types over time.

Together with enhanced diagnosis, antimicrobial stewardship, stringent infection control and cleaning practices, surveillance is recognised as vital to avoiding the heightened disease burden observed internationally, and to monitoring the impact of preventive measures in a timely manner. Our findings indicate a low proportion (2.3%) of hypervirulent C. difficile strains, although testing for hypervirulence was performed in only 52–69% of instances, and current testing practices may have low sensitivity. Enhanced diagnosis may be facilitated by education of practitioners and higher rates of confirmatory testing for hypervirulent strains of C. difficile. In particular, heightened awareness among general practitioners is necessary, given the observed proportion of community-associated infections. The use of standardised laboratory practices is acknowledged as necessary for refinement of the surveillance strategy. Although this is beyond the scope of VICNISS surveillance activities, infection control guidelines for C. difficile infection have been published by the Australasian Society for Infectious Diseases (ASID) and the Australian Infection Control Association, and ASID-endorsed recommendations for laboratory practices regarding C. difficile infection diagnosis have recently been reported.

Our data reflect successful implementation of a continuous surveillance strategy for C. difficile infection within the state of Victoria. This is a necessary public health response to the emergence of hypervirulent C. difficile infection strains, ensuring that changes in epidemiology (including disease burden and severity) can now be adequately monitored. With hypervirulent C. difficile infection reported elsewhere in Australia, development of a national data repository for C. difficile infection is timely and necessary to inform infection control resource allocation and ultimately prevent the disease becoming endemic at high levels.

Acknowledgements

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References

Point-prevalence study of inappropriate antibiotic use at a tertiary Australian hospital

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Key words antibiotic, prevalence, Australia, inappropriate.

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Abstract
A point-prevalence study at a tertiary Australian hospital found 199 of 462 inpatients (43%) to be receiving antibiotic therapy. Forty-seven per cent of antibiotic use was discordant with guidelines or microbiological results and hence considered inappropriate. Risk factors for inappropriate antibiotic prescribing included bone/joint infections, the absence of infection, creatinine level >120 μmol/L, carbapenem or macrolide use and being under the care of the aged care/rehabilitation team. In the setting of finite antimicrobial stewardship resources, identification of local determinants for inappropriate antibiotic use may enable more targeted interventions.

Inappropriate antibiotic use is associated with increased hospital length of stay, increased healthcare costs, development of antimicrobial resistance and adverse patient outcomes.1 Thirty one to 81% of antibiotic prescriptions within Australian hospitals are inappropriate.2,3 However, studies to date have targeted specific antibiotic classes (e.g. 3rd-generation cephalosporins)2 or settings (e.g. surgical prophylaxis), limiting their ability to compare rates of inappropriate antibiotic prescriptions (IAPs) between specific antibiotic classes or hospital departments. In the setting of finite antimicrobial stewardship resources, identification of local determinants of IAP may enable more targeted interventions. The aim of this study was to assess the prevalence of, and risk factors for, IAP in a hospital where antimicrobial stewardship is in its infancy.

We performed a hospital-wide point-prevalence study of antibacterial use at our adult tertiary hospital between September and October 2010. Clinical and demographic data on all patients receiving antibiotics were collected using a standardised data collection form. We excluded topical, inhaled, intra-peritoneal, antiviral, anti-fungal, anti-parasitic and anti-tuberculous therapy. Each inpatient hospital ward (excluding the emergency and hospital in the home departments) was audited sequentially over a 4-week period by an infectious diseases (ID) physician and ID pharmacist. Patients were reviewed at a single point in time, and hence, the duration of antibiotic therapy was not assessed. The appropriateness of antibiotic therapy was determined based upon a standardised method developed by Willemsen et al.4 This uses an algorithm to categorise antibiotic prescriptions as either appropriate or inappropriate according to local and national antibiotic guidelines and/or available microbiological results. IAP were in turn classified (in descending order of priority) as being due to unjustified antibiotic use, incorrect choice, incorrect dose, incorrect frequency, incorrect route of administration or incorrect duration. Antibiotic use was considered justified if either community-associated (CA) or healthcare-associated (HA) infection was present. CA infection was considered present if the admitting medical doctor or the doctor seeing the patient within 48 h since admission documented suspected or proven infection and there was evidence of fever (>37.5°C) or raised inflammatory markers (C-reactive protein >10 mg/L or erythrocyte sedimentation rate >20 mm/h or white cell count >11 ×10⁹/L). HA infections were defined using Centre for Disease Control and Prevention criteria.7 Criteria for intravenous to oral switch were: temperature <38°C, signs and symptoms improved or resolved, oral or nasogastric intake tolerated, suitable oral alternative available, patient likely to be adherent with oral therapy and the absence of a known indication for intravenous therapy (e.g. endocarditis). At the time of the audit, the newly established hospital antibiotic stewardship programme had two main arms, operated by a full time ID pharmacist with support from ID physicians and microbiologists. Firstly, verbal approval from an ID physician or microbiologist was required prior to initiation of certain high-cost and/or broad-spectrum restricted
antimicrobials. Secondly, a thrice-weekly ward based ‘review and feedback’ antimicrobial stewardship rounds was used to review the need for the ongoing use of restricted antimicrobials, and in addition, regular clinical meetings provided an opportunity for advice to be given to clinicians managing the intensive care unit and haematology units. Prior to this audit, the only means for gauging the distribution of antibiotic use within the hospital was by measuring the volumes dispensed to wards by the hospital pharmacy.

Variables from the data were analysed using both univariate and multivariate regression. The principal multivariate technique to determine which predictors had an impact on the appropriateness of antibiotic prescribing was binary logistic regression. Variables that were significant at a 5% significance level were retained in the final model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for this model. The data from this study were analysed using the statistical package R (version 2.11.1, R Development Core Team, Austria).

One hundred and ninety nine of 462 (43%) inpatients were receiving antibiotics, for a total of 262 antibiotic prescriptions. Twenty-eight different antibiotics were prescribed, with 69% of patients receiving a single antibiotic, 28% receiving two antibiotics and 5% receiving three or more antibiotics. The mean age of patients receiving antibiotic therapy was 60 years. Sixty-five per cent of antibiotics were being given intravenously, the remainder orally. Fifty-two per cent of antimicrobial use was empiric therapy, 36% was therapy directed according to microbiology culture results and 12% was prophylactic. The majority of infections were CA rather than HA (61% vs 39%). Restricted antibiotics accounted for one fifth of all prescriptions and in 29% of these, clinicians did not adhere to protocols regarding their correct use.

Overall, 47% of antibiotic therapy was inappropriate and was due to unjustified antibiotic use (35%), incorrect choice of antibiotic (29%), incorrect dose (14%), incorrect duration (12%), incorrect route of administration (7%) and incorrect frequency (3%). The rates of IAP varied between departments and the class of antibiotic being prescribed (Tables 1, 2). The percentage of patients receiving IAP for CA infections was significantly higher than for those with HA infections (61% vs 42%, \( P = 0.0097 \)). Patients receiving antibiotics for prophylactic purposes were more likely to receive IAP than those receiving treatment (63% vs 52%, \( P = 0.2569 \)). In the multivariate analysis, IAP was significantly associated with bone/joint infections (OR 11.2, 95% CI 2.0–60.2), absence of infection (OR 4.4, 95% CI 1.9–10.6), creatinine level >120 μmol/L (OR 3.4, 95% CI 1.2–9.4), carbapenem use (OR 9.4, 95% CI 1.8–49.2), macrolide use (OR 14.1, 95% CI 1.7–118.0) and being under the care of the aged care/rehabilitation team (OR 3.8, 95% CI 1.2–12.5). A positive microbiological diagnosis was significantly associated with increased odds of receiving an appropriate antibiotic prescription (OR 0.4, 95% CI 0.2–0.9).

<table>
<thead>
<tr>
<th>Department</th>
<th>Number of prescriptions (% of total)</th>
<th>Number of inappropriate prescriptions</th>
<th>Proportion of prescriptions that were inappropriate</th>
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</thead>
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<tr>
<td>General surgery</td>
<td>37 (14)</td>
<td>16</td>
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<tr>
<td>Intensive care unit</td>
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<tr>
<td>Respiratory</td>
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<td>Carbapenem</td>
<td>10 (4)</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>Clindamycin</td>
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<td>6</td>
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</tr>
<tr>
<td>Folate antagonist</td>
<td>8 (3)</td>
<td>4</td>
<td>0.5</td>
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<tr>
<td>Other</td>
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Table 1 The appropriateness of antibiotic prescriptions by hospital departments

Table 2 The appropriateness of antibiotic prescriptions according to class of antibiotic
In 2010, the Australian Commission on Safety and Quality in Healthcare identified antibiotic stewardship, including collection and reporting of unit- and ward-specific antimicrobial dispensing data, as a key initiative in the prevention and control of hospital-acquired infections. Although relatively easy to obtain, measuring volumes of antibiotics dispensed by hospital pharmacies offers only a crude means of achieving this. Hospital-wide audits of antimicrobial prescribing are labor intensive but have the advantage of allowing prescriptions to be related to individual patients. This allows more comprehensive analyses to be undertaken, including the quality of antibiotic prescriptions and determinants of IAP.

The high prevalence of antibiotic use among our hospital inpatients (43%) is in keeping with nationwide surveillance data that demonstrated that between 2005 and 2008 our institution was one of the heaviest users of antimicrobials among tertiary Australian public hospitals. The casemix at our centre, including the state cystic fibrosis and neurosurgical units may partially explain this finding. However, the high prevalence (47%) of IAP indicates the need for ongoing efforts to improve the quality of antibiotic prescribing at our hospital. That the majority of IAP was due to unjustified antibiotic use and incorrect choice of antibiotic was in keeping with another large Australian study. However, the variables that were associated with IAP in our study differed from those identified in other studies—such as increased patient age, HA infection, prophylaxis, and fluoroquinolone usage. This highlights the need for hospitals to conduct their own audits to identify site-specific factors associated with IAP. Such information could then be used to tailor their antimicrobial stewardship interventions.

Our finding that nearly one third of prescriptions for restricted antibiotics were not in keeping with hospital protocols parallels findings from other studies. Addressing misuse of restricted antibiotics is problematic and requires improved compliance with the pre-approval process and more effective measures to identify and limit their ongoing, unnecessary use. As a result of this, audit several interventions have been undertaken at our hospital. These include education of junior medical staff with regard to the use of antibiotic guidelines, targeting of meropenem usage during ‘review and feedback’ rounds and feedback of the audit results to departments with high rates of IAP to provide an incentive for improvement.

In conclusion, our study confirms that antibiotic use is widespread within our hospital and of concern is inappropriate nearly half of the time. Improving the quality of antibiotic usage in hospitals in which stewardship services are in their infancy is difficult. The use of point-prevalence surveys in order to identify and target high-risk antibiotic classes, patient groups or hospital departments offers a means of overcoming these challenges.

References

PERSONAL VIEWPOINT

Health workforce changes and the roles of information technology associated with these changes
“‘The Times They Are A-Changin’” (Bob Dylan, 1964)

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Key words
health workforce, technology, clinical decision support.

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Abstract
Healthcare is considered a service profession and most of what clinicians do is manage information. Thus, information is not a necessary adjunct to care. It is care and effective patient management that require effective management of patients’ clinical data. This perspective is supported by the World Health Organisation in its use of the quotation from Gonzalo Vecina Neto, head of the Brazilian National Health Regulatory Agency, ‘There is no health without management, and there is no management without information’.

This opinion paper discusses how traditional clinical decision-making led ‘by the doctor’ is unsustainable in the modern era and how e-technologies will facilitate distributed effective decision-making and new divisions of labour across the health workforce.

This paper provides a current perspective on the challenges of creating a sustaining health/workforce in Australia and the role of health information technologies (HIT) in managing these changes.

The thematic sequence of this paper is from the defined critical roles of information management and knowledge access in achieving high-quality healthcare delivery and management to the rapidly emerging use of HIT by patients for self-management. These changes are occurring with inertia among physicians who are finding it difficult to alter the existing ‘culture of medicine’. Finally, we document the essential tools required to accomplish our desired end-points for workforce changes in the reform of healthcare.

In discussing the issues relating to the essential changes in how healthcare might be delivered, it is important to understand the current definitions that describe healthcare delivery and its management in the 21st century.

Based on the World Health Organisation manifesto, Gonzalo Vecina Neto, Head of the Brazilian National Health Regulatory Agency states, ‘There is no health without management, and there is no management without information’.

Based on this definition, we know that health information management requires effective clinical decision support tools, and these must be e-health based as we know that the human brain is simply unable to manage the current and expanding information management needs of healthcare. This state of affairs was clearly defined in the initial Institute of Medicine (IOM) 1991 report into the use of e-technologies in clinical care. The report was titled, ‘The Computer-Based Patient Care Record the essential technology for health care’.

Evidence for the failures of the traditional models for care delivery with the learned physician as the primary director of care is abundant and can be seen in studies that measure factors, such as the quality, costs and variations in the management of patients and the outcomes of care. These studies also demonstrate the dependent linkages between the cost, quality and access to care.

To demonstrate the inherent failures of the unaided human clinical decision-making processes to meet the demands of modern healthcare, Stead and Starmer in an IOM (USA) report graphically documented how the current doctor-top down, unaided clinical decision-making, associated with rapidly expanding information and knowledge resources will continue to fail in

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healthcare. Thus a new division of labour with appropriate e-health tools is required to meet the new demands of clinical decision-making. Stead and Starmer use the example of the rapidly expanding field of genomics to emphasise this reality.

In Figure 1, Stead and Starmer demonstrate the rapidly expanding data sources clinicians (doctors, nurses, pharmacists, allied health and others) need to access and process now and in the future. The effective management of this information requires the use of effectively designed digital decision support tools that are not paper based and are standardised and integrated.

In Figure 2, Stead and Starmer clarify this complexity of care in the 21st century. This graphic shows the complexity of ‘facts’ that must be processed in the single speciality of genomics which does not include the other complex domains of care, such as preventive medicine, heart disease, obesity, renal disease, etc. The highlight of Figure 2 is the flatline for human cognitive capacity which is unchanging over time.

With the advent of the massive data and information generated and required for patient care, there are the associated expansions of the knowledge resources that are generated by research on these clinical databases.

**Figure 1** Growth in data and information sources and resources over time. Adapted from Stead and Starmer, with permission.

**Figure 2** Schematic contrasting human cognitive capacity (e.g. the number of sets of facts the brain can correlate in a decision) with the explosion of new biomedical data types. SNP, single nucleotide polymorphism. Adapted from Stead and Starmer, with permission.
Balas and Boren have shown that when using the traditional information management models (predominantly paper based), it can take up to 17 years for valid clinical trial data to become routine in daily clinical care. This reduced timely access to valid clinical knowledge resources is also a major factor in what has been defined as the variation phenomenon in healthcare. Not only are patients denied proven therapies, but the research investment is largely wasted.

In the 21st century, we know that care is distributed across many disciplines, and this strongly indicates the essential requirements for care must be adapted across a wide range of clinical disciplines that are not purely ‘doctor focussed’.

There is ample evidence demonstrating that the retention of the ‘doctor focussed’ approach is not working effectively and is impeding progress to effective information management solutions. This was shown in the publication in 2000 of the text, To Err Is Human. Five years after this report, Leape and Berwick document that despite the adoption of emerging health technologies to an essentially dysfunctional healthcare system, very little has actually changed with respect to improving patient care, a situation that persists in 2011.

Leape and Berwick indicate that one of the significant reasons why there has been very little improvement in care delivery has occurred was the ‘culture of medicine’. Leape and Berwick see healthcare as a system characterised by deeply rooted customs and training, with high standards of autonomous individual performance and a commitment to progress through research-led advances in biomedical science resulting in potential cures for millions. However, the advances in healthcare technologies have created challenges to safety not faced by other hazardous industries. The prime example is the improvement in airline safety since the Tenerife disaster of 1977. The deterioration of metal implants with subsequent breakdown and inflammation and continued use of these prostheses would be another example of this.

There is additional evidence that this slow response by physicians and health educators in using effective e-health technologies persists as reported by Osborn et al., Coiera and by Hannan. The documentation of physician resistance and the underuse of unique e-health tools, such as ‘knowledge coupling’, is recently addressed by L. L. Weed, one of the pioneers in ‘health informatics’. Weed and Weed in their book, Medicine In Denial, openly challenge how we currently manage healthcare delivery using conventional methods.

Weed and Weed in 2011 provocatively challenge us with their statement, ‘the traditional concept of the learned physician is not workable’. They see the medical profession remaining focused on a model of care that believes advanced medical science can be applied by doctors using extraordinarily prolonged and expensive ‘ordeals’ of education, apprenticeship and credentialing. This is simply not possible in the current era.

Therefore, healthcare in the 21st century requires the implementation of a multidisciplinary integrated care model particularly for chronic preventable disease states. Given the importance of rapid and seamless transfer of information across this ‘team’, it is also clear that information technology is not being used as it should in this context.

This healthcare challenge is not dissimilar to the response required for climate change issues or airline safety. Vincent and others note that little evidence exists for a sustained multidisciplinary collaboration in healthcare when compared with climate change which also offers a serious man-made threat to the public good. The science of climate change has led to the rapid creation of centres of climate change in which experts from multiple diverse disciplines are brought together to tackle the problem. In this field of climate change, integrated networks – technology based – are considered essential.

Despite significant increases in expenditure on health, we continue to see a poor correlation between these expenditures and health outcomes. There also remains the persistence of variations in access to care and the inappropriate variation in the use of resources, such as pharmacy items. In addition, a 2011 report from the Dartmouth Hitchcock Centre on hospital readmissions demonstrates marked variations across healthcare institutions, with the highest readmission rates being in high-level academic institutions.

Therefore, future healthcare systems should provide access to known and emerging data and knowledge management tools. These will allow physicians to be liberated from the need to process the massive amounts of clinical data generated and will enhance the involvement of non-physician team members (including patients) in care.

The modern healthcare system is demanding change as to how care is delivered and managed, and these changes must provide timely access by other clinicians and patients to the intellectual territory once solely ‘owned’ by physicians.

Excellent examples of the benefits from the increased involvement of patients in their care management come from the Californian Health Care Foundation (CHCF). In 2007, the CHCF produced a review of the Patient Health Record, looking at it from six different perspectives. There was the overall big picture perspective which includes business modelling. The other perspectives were
from experts in the field covering the consumer, physician, technology, employers and public health. These reports clarify the importance of HIT in the total information flow and decision-making across the health domains.

Additional evidence confirms the benefits of a migration away from doctor-centred care.31,34

These advances in the use of patient-centred technologies require the ongoing evaluation of these e-health implementations. This is critical as it cannot be assumed that all new HIT implementations are safe. In contrast to existing care systems, these e-health tools allow us to capture accurate clinical data that can be used to provide the mechanisms to assess accurately what we do.21,29

For HIT to work effectively, these tools need to become routine in care delivery while new HIT paradigms are being developed that will facilitate access to rapidly expanding knowledge resources.

Weed and Weed in ‘Medicine In Denial’ point out that knowledge management is an extremely complex process.20 However, effective knowledge management underlying clinical decision support has been shown to provide healthcare delivery benefits through computerised alerts, reminders, advising, critiquing, managing, etc.31,36–38

So the question to be asked is does well-designed HIT benefit care delivery?

Using the e-technologies that were available in the 1980s and 1990s, it was shown that there were many benefits from these. This may be from simple computer-generated alerts and reminders39–43 to complex clinical decision support as with severe adult respiratory distress syndrome, protocol-directed care plans for antibiotic therapy28 and in adverse drug event detection and prevention.4 These studies also demonstrated the direct link between clinical decision-making, knowledge access and the benefits to healthcare administrative functions.44

One excellent example of how systems can evolve to integrate expanding clinical knowledge into clinical care is from the Health Evaluation through Logical Processing (HELP) system.40 Using this e-record system and clinical care data, Pestotnik and others confirmed the benefits of computerised antibiotic guidelines across all levels of care, including costs, quality and patient outcomes.28 This antibiotic guidelines system has evolved in the Latter Day Saints Hospital, Utah, that uses one of the most advanced e-health systems in the world.40 This can be seen as a major advance on that institution’s earlier historical confirmation of automated laboratory alerts and other measurements of the quality of care.40

Therefore, if we consider the message from the Bob Dylan lyrics, The Times They Are A-Changin’, within the rapid technological and knowledge revolutions within healthcare, we can also visualise that healthcare (‘medicine’) as we understand it now will have to undergo a paradigm shift in its management in the immediate future.

Historically, the old paradigm of decision-making was hierarchical, with the physician at the top of the chain of command and the final conduit for most of the relevant information and decisions.

The new paradigm should see a system of healthcare delivery consisting of a multidisciplinary team of clinicians and non-clinician providers whose task is to provide comprehensive and coordinated care. Such providers include, but are not be limited to, physicians, nurses, nursing assistants, allied health professionals, clerks, technicians, therapists, administrators, patients and others.

The goal of care in this new paradigm is to optimise patient outcomes, both objective (clinical) and subjective (patient-centred).29,34,44 This will allow for better understanding of the patient’s problems and facilitate the making of correct healthcare decisions.

On the issue of how we involve the patient in their own decision-making, the Dartmouth Hitchcock experience has shown that presenting patients awaiting surgery with non-operative alternatives can reduce the surgery rate by up to 30 % in some instances.

Additional examples of patients better managing their health ‘without the doctor’ have been documented by the CHCF (http://www.chcf.org/) in their reports, Health Care Without the Doctor (2009) and How Smartphones are Changing Health Care for Consumers and Providers (2010).

Thus, the delivery of cost-effective, quality care requires appropriately designed and engineered HIT tools that deliver the most useful information and knowledge at the time and place it is needed.20,29

An additional problem to overcome is that documented by Weed and Weed. He states, even the most gifted and well-schooling intellects are not reliable when processing large amounts of information on the ‘fly’ (ward round, clinics, accreditation examinations) and therefore healthcare needs a new division of intellectual labour. He states that ‘This is a division between electronic tools that process information and users who based on that information and personal values, apply judgement to arrive at decisions (page 70)’.20

Thus, the processes involved in implementing these new information-knowledge management tools must not create a further information overload or its complex disorganisation that further exacerbates the cognitive weaknesses we are trying to avoid.

Therefore, two of the major components of our failing healthcare systems need to be resolved.

First, the ‘culture of medicine’ must drop the pretence that it can manage modern healthcare safely and effectively using the existing ‘record’ systems.
Second, we have to use the correct tools to accomplish our desired end-points.

These tools (adapted from Weed and Weed’s *Medicine in Denial*, page 70) must provide three major, standardised, interoperable and communicable functions.20

- They must provide storage and retrieval of general knowledge (e.g. Internet access to knowledge bases).
- They must provide life-long storage, timely retrieval and transmission of patient-specific data (e.g. electronic health records, teledmedicine, health-information-exchange networks, m-Health).45
- They must link patient-specific data with general knowledge necessary for decision-making purposes (e.g. Computerised Physician Order Entry)46 so that data inputs from patients can provide individualised clinical guidance on all aspects of healthcare delivery.12,47,48

If we were able to achieve this, what a difference it might make to healthcare delivery in the 21st century and what an influence it might have on how we train our health professionals and staff our facilities. It might be useful at least to test the hypothesis that HIT will improve patient care.

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A 65-year-old woman presented with abdominal pain, tenderness, weight loss and a palpable mass in the right upper abdomen. She had undergone mitral valve replacement 8 years earlier and had been taking warfarin ever since. Laboratory findings were normal except for anaemia. Initial abdominopelvic computed tomography (CT) scan suggested infiltrative colon cancer at the hepatic flexure (Fig. 1a). Colonoscopy showed ulcerations with whitish exudates near the hepatic flexure and failed to progress to the caecum due to luminal stenosis. Biopsy from the ulcerated area showed no evidence of malignancy. A review of her initial abdominopelvic CT scan noted calcific stenosis of the superior mesenteric artery which had initially been regarded as senile change (Fig. 1b). Catheter angiography with balloon angioplasty and stent insertion were performed (Fig. 2). After vascular intervention, the abdominal pain disappeared, and the tenderness of the right upper abdomen improved slowly on a daily basis. Follow-up abdominopelvic CT scan 3 months later showed a normal ascending colon...
and a patent stent (Fig. 1c). She completely recovered from pain and tenderness.

Ischaemic colitis is the most common form of intestinal ischaemia, with an incidence of 6.1 to 47 per 100 000 inhabitants/year in the United States.1 However, the correct diagnosis of ischaemic colitis of the ascending colon is less well recognised than its counterpart involving the left colon.2 This case illustrates that right-sided ischaemic colitis should be considered in older patients with right-sided abdominal pain, especially when they have underlying risk factors such as valvular heart disease.

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References

LETTERS TO THE EDITOR

Clinical-scientific notes

Human T-lymphotropic virus seroconversion associated with pooled human intravenous immunoglobulin therapy

The use of pooled human intravenous immunoglobulin (IVIG) can result in passive antibody transfer from donor to recipient. We present a case where a false positive serological test for a potentially blood borne or sexually transmitted infection led to significant patient anxiety and diagnostic confusion.

In early 2007, a 44-year-old man developed left foot drop. Neurological examination revealed weakness of the left ankle and globally depressed deep tendon reflexes. Sensory examination was normal. Neurophysiological investigations established that motor amplitudes were generally reduced, without evidence of focal conduction block. Magnetic resonance imaging (MRI) spine and CSF analysis were normal. Serum was non-reactive when tested for ANCA, ANA and anti-ganglioside antibodies (anti-GM 1). The provisional diagnosis was multifocal motor neuropathy (without conduction block) or a lower motor neurone presentation of motor neurone disease.1

By December 2007, and in the context of slow disease progression, a diagnostic treatment trial was commenced with pooled IVIG (Octagam). There was initial clinical benefit, and further IVIG infusions were continued (Octagam administered from December 2007 until September 2010 and Flebogamma from October 2010 until July 2011). However, clinical deterioration over 3 years led to a confirmed diagnosis of motor neurone disease.1

Early in the illness, further investigations were undertaken to determine the cause of the motor neuropathy. Enzyme immunoassay (EIA) serologic testing for human T-lymphotropic virus (HTLV) types I and II was reactive. HTLV infection can cause myelopathy or motor neuropathy, although the most common significant sequelae of HTLV infection are spastic paraparesis and adult T-cell leukaemia/lymphoma.2,3

The patient was born in Australia and worked in an outdoor occupation. He had no family history of neurological disease, had not received blood transfusion and did not use intravenous drugs. Travel history included short visits to South Africa, Bali and the United States.

We believe the serological findings in this case represent passive transfer of HTLV I and II antibodies from plasma donors (pooled from paid donors in the United States) to our patient. Prior to the first Octagam infusion, the patient’s serum tested negative for antibodies to HTLV (Figure 1). Following induction and during ongoing treatment, serum tested positive, then subsequently negative. HTLV nucleic acid was not detectable. Recently, clinicians have described HTLV antibody seroconversion, then seroreversion, in 2 recipients of Octagam for allogenic stem cell transplantation.4 Passive antibody transfer following immunoglobulin therapy is recognised for other infections, including hepatitis B.5

Transmission of HTLV may occur through perinatal, sexual or lymphoid cell transmission (including needle sharing or injury and blood transfusion).3 In the midst of coming to terms with chronic neurological illness, the positive result in December 2008 caused significant distress to the patient and his wife.

In Australia, IVIG is licensed for immune replacement or immune modulation of a wide spectrum of illnesses.6 The increasing demand for IVIG is estimated to be 14% per annum.7 There is an ongoing debate regarding quality and safety of imported human plasma.7 Clinicians need to be aware of the passive transfer of antibodies in pooled plasma products and consider the interpretation and patient counselling of positive serological tests, particularly for pathogens that are not screened for in donors.

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Hazards of potassium and multiple sources of sodium in causing osmotic demyelination

A 21-year-old female backpacker, normal weight 52 kg, consumed large amounts of water while trekking in Australia. She developed nausea, vomiting, dizziness and episodes of loss of consciousness. She had a past history of bulimia but no other important past or family history. Her blood pressure was 109/76 mm Hg, Glasgow coma score was 15. There were no other abnormalities on examination. Admission electrolytes are shown in Table 1.

She was given normal saline; 150 mL, 3% saline; sodium phosphate for hypophosphataemia; potassium in normal saline and as boluses of concentrated potassium chloride. A total of 390 mmol of intravenous potassium was administered.

The serum sodium rose by 23 mmol in 25 h to a level of 131 mmol/L and 136 mmol/L in 48 h; and the haemoglobin decreased to 117 g/L.

She was discharged and was re-admitted 9 days later with ataxia, blurred vision, intention tremor, dysphagia, cerebellar signs, slurred speech, nystagmus and paresthesias of the feet and hands. A diffusion weighted magnetic resonance imaging (MRI) showed a large area of demyelination in the pons (Fig. 1).

The patient developed moderate to severe sodium chloride depletion and hypokalaemia from vomiting and water intoxication from water intake. The normal Glasgow coma scale should have led to caution in the speed of correction of serum sodium, which should be less than 10–12 mmol/L in 24 h.1

The increase in serum sodium of 23 mmol in 25 h was probably due to failure to account for several different sources in sodium replacement: the use of isotonic normal saline, which was hypertonic compared with the patient’s serum sodium; 150 mL 3% hypertonic saline; sodium phosphate; and administration of potassium chloride, the most important. 390 mmol was given in normal saline and as boluses of concentrated potassium chloride via a central line.

Potassium is an important indirect source of sodium because over two thirds exchanges with extracellular sodium during potassium depletion and sodium return to the extra cellular compartment on replacement. Indeed, as Edelman2 emphasised, an isotonic solution of potassium increases tonicity to the same extent as isotonic normal saline until it is excreted. This has been re-emphasised recently.3

Table 1 Laboratory results

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A recent audit of 44 cases of severe euvoalaemic hyponatraemia, by the lead author, showed that potassium administration was an important cause in five of 11 cases of marked overcorrection (unpublished observations.) Normal saline containing 40 mmol potassium chloride results in a solution of sodium plus potassium of 190 mmol/L, which is almost double the tonicity of the patient’s serum sodium of 108 mmol/L. Estimation suggests that 1 L of this solution would have increased serum sodium by over 6 mmol/L. Hypokalaemia is an important risk factor in the development of osmotic demyelination and has been reported to occur in 86% of those with osmotic demyelination. This may be due to decreased activity of sodium potassium pumps or its effect in increasing serum sodium when potassium is replaced.

A spontaneous water diuresis may have contributed to the rapid rise of serum sodium, but was not identified because urine electrolytes were not measured.

Potassium should be given in 5% dextrose water if serum sodium increases too rapidly to limit the rise in serum sodium. The concentration should exceed 40 mmol/L to prevent cardiac arrhythmias and to increase serum potassium.

In conclusion, it is important that potassium administration is an indirect source of sodium in severe hyponatraemia with hypokalaemia. Failure to count several direct and indirect sources of sodium, especially potassium, or detect the onset of a water diuresis predisposes to an excessive rise in serum sodium.

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References
Cefepime: a rare cause of encephalopathy

A 70-year-old white woman presented with a 24-h history of dysphasia, myoclonus, stupor and oliguria. Eleven days previously, she had commenced home intravenous cefepime 2 g twice daily for *Pseudomonas aeruginosa* left heel osteomyelitis. Medical history included type II diabetes mellitus with mild chronic renal impairment (glomerular filtration rate (GFR) <50–55 mL/min), peripheral vascular disease and right below-knee amputation, neuropathic pain, hypertension, cerebrovascular disease, hydatid cyst and right below-knee amputation (glomerular filtration rate (GFR) <10 mL/min). Encephalopathy and myoclonus resolved, and deteriorated, requiring readmission to ICU for ventilation. On this occasion, renal function, CSF analysis and ammonia were normal. Cefepime was stopped indefinitely. She gradually improved and was discharged home 2 months after initial presentation, walking independently. A final diagnosis of cefepime-induced encephalopathy was made. This is the first reported case of this condition in Australasia.

Cefepime is an extended-spectrum, fourth-generation cephalosporin used to treat mild-to-severe infections and febrile neutropenia.\(^1,2\) It undergoes hepatic metabolism but is mainly excreted through renal elimination.\(^3\) The dose with normal renal function is 2 g every 12 h, and dose adjustment is recommended if the GFR is <50 mL/min.\(^2\) The half-life of cefepime in those with GFR <10 mL/min is approximately five times longer than those with normal renal function.\(^4\)

Cefepime-induced encephalopathy has been sporadically reported worldwide over the last decade.\(^5,6,12\) Encephalopathy manifests as altered mental status, confusion, hallucinations, cognitive disturbances, myoclonus, seizures or non-convulsive status epilepticus.\(^5\) A review of 42 cases of cefepime-induced encephalopathy most commonly observed confusion with temporospatial disorientation (96%), myoclonus (33%) and seizures (13%) in affected patients.\(^13\) Coma leading to death has been observed.\(^6,7,12,14\)

A clear association exists with the presence of renal impairment, an important risk factor.\(^2,5,7,9,14\) A prospective cohort study over 1 year following 498 patients prescribed cefepime, found 5 out of 111 patients with GFR < 60 mL/min were diagnosed with cefepime-induced encephalopathy.\(^6\) The mean GFR in those with encephalopathy was 17.2 mL/min, versus 32.6 mL/min in those without encephalopathy \((P = 0.025)\). Sonck *et al.* undertook a retrospective review of renal failure patients treated with cefepime who developed neurological complications.\(^7\) All eight patients who developed neurological symptoms died within 42 days of becoming symptomatic. Cefepime-induced encephalopathy has also been described in patients with normal renal function\(^10,11\) and cirrhosis.\(^9\) Advancing patient age and physician unawareness may also increase the risk.\(^13\)

The neurotoxic side-effects of beta-lactam antibiotics are probably secondary to suppression of inhibitory neurotransmission mediated through gamma-aminobutyric acid-A receptors.\(^10,17\) In renal failure, the neurotoxic effects are associated with a rise in the CSF concentration of cefepime.\(^7,12\) Haemodialysis rapidly removes cefepime from the blood and may be used in patients with encephalopathy and renal impairment, although it does not always improve outcome.\(^5,9,14\) Monitoring of plasma cefepime concentration levels has also been proposed.\(^5,11,14\)
In our patient, symptoms of encephalopathy were noted approximately 8 days after starting cefepime, consistent with the reported latency range of 1–10 days. Symptoms usually regress within 2–7 days after stopping cefepime. Other causes of encephalopathy (medication toxicity, hepatic encephalopathy and central nervous system infection) were considered and excluded before attributing this presentation to cefepime.

The safety profile of cefepime has been evaluated recently and caution regarding its use has been advised. A meta-analysis showed increased mortality in patients treated for severe infection with cefepime compared with other beta-lactam antibiotics and proposed that this might be secondary to toxicity. The US Food and Drug Administration responded by performing their own meta-analyses and did not identify a significant increase in mortality among cefepime-treated patients, compared with those treated with other antibiotics.

This is the first reported case of cefepime-induced encephalopathy in Australasia and carries more certainty than previous case reports, because rechallenge with cefepime established causality. Myoclonus was an important clue to the onset of encephalopathy. Whilst uncommon, physicians need to be aware of this potentially life-threatening adverse effect. To avoid this complication, dose adjustment and/or monitoring of cefepime levels should be undertaken in patients with renal impairment, the elderly and those with multiple medical co-morbidities. When a patient treated with cefepime develops neurological symptoms, the drug should be stopped immediately.

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References
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Plasmapheresis in systemic lupus erythematosus with thrombotic microangiopathy

We thank Samson et al. for reporting an interesting case of haemolytic-uraemic syndrome during severe lupus nephritis (LN) and efficacy of plasma exchange. The authors have reported improvement of renal functions with immunosuppressive drugs and plasma exchange.1

We also had a similar patient of systemic lupus erythematosus (SLE) with nephrotic syndrome (serum creatinine 0.8 mg%) and biopsy-proved LN (class IV) treated with six pulses of cyclophosphamide and steroids. The patient achieved remission with the said regimen. One year later, the patient had a nephritic flare (serum creatinine 5.8 mg%) with thrombotic microangiopathy (TMA) and biopsy suggestive of class IV LN. The patient was treated with rituximab, as she had received cyclophosphamide (9 g) in past. In view of no response to rituximab, the patient was started on plasmapheresis (eight sessions) and intravenous immunoglobulin (IVIG), serum creatinine fell to 5.8 mg% to 2.2 mg% after 15 days of plasmapheresis session and was maintained on mycophenolate mofetil and steroids.

In a large series of 2461 SLE patients, 25 (1.01%) cases of TMA were reported. Infection was one of the major triggers for SLE flare with TMA. LN was diagnosed in 21 patients and 11 underwent biopsy confirmation. Patients were treated with immunosuppressants, including corticosteroids, cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab or IVIG and plasmapheresis. Patients undergoing ≥7 plasma exchanges had higher complete remission of acute renal failure.2 The earlier mentioned study is one of the largest evidence plasma exchanges in TMA in patients with SLE/LN. The index case reported by Samson et al. underwent seven sessions of plasmapheresis and had good outcome supporting the evidence generated by Chen et al. As the authors have emphasised use of plasma exchange in the index patient of SLE with TMA, it would have been worthwhile to mention the study reported by Chen et al.2

The patient reported by Samson et al. received 9 monthly pulses of cyclophosphamide in spite of achieving response after 1 month of therapy. However, most of the current literature advocates use of only 6 monthly pulses of cyclophosphamide as induction therapy for LN.3

Finally, the case reported by Samson et al. is a good description and strengthens evidence of use of plasma exchange along with immunosuppressive therapy for treatment of LN with TMA.

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References

Physicians and the indigenous patient

The article by Durey et al.1 is timely in that although health professionals have been encouraged to behave in a more culturally appropriate manner towards their indigenous patients, there is still a long way to go. As a clinician whose first contact with such patients began in 1956 and largely ended on retirement in 1996, I can identify with many of the points made by the authors. A variant of their man, Mr K comes to mind. It took me some time to realise why Aboriginal patients living more traditional lifestyles with severe chronic lung disease rarely complained of breathlessness on exertion. In such circumstances, they would exert less or sometimes not at all...
all: problem solved, until the patient unexpectedly goes into respiratory failure!

There are two commissions and a few omissions in the paper that should be mentioned. In the first paragraph of the Introduction, the authors suggest that the interaction between indigenous patients and non-indigenous health-careers should not be difficult. We believe that all such encounters between those of totally different cultures will be difficult, certainly a challenge. In the next sentence, we understand the authors to imply that marked improvement in Aboriginal health is largely determined by dedicated informed health professionals armed with lots of money. Just as improvements in European-Australian morbidity and mortality can be attributed only in small part to western healthcare, so only education and socio-economic advancement will do the same for indigenous Australians. The improvement in life expectancy for NSW Aborigines does seem to correlate well with an improving socio-economic status for many, but of course not all. One prominent omission was that no mention was made that the indigenous population in this country is a very heterogeneous one. Three quarters now live in cities and have English as a first language, although sometimes with a limited vocabulary. In other words, ‘one size does not fit all’. Yes, it is important to involve Aboriginal health workers, but a health worker not known or related (however distantly) to the patient and of a different sex will not immediately relate particularly to patients evacuated from remote centres. Remember that the definition of Aboriginality is becoming less and less biological and more sociological, so that blue-eyed and fair-haired healthcare workers known and accepted in their communities may struggle for recognition in different communities. One solution to involving appropriate Aboriginal healthcare workers is for physicians in particular, to increase their outreach activities and see the patient on site. We gather that among Fellows of The Royal Australasian College of Physicians, this is already happening and seems likely to increase.

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Reference


Unilateral conjunctival icterus and no ‘glass eye’

We were prompted by this Journal’s recent publication showing unilateral scleral icterus in a patient with a ‘glass eye’, putatively explained by hepatic metastases from a previous choroidal melanoma.¹

In this case, we noticed on a ward round 5 days after admission that a 42-year-old male alcoholic patient had unilateral icterus (Fig. 1). There was no ocular prosthesis in this case, thus provoking our earnest consideration.

Scleral icterus is more accurately termed conjunctival icterus, as this is where the majority of bilirubin staining is seen on unstained histology.²⁻⁴ It is usually bilateral. Previous suggestions that staining occurs in the conjunctiva, and not the sclera, due to elastin content are not supported anatomically.⁵⁻⁶ It is possible that the increased level of bilirubin in the extracellular fluid from the inflammatory exudates explains these changes.⁷ Further histological research is needed.

Unilateral conjunctival icterus is a relatively rare clinical finding in the setting of jaundice. It is more commonly seen in resolving unilateral subconjunctival

**Figure 1** Unilateral conjunctival icterus of the right eye.
haemorrhage, although in this setting, it would not normally be labelled as icterus. It has also been reported as being due to hyperbilirubinaemia in a monocular patient (in both reported cases secondary to enucleation for previous choroidal melanoma with new liver metastasis), asymmetric oedema and staining of tissues by prolonged use of certain local eye medications, such as mercurials, iodides and proteinated silver preparations. Asymmetric oedema is due to abnormal vascular tone following neurological damage. Oedema appears in the paralysed side and remains uncoloured in jaundiced states. The mechanism remains unknown.

In our case, the patient was noted to have mild jaundice and bilateral conjunctival icterus earlier during the admission due to alcoholic liver disease. As the bilirubin level fell during the admission, the icterus remained in the right sclera. On history taking, the patient reported a recent episode of conjunctivitis in this eye, and presumably, the bilirubin was retained in association with the hyperaemia and inflammation.

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References


Erratum

The publisher would like to draw the reader’s attention to an error in the following article:


In the sentence on p. 474, in Line 9 of the first paragraph of the right hand column it reads:

“In the first half of 1997, Ian Gawler and his then wife Grace headed to the Philippines” – should read “In the first half of 1977” (not 1997).

The authors apologise for this error and for any confusion caused.