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Silent cerebral infarction and mean platelet volume
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EDITORIAL

Mortality from common drug interactions, knowledge and clinical reasoning to optimise prescribing

The case report of a near death from the addition of a macrolide antibiotic to a patient stable on simvastatin is neither novel nor uncommon. As often occurs, this patient exhibited no apparent signs of myopathy while taking a concomitant low dose of macrolide, but when the dose was doubled, a significant reaction occurred, including raised troponin and creatinine kinase without an obvious cardiac event.

The case is an example of a predictable clinically significant drug interaction as a result of CYP3A4 inhibition that has been commonly reported. Yet it continues to occur, despite education, electronic prescribing with decision support in general practice and some hospitals, pharmacy reviews, and easily accessible websites. A quick PubMed search found several published cases about drug interactions with simvastatin alone in the past 3 years, and many more with other statins.

As the authors of this report show, the simple overlooking of a well-known drug interaction, although recognised before a terminal event, resulted in severe morbidity and an avoidable 2 weeks of acute hospital care. The authors did not discuss the cost of this, although using estimates of health professional time and standard bed cost, a conservative estimate would place this single adverse event at around $15–20 000AUD. We know of other examples where similar statin interactions resulted in a preventable death.

In a recent series of 15 cases of severe myotoxicity reactions described in Aboriginal and Torres Strait islanders in this Journal, drugs well-known to interact with statins were involved in seven cases. Three of those seven died and two have permanent harm. In addition to the obvious harms to those patients and their families, the impact of these visible adverse effects from taking statins is likely to impact on adherence by other patients taking statins.

There is a perception that adverse events from known drug interactions are an expected part of routine care and therefore after a period of familiarity with the drug are not always reported to the Therapeutic Goods Administration. This is especially so with common drugs such as statins. Here, over 24 million prescriptions were dispensed in 2010–2011, that is, 15% of our population are currently taking one. Statins are generally well tolerated, although adverse effects on skeletal muscle are recognised.

The incidence of statin-associated myotoxicity, ranging from myalgia to rhabdomyolysis is reported at 1–5% in observational studies and myalgia reported in 1–25% of clinical trials. The risk increases significantly in patients on concomitant therapy including inhibitors of CYP3A4, such as macrolide antibiotics, azole antifungals, diltiazem and protease inhibitors such as ritonavir and saquinavir. We support a transparent and rigorous reporting system for adverse events, backed up by analysis of underlying factors and an organisation-wide medicine safety strategy combined with a better supported reporting system to the national regulator.

As well as complacency for a common event, we believe there are other factors contributing to these recurrent occurrences, which require a combined systems and individual approach to address.

Systems factors underlie many prescribing errors. Patients often see multiple prescribers in hospital and in general practice without a consistently accurate and current medication history being transferred. In these situations, a drug such as a statin could be initiated by one prescriber and additional short-term agents such as antibiotics or antifungals be prescribed by another clinician who may not be fully aware of concurrent therapy nor identify, anticipate or prevent the outcome of these interactions. It could also be possible that the pharmacist who dispensed the antibiotic was unaware of the patients’ concurrent therapies.

Clinical decision support associated with both a unique patient identifier and fully integrated electronic prescribing systems with minimisation of override systems can significantly reduce prescribing errors such as these. For example, it could be expected that the prescriber of the clarithromycin identified or been alerted by their decision support system. However, if the simvastatin combination was not in the same computer system, this safety barrier is ineffective.

We believe there are also contributing factors in our so called ‘safety systems’ – designed to prevent the very things they end up causing. For example, increasing numbers of ‘checking’ and ‘double checking’ as in nursing and pharmacy routine may have led to behaviour whereby the words are said, but the mental checking and clinical reasoning do not occur. This is slightly different but also relevant to the common scenario where one
professional assumes that somebody else is actually taking full responsibility for a management decision and in fact nobody is. Similarly, tasks that are demanded by safety and quality standards such as medication reconciliation may lead pharmacy staff to prepare lists of medicines from patients’ history and compare them against current prescribed medication without considering appropriateness for the individual.

Pharmacists undertaking medication reviews and reconciliation must ensure that they (as must the prescriber) remain focused on the specific medications prescribed for the individual patient and work with prescribers to anticipate, investigate and minimise harm from drug interactions.7

Multiple consults in the hospital whereby many teams from different specialties consult on specific organ dysfunctions in what is essentially a general medical patient prevent the opportunity for a ‘whole patient’ review and its systems physiology to occur. This reduces the ability to consider the likely impact of a prescribing decision on a variety of measures.

The pressures on individuals in today’s complex healthcare system lead to inadequate human thinking under conditions of complexity, interruptions, uncertainty and time pressures. Factors associated with individual clinicians’ knowledge, skills and clinical reasoning underlie many flawed management decisions such as initiating a prescription or changing the dose of medication leading to a ‘well-known’ drug interaction. To anticipate effectively and recognise the adverse outcome of a drug–drug interaction requires underlying knowledge, awareness of risks and critically the ability to make the correct management decisions based on extensive knowledge of the drugs and the patient, and their own clinical experience. Clinicians have been reported to stay wedded to an incorrect diagnosis even if the correct one is suggested by colleagues or by decision support tools. An example of this is not considering the interaction even if alerted – clinicians may choose to ignore the alert as they have not previously been exposed to or have seen the clinical manifestation of potential interactions – so-called alert bias.

There are at least three other contributing individual factors:

1. Individuals often assume that hospitals are ‘safe’ – that there are multiple checks and balances and that somebody will check the chart if there is a problem. However, despite the increasing workforce in medicine and pharmacy, these events are still occurring, even at our teaching hospital. In a recent example, a patient with a statin-CYP3A4 inhibitor (azole)-induced rhabdomyolysis was seen by several physicians and pharmacists without registration that a drug interaction was to blame. Lack of awareness of actual adverse drug events, even when symptoms are florid and time course is classic – is a major problem.

2. Lack of medication reviews for some patients. For example our ageing population who may have been 60 when they started on statin are now over 80, with many changes to cardiovascular risk, and many known and unknown changes on the pharmacokinetic and pharmacodynamic effects of long-term statins, of ageing. In addition, the likelihood of benefit in this group is unknown.

3. Going with the flow – as a group, we are not good at questioning why we prescribe in a specific way. Many can quote ‘treat to target’ mantra such as low density lipoprotein and blood pressure ‘targets’ without knowing who the evidence applies to, which is not usually the patients in hospital who may be multimorbid, elderly and at the extremes of body size.

At the system level, several interventions can improve decision quality for clinicians. These include clinical decision support systems that remind and prompt clinicians to consider evidence-based decisions. However, these systems can cause alert fatigue. In the case of preventing fatal drug interactions, the importance of a full accurate medication history before prescribing and dispensing is clearly a critical factor to prevent patient harm. Recharting of medication is not an administrative ‘hassle’ but arguably one of the most important tasks for the prescriber and should be treated as such.

Other system level approaches include education and training, and ongoing professional development that expands and updates clinical expertise. In particular, the need for applied contextualised clinical pharmacology training, a core part of medical training but often absent as the number of academic and hospital clinical pharmacology posts are reduced. Individual clinicians’ awareness of potentially relevant drug – drug interactions is pivotal for effective and safe prescribing, as is awareness of common and potentially harmful patient factors that can increase the severity of these interactions, including frailty, elderly, renal or hepatic impairment. It needs to be core knowledge that in patients with altered pharmacokinetics (predominantly metabolism and clearance) that relatively small doses can kill patients if an interacting drug is given.

In this case, the patient had been receiving clarithromycin, well known to increase the concentrations of simvastatin, for some weeks without any apparent signs of myopathy. Sadly, these events are not due to chance, are entirely preventable and occur not just in small or peripheral hospitals. As Page et al. report, we have also witnessed these events in a high-technology developed
healthcare system, where decision support and interaction alert software are present.

We suspect that an adverse event from a patient being exposed to a similar significant adverse event if it had occurred directly due to hospital care such as wrong blood type or from a patient dying from wrong site surgery would make headlines. This is quite different to the silence around the daily occurrences of patients admitted with adverse drug events secondary to drug–drug interactions.

Overall, we believe there are three aspects to the safety of medical care of patients on statins that are addressable. First, for patients to have daily reviews of their medication chart, with consideration of all new or ceased therapies and changes in pharmacokinetic and dynamic parameters that could affect outcomes. Second, although it should be part of training for all medical students, residents and registrars that specific drugs are potent inhibitors of CYP3A4, the major enzyme responsible for simvastatin and atorvastatin metabolism, many seem not to be aware. Knowledge that there are factors that may occur or increase during the period of admission to hospital or period of sickness, which may increase the risk of drug interaction causing death (such as impaired renal or liver function) are also core knowledge that needs to be imparted. Increasing the doses of HMG-CoA reductase inhibitors on a ‘treat-to-target’ mission is also problematic. Third, the importance of counter-detailing of Pharma marketing of new therapies is important. For example, when a new azole antifungal or macrolide is marketed for use, information sessions should be shared with a medication expert so that prescribers are aware of likely or potential issues when these drugs are used in populations that are different to the homogeneous and often relatively narrow and controlled population groups in Pharma trials. Phase IV data of these agents in real population groups should be widely disseminated by medication experts, as was done perhaps belatedly with the new anticoagulants and that subsequently led to local guidelines for use.21

Prescribers require adequate information about a patient including their current medications and doses, and pharmacokinetic status. Clinical pharmacists who undertake daily review of patients’ therapy are responsible for providing patient-specific drug information to assist prescribers to optimise drug selection and dosing. Further, visual alerts for patients in whom pharmacokinetic status is changing could help remind prescribers that drugs or doses that were previously safe may now not be.

We thus recommend a multipronged approach including improved quality and quality of clinical pharmacology teaching and training across the medical degree, support for open disclosure and analysis of medical errors, support for clinical pharmacists and clinical pharmacology posts (which are numerically declining but which services could be provided by the larger institutions with telehealth available for smaller or rural hospitals.22,23) Clinical pharmacologists and pharmacists should review patients that do not fit the typical ‘pattern’ of a standard clinical presentation to ascertain if drug interactions or adverse drug events are involved. Our systems approach includes a policy where the example the treating team have ownership over all of the patient’s problems and drugs, regardless of the original prescriber.

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References

**CLINICAL PERSPECTIVES**

**Interferon-gamma release assays and the diagnosis of tuberculosis: have they found their place?**

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tuberculosis, IGRA, LTBI, screening.

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**Abstract**

Tuberculosis (TB) remains an important issue in Australia with more than 85% of active cases contributed by overseas-born persons. Other risk groups include older Australians who acquired TB in the past and indigenous people. Immune suppression is an emerging risk factor for TB, particularly due to the expanding group of conditions for which potent immunosuppressive therapies is now used. Screening for latent TB is recommended in many risk groups including recent contacts of those with transmissible TB, those undergoing immune suppressive therapy, recently arrived refugees or migrants from high-risk countries and indigenous people with high rates of TB in the local community. Interferon-gamma release assay (IGRA) has now been available for several years for the diagnosis of latent TB. It is now used in many clinical situations, and despite the rapid rate of new publications, there are still gaps in our knowledge. This paper reviews the current role of interferon-gamma release assay in various situations, to determine its place in current practice and to explore where uncertainties exist.
Introduction

Tuberculosis (TB) remains an important issue in Australia. In 2009, 1322 cases of active TB were notified, which represents an incidence rate of 6.0 per 100 000 population.1 TB in overseas-born people contributed more than 85% of these cases, often in recent migrants, overseas-born students and refugees. However, TB was more prevalent in Australian-born people in the past,1 and with the increasing use of immune suppressive medications for a variety of conditions, the ageing population, and more widespread travel, it is likely that a broad range of physicians, surgeons and general practitioners will encounter TB in patients from many different backgrounds. This may involve the diagnosis of an active case of TB or more commonly the screening for (the dormant form), latent TB (LTB) in patients undergoing immune suppression.

Interferon-gamma release assay (IGRA) has been available for several years for the diagnosis of LTB. It detects a cell-mediated immune response by measuring in vitro interferon-gamma (IFN-γ) production in response to stimulation by microbial antigens, in this case, antigens derived from Mycobacterium tuberculosis. The two tests available in Australia are the QuantiFERON-TB Gold In-Tube Test (QFG), Cellestis/Qiagen and the T-SPOT.TB test (T-Spot), Oxford Immunotec. The QFG measures the amount of IFN-γ produced, while the T-Spot measures the number of T-cell-producing IFN-γ, in response to TB antigen stimulation.

IGRA is now being used in many clinical situations. The rapid rate of publication of data regarding the role of IGRA is filling some gaps of our understanding, but as with many other new diagnostic tests, its clinical use has often progressed ahead of the evidence base.

Context of TB diagnosis – two faces of TB

It is important to distinguish the two different forms of TB, active TB and LTB. LTB is an asymptomatic state, where bacilli are dormant within the lung and regional lymph nodes, and possibly other organs. Active TB is a symptomatic clinical illness and may occur many years after primary infection, but the highest risks are in the 1–2 years following acquisition of infection and at times of reduced cell-mediated immunity. Factors contributing to reduced immunity include extremes of age, human immunodeficiency virus (HIV) infection, immune suppressive medications (such as corticosteroids or chemotherapy), solid organ transplantation and chronic renal failure requiring dialysis.7

Who to screen for LTB infection

Screening to identify people with LTB offers an opportunity to provide preventive antimicrobial therapy to asymptomatic people to reduce the risk of future development of active TB. The decision to perform a test for LTB should generally be done with the intention to treat if the screening result is positive. Currently the recommended treatment for LTB is 6–9 months of isoniazid. The US Centers for Disease Control and Prevention (CDC) considers the targeted testing of specific patient populations, to identify those with LTB with a view to offering such treatment, an integral part of the strategy to control TB.2 These guidelines emphasise the value of targeting those people <35 years of age who are at high risk of recent infection with TB (e.g. due to residence in an endemic area), and those people with conditions that increase the risk of TB reactivation (e.g. immunosuppression), regardless of age. In the Australian context, it is difficult to provide firm recommendations for patient groups in whom to screen for LTB. In general, the principles set out by international guidelines apply; however, there are some regional differences that should be noted for the local context. Table 1 represents the author’s recommendations for appropriate groups in whom to consider screening for LTB in Australia currently. The Australian National TB Advisory Committee has identified priority populations in their latest strategic plan for control of TB in Australia,4 which are summarised in Table 2.

The place of IGRA: a diagnostic aid for LTB

A positive IGRA does not distinguish between active or LTB

IGRA should generally be viewed as a test used to diagnose LTB. The diagnosis of active TB requires a combination of microbiological, histological and radiological findings in the appropriate clinical setting. IGRA is neither sufficiently sensitive nor specific to justify routine use for the diagnosis of active TB. IGRA has been systematically reviewed for the diagnosis of active TB and found to have poor value as a diagnostic aid and no better than the Tuberculin Skin Test (TST).6 In the general workup of a patient with suspected active TB, they rarely add value beyond what is already clinically known. If an IGRA is positive, this does not confirm active TB and additional testing is still necessary. If an IGRA is negative, this does
not sufficiently rule out active disease with TB, therefore, TB still remains a differential on the list of possibilities. There may be specific circumstances where they assist in the overall interpretation of the clinical picture. For example, if a patient has a low pretest probability of having prior TB exposure and an IGRA is positive, this may provide a clinical clue to evaluate for active TB more thoroughly. However, generally, they should not be used in this context and some have suggested they are currently over-ordered. There are also few data to support the use of IGRA in treatment monitoring for active TB therapy.

**LTB infection**

The diagnosis of LTB relies on tests using immunological methods as the patient is asymptomatic and dormant TB is unable to be cultured. For many years, the diagnosis of LTB has relied on the TST, otherwise known as a Mantoux test. This test uses a purified protein derivative, a heterogeneous protein mixture, from a sterilised culture of *Mycobacterium tuberculosis*. An intradermal injection of 0.1 mL of solution is placed on the ventral forearm, and the degree of resultant induration (measured in millimetres) is assessed between 48 and 72 h later.

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**Table 1** Current risk groups where TB screening should be considered

<table>
<thead>
<tr>
<th>Risk groups for recent contact with TB</th>
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<tr>
<td>• High priority</td>
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<tr>
<td>• Close contacts of those with transmissible (especially smear positive) pulmonary TB</td>
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<tr>
<td>• Recently arrived refugees, ideally &lt;2 months after arrival, up to 2 years after arrival, regardless of age</td>
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<tr>
<td>• Other groups</td>
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<tr>
<td>• Migrants aged &lt;35 years from high incidence countries, or where CXR findings consistent with past TB, up to 2 years after arrival</td>
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<tr>
<td>• Aboriginal and Torres Strait Island people with high rates of TB in community.</td>
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<td>• HCW</td>
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Higher rate of reactivation

<table>
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<th>Higher rate of reactivation</th>
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<tr>
<td>• High priority</td>
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<tr>
<td>• Those undergoing immune suppression, including:</td>
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<tr>
<td>• Immune modulation therapy with biological agents, particularly tumour necrosis factor inhibitors (Infliximab, Adalimumab, Etanercept, Certolizumab pegol, Golimumab)</td>
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<tr>
<td>• Prospective recipients of solid organ transplantation</td>
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<tr>
<td>• People with haematological malignancies, prior to receiving chemotherapy or other bone marrow suppressive medication, or (autologous or allogeneic) bone marrow transplantation</td>
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<tr>
<td>• People receiving prolonged corticosteroids, e.g. ≥15 mg/d for &gt;1 month</td>
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<tr>
<td>• Those with HIV infection, usually at diagnosis, at any CD4 count or stage of infection</td>
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<tr>
<td>• Other groups – Consider TB screening if additional risk factors exist</td>
</tr>
<tr>
<td>• People receiving new immune-modulating therapies with unknown TB risk but potent immune suppression</td>
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Additional risk groups targeted in overseas guidelines

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<th>Additional risk groups targeted in overseas guidelines</th>
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<tr>
<td>• People with silicosis</td>
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<tr>
<td>• Patients with gastrectomy</td>
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<tr>
<td>• Imprisoned population, homeless people, users of intravenous or illicit drugs</td>
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<tr>
<td>• Patients with underlying malignancy, e.g. head and neck cancer</td>
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<tr>
<td>• Those undergoing chronic renal replacement, e.g. maintenance peritoneal or haemodialysis</td>
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<tr>
<td>• People with diabetes mellitus</td>
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This is a compilation of CDC risk groups and author’s recommendations. In low-burden TB countries, routine screening of all HCW may not be necessary and targeted screening may be considered for those more likely to encounter TB patients, e.g. bronchoscopy suite and emergency department staff, Chest Clinic or Infectious Diseases clinic staff, laboratory staff. Overall RR for corticosteroid use 4.9. TB risk also demonstrated on lower doses of corticosteroids; <15 mg/day RR 2.9, ≥15 mg/d RR 7.7. These groups may be at elevated risk depending on the TB epidemiology in individual countries. In the Australian setting, they are currently viewed as having either no increased risk, or there is limited evidence to guide recommendations, thus they are generally not high priority for routine screening. CD4, cluster of differentiation 4; CDC, US Centers for Disease Control and Prevention; CXR, chest X-ray; HCW, healthcare worker; HIV, human immunodeficiency virus; LTB, latent tuberculosis; RR, relative risk; TB, tuberculosis.

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**Table 2** Priority populations for control of TB in Australia

<table>
<thead>
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<th>Priority populations for control of TB in Australia</th>
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<tr>
<td>Close contacts of those with active transmissible (pulmonary) disease</td>
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<tr>
<td>Indigenous Australians</td>
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<tr>
<td>Overseas-born persons, in particular secondary and tertiary students, overseas-born healthcare workers</td>
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<tr>
<td>Elderly and immunosuppressed persons</td>
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<tr>
<td>People living with HIV</td>
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HIV, human immunodeficiency virus; TB, tuberculosis.
Table 3 Advantages and disadvantages of IGRA

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<thead>
<tr>
<th>Advantages of IGRA</th>
<th>Limitations of IGRA</th>
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<tr>
<td>• In-built positive and negative controls</td>
<td>• No requirement for experienced personnel or specialised training at site of testing</td>
</tr>
<tr>
<td>• Lack of cross reactivity with prior Bacille–Calmette–Guérin vaccine administration</td>
<td>• Indeterminate results common, especially in immune-compromised persons</td>
</tr>
<tr>
<td>• Lack of cross reactivity with antigens from environmental mycobacteria, with the exception of Mycobacterium marinum, Mycobacterium kansasi and Mycobacterium szulgai</td>
<td>• Window period (as per the TST)</td>
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<tr>
<td>• Greater specificity than TST</td>
<td>• Serial testing/reproducibility</td>
</tr>
<tr>
<td></td>
<td>• Lack of reliability in children</td>
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<td></td>
<td>• Cost</td>
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Advantages of the TST include the long history and familiarity of use, the broad settings in which it can be conducted and the lack of any necessary laboratory support. Disadvantages of the TST include the requirement of staff time, with expertise in administration and reading the result, the requirement for two visits, and false-positive results with cross-reaction with Bacille–Calmette–Guérin (BCG) vaccine and other environmental mycobacteria (Table 3). False-negative tests may be caused by either incorrect administration or an anergic response, as a delayed-type hypersensitivity response is required to produce induration.

There are two commercially available IGRA for TB diagnosis: the QuantiFERON-TB Gold In-Tube and the T-Spot.TB test. Both of these also rely on a cell-mediated immune response to TB antigens, with IFN-γ being produced from peripheral blood mononuclear cells in response to stimulation by TB antigens.

The QFG test is an in vitro enzyme-linked immunosorbent assay email-based assay, consisting of three components: positive control (Mitogen tube), negative control (Nil tube) and a TB antigen tube. Following incubation with three TB-specific antigens, early secreted antigenic target 6 kDa (ESAT-6), culture filtrate 10 kDa (CFP-10) and TB7.7, IFN-γ production is measured within the collection tube. The T-Spot is also an in vitro IGRA, but uses an enzyme-linked immunosorbent spot technology. This test involves counting the number of T-cell-producing IFN-γ following stimulation by the TB-specific antigens ESAT-6 and CFP-10.

For both IGRA, collection tubes must be handled correctly and promptly delivered to the laboratory, as viable T cells are required for the tests to function properly. The QFG involves an initial incubation within the tube, whereas the T-Spot incubation occurs in a microtitre well in the laboratory.

Technical aspects of IGRA – how they were evaluated

Without a ‘gold standard’ diagnostic test for LTB, an evaluation of IGRA has relied on other comparators, mainly with the TST in various risk groups where predictions of TB likelihood can be made. For example, those with confirmed active TB as a measure of sensitivity, or in a community with very low TB prevalence for specificity.

Many patients with active TB, including those with disseminated disease, may have a negative TST because of an anergic response (i.e. an attenuated immune response during acute disease).9-11 This has also been seen in patients with IGRA testing. Determining sensitivity and a false-negative rate using a group with known active TB as a surrogate measure may lead to a falsely lower calculation of these values when they are applied to the LTB setting. Evaluating specificity has relied on testing those highly unlikely to have LTB. Again, without a gold standard, this population may contain some who have previously been exposed to TB.

Despite these limitations, calculations have been made regarding sensitivity and specificity with IGRAs. A meta-analysis has found that IGRAs have a sensitivity at least as good as the TST, which is around 80%, with the T.Spot TB test as high as 90%.12 Both of the commercial IGRA tests, particularly the QFG, have been designed with a cut-off to optimise specificity, which has been reported as >95%.

An IGRA result alone should not form the basis of a diagnosis of LTB. Each patient should be evaluated based on a complete risk profile, including country of origin, TB exposure history, prior personal or family history of TB and generally with the addition of a chest X-ray. With sensitivity measures for IGRA as described, some patients may still be deemed high risk for TB reactivation based on TB risk factors, and candidates for therapy despite a negative or indeterminate/borderline IGRA. These patients should be referred for further assessment and consideration for treatment of LTB treatment.

Interpreting a result

QFG results are given as ‘TB likely’ (TB antigen ≥ 0.35 IU/mL), ‘TB unlikely’ (TB antigen < 0.35 IU/mL), or an ‘indeterminate’ result (see below).
T-spot results are given as positive (>8 spots), negative (<4 spots), borderline (5, 6 or 7 spots) or invalid.

Results provided as either ‘TB likely’ on a QFG or ‘positive’ on a T-spot indicate the individual has been previously exposed to TB and requires a full evaluation, including clinical review, chest radiograph and where appropriate, microbiological samples, to exclude active TB. The result does not provide any information regarding activity of disease (active vs latent), timing of infection or the outcome of any previous TB treatment. A ‘TB unlikely’ QFG result or a ‘negative’ T-spot result indicates that there is no immunological memory of exposure to TB.

While there are no data supporting the quantitative evaluation of IGRA results, it is important to look at the exact numerical value as well as the categorical report provided. This was emphasised in the CDC updated guidelines to ‘permit more refined assessment of results and promote understanding of the tests’. For all patients, but particularly if a result is unexpected from an epidemiological perspective, the results should be interrogated to ensure that the mitogen result is strong, the background IFN value is low and mitogen value does not fall close to the cut-off.

**Indeterminate or invalid results**

One drawback of IGRA is the possibility of an invalid test result (T-spot), or an indeterminate result (QFG). An indeterminate QFG result occurs when the negative control tube (background IFN-γ) is unacceptably high, or more commonly when the mitogen tube (positive control) reacts poorly. The same concept is reported with T-spot as an invalid result; however, a borderline category is also included where the test functioned properly, but the spot count is 5, 6 or 7. The rate of indeterminate results has been shown to be higher in immunocompromised patients and in children of <5 years. An indeterminate result does however show the requesting practitioner that the result is unable to be interpreted, distinguishing this from a false-negative or false-positive test. In most instances, it is appropriate to retest an indeterminate or invalid result from a fresh patient sample, as blood-handling steps in the laboratory may contribute to an indeterminate result. If possible, immunocompromised patients should have this performed when they are on a lesser degree of immune suppression, or if HIV positive, when the patient achieves a higher CD4 cell count. Repeat indeterminate results mean that the determination of a patient’s LTB status must be evaluated with other factors such as epidemiology, clinical circumstance and chest radiography findings.

**Values close to the cut-off**

Occasionally, values do occur around the predetermined cut-off, and there are several reasons why a value may be artificially elevated or reduced, including patient factors and laboratory handling and processing. The significance of these low-positive or high-negative values remains to be determined, as best described with the QFG, where the TB antigen cut-off of 0.35 IU/mL defines a positive result. As with any test, in areas of low prevalence, the positive predictive value will be reduced. When screening low-risk individuals, specificity should be optimised and authors have recommended the introduction of a ‘grey’ zone where effectively the result would be equivocal, as is the case with the T-spot. In testing specific risk groups, such as immunocompromised patients where their ability to produce IFN-γ may be blunted, some have recommended this cut-off be reduced to improve the sensitivity. This may reduce specificity making a clear recommendation difficult in this group.

These examples emphasise the importance for laboratories to report and for clinicians to evaluate the exact result rather than relying on the interpretative category the result falls into. If a result does not make sense with respect to the clinical situation, it is recommended either to repeat the test on a fresh sample or disregard the result, instead relying on clinical judgement in conjunction with other information that may be available, such as radiological investigations.

**Negative predictive value/positive predictive value**

The true value of a test for LTB is the positive and negative predictive value for the development of active TB. Several studies have now been published addressing these points, suggesting they perform well for the prediction of future development of active TB. However, while some studies have shown a superior ability of IGRA to predict active TB in both HIV-infected and HIV-uninfected populations, others are unable to detect a difference to the TST. Some of this difference may be due to heterogeneity in trial design and reporting.

A recent meta-analysis comparing the predictive value of IGRA and TST for the development of incident cases of active TB found that both tests performed similarly, with about a twofold chance of developing active TB in people with positive screening tests compared with those with negative tests. In immunocompetent adults, who are not at ongoing high risk of exposure to TB, the use of IGRA as a test to ‘rule out’ future development of active TB appears possible. In one meta-analysis, the negative
predictive value in immunocompetent adults for progression to active TB within 2 years was high, 97.8% for T-Spot and 99.8% for QFG.\textsuperscript{14}

**Contact tracing and window periods**

As these tests rely on a host immune response, there is a window period after exposure to TB before the detection of a positive reaction. In contact-tracing activities, when testing a contact of a patient with pulmonary TB, it has been routine practice to perform an initial baseline and a ‘break of contact’ TST, 8–12 weeks after the last contact with the index case. While more data are needed, IGRA conversion appears to be similar and this particular aspect of operational TB activities will be similar with the introduction of IGRA.\textsuperscript{7,15}

**Healthcare workers (HCW)**

The main benefits of IGRA in screening HCW for LTBI include the capability for a valid result with only one visit, and the improved specificity, preventing unnecessary courses of preventive antibiotics. Some centres have practised a two-stage approach, with an initial TST, followed by a confirmatory IGRA only for those with positive TST. This strategy is cheaper, saving unnecessary IGRA testing on all HCW; however, limitations include the incomplete testing because of non-attendance for the second TST visit. It also may miss a substantial population of TST negative, IGRA positive individuals. Unlike the TST, IGRA benefits from not being boosted by prior testing. The CDC recommends that either test may be used in this setting.\textsuperscript{7} As with contact investigations, following significant exposure to a patient with infectious TB, HCW screening using the TST or an IGRA should be performed at baseline and repeated at 8–12 weeks to delineate those with recent acquisition from past exposure. There is some concern that a TST may boost a subsequent IGRA, with the effect lasting for up to 3 months, although most pronounced in those already in the positive IGRA range.\textsuperscript{16}

**Serial testing**

Serial testing with IGRA is complicated by results that may fluctuate between positive and negative. A ‘conversion’ has been defined as a previous negative result that converts to positive, and a ‘reversion’ is described as a previous positive test that reverts to negative. When these occur around the cut-off, interpretation is difficult, with the significance poorly understood and the subject of ongoing research.\textsuperscript{17} A strong conversion in the appropriate clinical circumstance is, however, likely to indicate recent TB infection. Patients known to be positive on a prior IGRA are generally assumed to be positive on this test for life, although some patients appear to have a biological flux with values around the cut-off. As with any assay, the cut-off has been determined with respect to optimising the receiver operating characteristic curve. However, each result must be interpreted for an individual patient, taking into account their previous risk profile for likelihood of TB exposure, and the original indication for testing.

The challenge of serial testing was illustrated by a large retrospective analysis of pre-employment QFG screening of HCW and reviewing those who had serial testing performed. Of 1857 who had serial testing, 2.8% (52) were identified as converters (converted from negative to positive), but with a mean value of 0.63 IU/mL on testing, and 71% of those who converted had a value of <1 IU/mL.\textsuperscript{18} None of these was said to have active TB or was part of an outbreak investigation. Clinical evaluation and individual assessment was emphasised to prevent unnecessary preventive therapy.

From a practical sense, if a test result that is marginally positive does not make sense for a patient that seemingly has no risk factors for exposure to TB in a low endemic setting such as Australia, it is worth repeating the test from a separate bleed. There are several steps in the laboratory and in pretest handling that are subject to variation, which if not performed correctly may result in low-grade false-positive results.

**Paediatric testing**

Despite several studies now published on IGRA in children, there are still no clear consensus guidelines for its use. Published reviews have reported higher specificity, particularly in BCG-vaccinated individuals, thus avoiding children unnecessarily taking preventive therapy for a false-positive TST, and with a sensitivity equivalent to the TST.\textsuperscript{15,20} Other studies have demonstrated limitations, in particular lacking sensitivity compared with TST in children under 14 years and with a higher rate of indeterminate results in those <5 years of age. In specific circumstances, an IGRA may be beneficial to assist interpretation of the TB status, but this should not be routinely employed. Venesecion is a more significant procedure in a child, and this should be taken into account when considering which test to use.

Both the TST and IGRA results should be interpreted with caution in children, taking into account BCG status, child’s age, nutritional assessment and HIV status.\textsuperscript{21} Children <5 years of age who are household contacts of an individual with pulmonary TB are considered high risk for developing disease. Active TB requires exclusion by
clinical assessment and LTB therapy is usually then commenced, regardless of the initial test result. If the repeat TST result 8–12 weeks later is negative, preventive therapy is usually discontinued.

**Immune-compromised patients**

**HIV**

There is a strong link between HIV and TB. People living with HIV and exposed to TB have an elevated risk of TB reactivation of between 5 and 10% per year, and all HIV-positive individuals should be tested for LTB. Australia is a low-incidence country for TB and HIV, with HIV-related TB accounting for only 3% of all notified cases of TB, with most cases in overseas-born individuals. HIV-related immune suppression reduces the sensitivity of both the TST and IGRA, and furthermore these results are not entirely concordant. False-negative TST results may be seen in advanced immunosuppression with a CD4 count of <200 cells/mm³, and studies on IGRA have reported an increased indeterminate rate. Repeated testing may be considered when the CD4 count rises following effective anti-retroviral therapy. A meta-analysis found no significant differences in performance between TST or IGRA in HIV-infected patients recommending either as an option for diagnosing LTB, depending on local country resources. As results are not entirely concordant, some guidelines recommend either simultaneous testing with both TST and IGRA, or sequential testing with an IGRA only if the TST is negative, to improve overall sensitivity. A positive test in either is considered evidence for LTB because of the high risk of reactivation.

If an HIV-positive patient has either a positive IGRA or TST, an exhaustive search for active TB should be undertaken prior to consideration of LTB treatment. Smear-negative pulmonary TB, extra-pulmonary and disseminated TB is more common in this group of patients.

**Immune modulation therapy – prednisolone, tumour necrosis factor (TNF) recipients**

Testing with IGRA in the setting of exogenous immune suppression has had limited evaluation. The sensitivity in this setting is reduced and comparable with the TST; however, specificity should remain high. In studies addressing immune-compromised populations, there is a higher rate of indeterminate results because of the differences in response to mitogen stimulation (positive control), making the interpretation of the test invalid.

Patients receiving anti-TNF therapy have been identified as having a high risk of TB reactivation. All patients receiving anti-TNF therapy should be screened for LTB prior to commencement of the agent, and IGRA has now largely replaced the TST in most Australian centres for this indication. Patients undergoing anti-TNF therapy are usually escalated to this after a period on other medications (e.g. methotrexate, azathioprine, leflunomide or corticosteroids). Testing patients at the lowest possible state of immune suppression (either no medication or mild to moderate immune suppression) may improve test performance. There is a large population of patients on these moderate immune suppressive medications, and not all are at elevated risk of TB reactivation. Therefore, those at high risk of escalating therapy should be targeted for TB screening, and where possible prior to receiving potent systemic therapy. For example, patients with psoriasis who have high disease severity scores are more likely to require systemic therapy; patients with fistulating Crohn disease are at higher risk for requiring anti-TNF therapy. This strategy will permit identification of people with LTB and early treatment with isoniazid before TNF inhibition is required.

A challenging clinical situation is that of a recipient of anti-TNF therapy who travels to a TB endemic country. These patients should receive appropriate pre- and post-travel counselling and advice regarding the risks of acquisition of TB and likelihood of progression to active disease. Consideration may be given to performing a repeat IGRA upon return from travel to identify possible acquisition of TB with a view to early treatment.

New immune-modulating agents are being rapidly developed and introduced into medical practice. It is important to maintain vigilance for increased reactivation of infections such as TB in recipients of these medications, particularly as post-marketing surveillance is often the mechanism of detecting such events. In addition, many patients receive multiple co-administered medications and studies are often not designed to examine this additive effect accurately.

**Future directions and uncertainties**

Many uncertainties still exist in the application and interpretation of IGRA results, including the significance of reversions in serial testing, reliability in immune-compromised patients, results close to the cut-off and the significance of the magnitude of IGRA response. There is a need for ongoing research to predict accurately those with LTB with the highest risk of progression to active TB, to identify those who would benefit from preventive therapy. Patients testing positive for LTB on current tests may either still harbour viable organisms or have cleared infection spontaneously. If we could accurately identify this subset of individuals,
preventive therapy would not be necessary. Another active field is the search for biomarkers of specific states of TB infection, such as active TB, LTB and monitoring response to treatment. IGRA is being evaluated for use with body fluids other than blood for extrapulmonary TB such as cerebrospinal fluid for meningeal TB and pleural fluid for pleural TB. These sites are frequently culture negative and often treatment must be commenced on clinical grounds alone.

IGRA is now established in appropriate testing algorithms. There are several differing published international guidelines, making consensus recommendations difficult. A position statement by the Australian National Tuberculosis Advisory Committee on IGRA for the diagnosis of LTB has been published.6 This suggests that TST remains the preferred test for LTB in most patient groups, despite the widespread use of IGRA in clinical medicine, and the now rare use of the TST in many settings.

IGRA is a step forward for TB diagnostics, by improving test accuracy, in particular specificity, incorporating controls, improving our ability to select patients for therapy and to provide more accurate counselling. However, gaps in our knowledge remain, and more work is required to understand their utility in paediatric patients, immunocompromised groups, serial testing and for active TB. The suboptimal sensitivity of all currently available tests for LTB is not widely appreciated in the general medical community. Especially when dealing with immunocompromised patients a broader risk assessment for TB exposure should be undertaken to avoid missed opportunities for preventive therapy.

Conclusion
TB is a condition of relevance to diverse specialist medical disciplines. This includes caring for patients at risk because of recent exposure to TB, such as a close contact of an infectious case and recent overseas arrivals including refugees. There is also a large and expanding group of patients at risk of reactivation TB who are immune compromised.

While many uncertainties exist around the interpretation and appropriate application of IGRA, they are a useful addition for the management of patients with suspected LTB infection. They are now well established as an alternative method to the TST and in areas where they are routinely available have largely replaced the TST. However, they should be used with caution and carefully interpreted in light of the clinical context and with specific attention to the numerical value rather than the interpretive category of the result. In the future, we may see next-generation IGRA with improvements made by targeting different cytokines produced in relation to antigen stimulation or by using alternative TB antigens. There is still a role for TST in particular circumstances such as in paediatric patients, possibly improving sensitivity in immune-compromised patients in addition to an IGRA, and in remote locations where IGRA is not easily obtainable.

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ORIGINAL ARTICLES

Adverse drug events are a major cause of acute medical admission

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Key words
drug-related side effect and adverse reaction, patient admission, clinical coding, patient readmission, recreational drug.

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Background: Adverse drug events (ADE) contribute significantly to hospital admissions. Prospective New Zealand data are scant, and the ability of clinical coding to identify ADE associated admissions is uncertain. Outcomes after cessation of causative medications are unknown.

Aims: To assess the frequency, nature and causality of ADE associated with acute admissions to General Medicine at Christchurch Hospital.

Methods: Prospective observational study of patients admitted to our medical team over 20 weeks.

Results: Of 336 admissions, 96 (28.6%) were ADE related. Sixty-five (19.3%) were caused by an ADE, and 31 (9.2%) were contributed to by an ADE. The mean age of non-ADE patients was 64.3 years (range 16–91), which was similar to the mean age of ADE patients (65.9 years; 21–92). However, if intentional overdoses and recreational drug use were excluded, ADE patients were significantly older at 72.4 years (21–92) (P = 0.0007). ADE patients took more regular medications on admission (mean 6.6, range 0–22) than non-ADE patients (mean 5.0, 0–18), (P = 0.003). The average length of stay was similar. The commonest medications implicated were vasodilators, psychotropics and diuretics. The most common adverse effects were postural hypotension and/or vasovagal syncope (29% of ADE), intentional overdoses and recreational drug use (15%) and acute renal failure and/or clinical dehydration (10%). Seventy-six patients had culprit medications stopped or reduced, and this potentially contributed to six readmissions. Coding identified 61% of ADE associated admissions.

Conclusion: ADE are a common cause of hospital admission. The most frequent problems are postural hypotension and vasovagal syncope, intentional drug misuse and dehydration.

Introduction

Adverse drug events (ADE) cause a significant burden to individual patients and healthcare systems. Regular medication for the treatment or prevention of disease provides benefit in many situations, but should always be weighed against the potential for harm, particularly in the elderly. Published studies have shown large variation in the frequency of hospital admissions secondary to ADE. Much of this relates to study method and patient selection. Prospective observational studies using clinical chart review in Europe1–4 have found between 3.4% and 20.9% of hospital admissions are caused or contributed to by ADE. A review of Australian studies published between 1988 and 1996 found a similar range of frequency: 2.4% to 22.0%.7 In the elderly, the frequency has been reported to be even higher at 30.4%.8 Retrospective studies usually report lower frequencies, for example, a retrospective chart review audit of acute geriatric admissions found that 5.7% of acute admissions were secondary to ADE.7 Furthermore, studies using computer database codes to identify ADE related admissions report even lower frequencies: A review of the Netherlands’ nationwide computer database found a frequency of 1.83%10 and in England 0.31%.11 Thus, it is recognised that retrospective studies using coding underestimate ADE frequency.12 Other important sources of variation include acute versus arranged admissions and the nature of the admitting ward(s).13 When considering prospective studies of acute admissions, a key factor affecting ADE frequency is causality, that is, the strength...
of the relationship between the patient’s presentation and the suspected culprit drug. Causality has been assessed in a variety of ways\textsuperscript{1,4,8,13,14} including what action is taken by the admitting doctors with regard to the drug(s). Methods using a scoring system such as the Naranjo adverse drug reaction probability scale demonstrate improved intra- and inter-observer reliability.\textsuperscript{14} However, many of these scales include re-challenge, a placebo challenge and/or an assessment of dose response, which are often not possible or practicable. Classification of ADE as certain or probable therefore becomes difficult to achieve. Causality criteria are by no means universal. However, we aimed to assess causality for each ADE so that our data are transparent and therefore comparable with other studies.

There can be a reluctance to stop regular medications even after they have resulted in an ADE requiring hospital admission.\textsuperscript{15} There is a lack of published data on outcomes such as readmission rates following alteration of regular medications due to an ADE related admission.

Aims

Our aim was to assess the frequency, nature and causality of ADE affecting medical patients admitted acutely to Christchurch Hospital. We also aimed to evaluate the accuracy of clinical coding for identifying ADE-related admissions, and to assess the frequency of readmission resulting from alteration of medications following an ADE.

Methods

Our department admits approximately 12 000 patients per year, divided among 12 teams. Acute cardiology and a small number of sub-specialty patients are not included. Our general medical team collected data on all patients admitted overnight or longer on our on-call days during two periods, 1 October to 11 November 2011 and 24 December 2011 to 4 April 2012 (20 weeks, 23 on-call days). On the post-take ward round the consultant and registrar assessed whether each admission was caused or contributed to by an ADE. An ADE was defined as any side effect or adverse reaction to a drug (prescribed or non-prescribed) or its withdrawal.\textsuperscript{16} This comprises mainly adverse drug reactions (which occur at recommended doses) but also intentional or unintentional overdoses, alcohol use or withdrawal and recreational drug use as a separate subgroup. Therapeutic drug failures were excluded. For ADE-associated admissions, we collected the following data: age, gender, culprit medication(s), changes made to culprit medication during the admission, total number of regular medications on admission (including inhaled or topical treatments), past medical history, duration of admission in number of nights, the primary diagnosis for the admission and a secondary diagnosis if this related to an ADE. For non-ADE admissions, we collected data on age, gender, number of regular medications on admission and length of hospital stay. Data were collected from ward rounds, clinical notes and the electronic discharge summary at the time of discharge. One investigator assessed the strength of the causality of each ADE against the World Health Organization (WHO) Uppsala Monitoring Centre criteria\textsuperscript{17} and against the Naranjo criteria.\textsuperscript{14} Six months after the date of discharge, the electronic hospital record was reviewed to identify any readmissions relating to drugs that had been stopped, dose reduced or changed to an alternative. A relevant readmission was one that required one of the altered medications to be restarted or the dose increased, or that required an alternative medication started for the same indication. Clinical coding data were obtained for each ADE admission, and we assessed whether the contribution of an ADE was identified in the codes assigned to the admission. As this was an audit as defined by the Operational Standards for Ethics Committees, Ethics Committee approval was not required.

Data were analysed in Excel and R 2.14.1 with the assistance of a Canterbury District Health Board biostatistician. Student t-test (or Mann–Whitney test when normality assumption does not hold) was used to assess two-sample differences for continuous variables. Chi-squared test was used for categorical variables. Statistical significance was determined at 0.05. Both total ADE and ADE excluding the ‘overdose subgroup’ (see above) were compared with non-ADE patients.

Results

Over the 20 weeks, we admitted 336 patients for one or more nights. Adverse drug events were associated with 96 (28.6\%) of these admissions. In 65 patients (19.3\%) an ADE was the primary cause for admission, and in 31 (9.2\%) an ADE contributed to admission. Common examples of ‘contributing ADE’ were dehydration, acute renal failure or postural hypotension exacerbated by continued diuretics or vasodilators during an acute illness. Out of the 65 patients admitted primarily due to an ADE, 16 were admitted following intentional overdoses, recreational drug use or alcohol or its withdrawal (4.8\% of all admissions). Some patients experienced more than one ADE, and in many cases we identified multiple medications that contributed to a single ADE.

Of the 65 admissions for primary ADE, causality relationship was assessed as certain or probable in over 50\%, whether the WHO criteria or the Naranjo criteria were
used. Causality was less secure for the ADE contributed admissions, with 36 to 45% assessed as certain or probable (Table 1). Therefore, if we include only primary ADE admissions with a certain or probable association, then the frequency of ADE drops to 10.4–13.7% of our acute general medical admissions.

The mean age of ADE patients was similar to non-ADE patients: 65.9 years (range 21–92 years) versus 64.3 years (range 16–91) \( (P = 0.54) \). However, when intentional overdoses and recreational drug use were excluded, the ADE patient group was significantly older: 72.4 years (range 21–92 years) \( (P = 0.0007) \) (Table 2). The ADE patient group tended to have a higher proportion of males: 41% versus 32% \( (P = 0.14) \).

ADE patients took significantly more regular medications on admission (median 6.5, range 0–22) than non-ADE patients (median 4.0, range 0–18) \( (P = 0.003) \). Some ADE were caused by non-regular medications, for example respiratory arrest following IV fentanyl and midazolam for an outpatient procedure, hence the inclusion of zero in the range for both groups. The median length of stay in nights for ADE patients was 4.0 (range 1–29) and for non-ADE patients was also 4.0 (range 1–29) \( (P = 0.24) \). ADE patients had a high burden of medical comorbidity (Fig. 1). Of the patients, 45.8% suffered hypertension, 30.2% depression, 29.2% ischaemic heart disease and 22.9% diabetes.

The most common class of ADE was postural hypotension/vasovagal syncope, accounting for 29% of all ADE. Of the ADE, 15% of ADE were intentional overdoses, and a further 2% were due to recreational drug use or its withdrawal. Other common diagnoses included acute renal failure/clinical dehydration (10% of ADE) and confusion, delirium or drowsiness secondary to medication (6%). Other adverse effects were diverse (Fig. 2).

During the admission 59.5% of implicated medications were stopped, 22.8% were dose reduced, 3.7% were changed to an alternative medication and 14.0% were continued. Seventy-six patients had regular medications stopped, reduced or changed as a result of their ADE. Follow up at 6 months showed these medication changes may have contributed to six readmissions resulting in a readmission rate of 8% among patients whose medications were altered (Table 4).

Clinical coding data were obtained for nearly all (95/96) of the ADE patients. It correctly identified 61% of the ADE associated with the admission and partially identified a further 7% (one ADE identified but a significant second contributor omitted). In 32% of ADE admissions, no drug-related effect was included in the coding.

### Table 1: Causality assessments of adverse drug events (ADE)

<table>
<thead>
<tr>
<th>Causality criteria</th>
<th>WHO UMC†</th>
<th>Naranjo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary ADE admissions</td>
<td>Certain</td>
<td>28%</td>
</tr>
<tr>
<td>( n = 65 )</td>
<td>Probable</td>
<td>43%</td>
</tr>
<tr>
<td>Possible</td>
<td>29%</td>
<td>Possible</td>
</tr>
<tr>
<td>Contributing ADE</td>
<td>Certain</td>
<td>9%</td>
</tr>
<tr>
<td>( n = 31 )</td>
<td>Probable</td>
<td>36%</td>
</tr>
<tr>
<td>Possible</td>
<td>55%</td>
<td>Possible</td>
</tr>
</tbody>
</table>

†World Health Organization Uppsala Monitoring Centre.

### Table 2: Comparison of adverse drug event (ADE) admissions with non-ADE-associated admissions

<table>
<thead>
<tr>
<th></th>
<th>Non-ADE</th>
<th>All ADE-associated admissions</th>
<th>ADE admissions excluding recreational drugs and overdoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range) [years]</td>
<td>64.3 [16–91]</td>
<td>65.9 [21–92]</td>
<td>( P = 0.54 )</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>32%</td>
<td>41%</td>
<td>( P = 0.14 )</td>
</tr>
<tr>
<td>No. medications on admission, median (range)</td>
<td>4.0 [0–18]</td>
<td>6.5 [0–22]</td>
<td>( P = 0.003^* )</td>
</tr>
<tr>
<td>Length of stay in nights, median (range)</td>
<td>2.0 [1–29]</td>
<td>2.5 [1–29]</td>
<td>( P = 0.24 )</td>
</tr>
</tbody>
</table>

*Statistically significant at \( P < 0.05 \).
We found a very high proportion of acute general medical admissions (almost 30%) are attributable to, or contributed to, by an ADE. Even if we decrease the frequency (to 10.4–13.7%) by accepting only primary ADE admissions with certain or probable causality (see above) ADE still remains a common cause for medical admission. This is consistent with results from other prospective studies including patient interview and/or medical chart screening, which have been demonstrated to identify the highest frequency of ADE-associated admissions.13,18 We also included intentional overdoses, recreational drug use, and alcohol effects, in order to capture the contribution of drugs in the widest definition, and this will have further increased our ADE associated admissions. However, we did not include therapeutic drug failure in our ADE total.

The most common ADE category we recognised was postural hypotension/vasovagal syncope, and this was consistent with the most frequent culprit medications (vasodilators, antidepressants and diuretics) and the relatively high frequency of hypertension in our patients.

### Table 3: Medications responsible for adverse drug event (ADE)-associated admissions

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Events</th>
<th>% of ADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilators</td>
<td>ACE inhibitors, alpha receptor blockers, angiotensin receptor blockers, felodipine, isosorbide mononitrate</td>
<td>36</td>
<td>23%</td>
</tr>
<tr>
<td>Psychotropics</td>
<td>Benzodiazepines, bupropion, chlorpromazine, methylphenidate, phenytoin, quetiapine, selective noradrenaline reuptake inhibitors, selective serotonin reuptake inhibitors, sodium valproate, tricyclic antidepressants</td>
<td>28</td>
<td>18%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Furosemide, spironolactone, thiazide diuretics</td>
<td>25</td>
<td>16%</td>
</tr>
<tr>
<td>Chronotropes</td>
<td>Amiodarone, beta blockers, diltiazem, digoxin</td>
<td>18</td>
<td>11%</td>
</tr>
<tr>
<td>Opiates</td>
<td>Codeine, fentanyl, morphine, oxycodone</td>
<td>12</td>
<td>8%</td>
</tr>
<tr>
<td>Others</td>
<td>Adalimumab, alcohol, alendronate, amantadine, antibiotics, aspirin, carbidopa/levodopa, chemotherapy for malignancy, domperidone, ferrous fumarate, heroin, IV contrast, lisuride, omeprazole, paracetamol, phenylephrine, prednisone, promethazine, sulfasalazine, trial medication (MIS 416), unknown recreational drug, warfarin</td>
<td>39</td>
<td>25%</td>
</tr>
</tbody>
</table>

### Discussion

We found a very high proportion of acute general medical admissions (almost 30%) are attributable to, or contributed to, by an ADE. Even if we decrease the frequency (to 10.4–13.7%) by accepting only primary ADE admissions with certain or probable causality (see above) ADE still remains a common cause for medical admission. This is consistent with results from other prospective studies including patient interview and/or medical chart screening, which have been demonstrated to identify the highest frequency of ADE-associated admissions.13,18 We also included intentional overdoses, recreational drug use, and alcohol effects, in order to capture the contribution of drugs in the widest definition, and this will have further increased our ADE associated admissions. However, we did not include therapeutic drug failure in our ADE total.

The most common ADE category we recognised was postural hypotension/vasovagal syncope, and this was consistent with the most frequent culprit medications (vasodilators, antidepressants and diuretics) and the relatively high frequency of hypertension in our patients. General practitioners and cardiologists are under pressure...
ADE are a major cause of admission from many sources to treat systolic hypertension aggressively in the elderly. A consequence of this is that the incidence of iatrogenic postural hypotension and vasovagal syncope will increase. This trend may be underreported in some ADE studies. First, the history may not be clear, and is often non-specific (e.g. falls). Second, junior doctors tend to defer the measurement of standing blood pressure to the nurses. Third, postural hypotension is sometimes transient (and therefore hard to diagnose with intermittent manual BP measurements) but still severe enough to cause syncope. It is very important that doctors make the diagnosis and are therefore confident enough to stop or adjust culprit medications in the knowledge that they are improving patient quality of life.

For 14% of the implicated medications, drugs and doses were not altered as we assessed that despite the adverse event, the benefit of that medication still outweighed the risk. Of the 76 patients who had medications stopped, altered or dose reduced, we identified only six who experienced a readmission that was potentially contributed to by that medication change. Given these medications had contributed to 76 admissions in the first place, and had been the primary cause of 49 of those admissions, we feel six readmissions (8%) is an acceptable rate.

We did not identify readmissions occurring elsewhere in New Zealand or overseas, and we did not collect data on medications that were subsequently restarted by the general practitioner or in the outpatient setting. However, as ours is the only acute admitting hospital in Christchurch, we will have identified all local presentations requiring readmission.

A further weakness of our study is that we only included general medical patients admitted to Christchurch Hospital, which is a tertiary centre with multiple subspecialty departments. Patients with a presentation related to a single organ system are frequently excluded from the population admitted under general medicine. As a rule, the subspecialty departments admit younger patients with a lower risk of ADE – local data from our 'Decision Support service' shows the mean age of patients admitted to our respiratory and cardiology services is 63 and 62 years respectively, compared to 75 years for general medicine. This has the dual effect of decreasing non-ADE admissions and increasing the average age of general medical patients. Both will tend to increase the ADE frequency in our department, as the elderly are known to have higher rates of ADE. We also have not captured patients with gastrointestinal bleeding secondary to anticoagulants or anti-platelet drugs, as in our hospital upper gastrointestinal haemorrhage is admitted under general surgery or gastroenterology. Furthermore, patients admitted to orthopaedic, neurosurgical or general surgical wards with traumatic complications of ADE such as syncope resulting in fractured neck of femur were not identified, nor patients admitted under cardiology with medication-induced arrhythmia. Our study also excluded patients assessed in the emergency department or by the general medical team and discharged home the same day, and this group of patients may include a significant number of ADE. Despite these limitations, we have shown that ADE are a large burden on our general medicine department and on our patient population. In fact, of the diagnostic categories recorded by our information service (DRG coding), we estimate that ADE has become the commonest admission diagnosis in our service, well ahead of the traditional ‘favourites’ including acute respiratory illness, heart failure and stroke.

Other limitations on our study include the possibility of over-attribute of conditions to ADE and/or bias in the assessment of causality, which was determined prospectively by the medical team conducting the study, and then quantitatively by one investigator applying the Naranjo and WHO causality criteria. The accuracy of causality assessment is a limitation for all studies seeking to quantitate the frequency of ADE. Our methods could have been made more objective by using an independent panel of investigators to apply causality criteria, but are at least transparent allowing comparisons with other studies.

The proportion of ADE that were identified by clinical coding was higher than has been found in previous studies. Since the clinical team that was carrying out the study was also completing the discharge paperwork, we may have been more aware of and more likely to document ADE clearly on the discharge summary. It is possible that the proportion identified on coding at other times and by other teams is lower than our results suggest.

Strengths of our study include prospective data collection over a 5-month period, collected by a single medical team thereby ensuring consistency of methods. Our assessment of causality is transparent, and acknowledgement of uncertainty in causation allows for measurement of all possible ADE or alternatively inclusion of only probable/certain ADE. We have compared coding data with our identified rates of ADE, and have followed up all patients for a period of 6 months to identify readmission outcomes following cessation of medications implicated in ADE.

**Conclusion**

ADE are a common cause of acute general medical admission to Christchurch Hospital. Of the admissions,
28.6% were associated with an ADE, in 19.3% the primary reason for admission was an ADE, and up to 13.7% of admissions were caused by a probable or certain ADE. Patients with ADE-associated admissions tended to be older and are on more regular medications than the other patients. Vasodilating medications and diuretics accounted for 39% of all ADE-associated admissions, and the commonest adverse events were postural hypotension and vasovagal syncope.

Acknowledgements

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References

Hereditary haemorrhagic telangiectasia, an Australian cohort: clinical and investigative features

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Key words
HHT, hereditary haemorrhagic telangiectasia, arteriovenous malformation (AVM), ENG gene, ACVRL1 gene, SMAD4 gene.

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Abstract

Aim: The present study aims to describe the phenotypic features of patients with hereditary haemorrhagic telangiectasia (HHT) seen at Royal Melbourne Hospital, Victoria, Australia, and to customise a protocol for surveillance of patients with HHT.

Methods: This is a retrospective study in a tertiary referral hospital of all patients referred to the Clinical Genetics Service between 2007 and 2011 with a suspected diagnosis of HHT. Data abstracted from patient clinical records were analysed for clinical features, types of HHT and genetic testing results where available.

Results: Our cohort comprising 40 females and 23 males patients was assessed using the Curacao criteria. Twenty-two patients fulfilled the criteria for a definite diagnosis, 30 had a possible diagnosis, and 11 patients were assessed as unlikely to have HHT at the time of data analysis. Seventeen patients had pulmonary arteriovenous malformations (AVM), five had cerebral AVM, five had hepatic AVM, three had confirmed bowel telangiectasia, and one patient had a pancreatic AVM. Two female patients with HHT had complicated pregnancies during their follow up with us. Three families had mutations in the endoglin (ENG gene), three had mutations in the ACVRL1 gene, and two families had mutations in the SMAD4 gene.

Conclusion: HHT is a multisystemic disorder and needs involvement of a team with experience in managing patients with HHT.

Introduction

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterised by vascular malformations in multiple organ systems. The clinical features include epistaxis, mucocutaneous telangiectasias and arteriovenous malformations (AVM) in the lungs, brain and liver.1,2 Acute complications, such as massive epistaxis, haematemesis, melaena, haematochezia, haemothorax, haemoptysis, transient ischaemic attacks (TIA)/stroke, haemorrhagic stroke and brain abscess, have been reported in patients with HHT.1

For a clinical diagnosis of HHT to be considered definite, the Curacao criteria state that at least three of the following four features should be present.2 The presence of two features suggests a possible diagnosis. These criteria are best suited to diagnosis in adulthood.

• Epistaxis
• Mucocutaneous telangiectasia
• Visceral AVM
• A family history of HHT

Epistaxis is a common symptom in the general population; significant epistaxis may occur with bleeding disorders, for example Von Willebrand disease.2 Skin telangiectasia are seen in ataxia telangiectasia, hereditary benign telangiectasia, chronic liver disease and CREST (calcinosis, Raynaud phenomenon, sclerodactyly, oesophageal dysmotility telangiectasia). Pulmonary AVM is rarely sporadic and usually is not suggestive of any other conditions.2

Of those with a clinical diagnosis of HHT, 85% have an underlying mutation in a HHT gene. The majority has mutations in the endoglin (ENG) (HHT1) (53%) or ACVRL1 (HHT2) (47%) genes. Mutations in a third gene known as SMAD4 account for a small proportion (1–2%) of individuals with HHT, however may present in the form of a combined syndrome of juvenile polyposis and HHT (JP-HHT).2,4 An unidentified gene mutation causing HHT3 has been linked to chromosome 5 (locus 5q31.3–5q32).5

The distribution of telangiectasia differs in HHT1 and HHT2. Letteboer et al. have shown that oral and nasal telangiectasia are evident at a younger age in patients with HHT1 than in patients with HHT2, whereas dermal lesions appeared earlier in life in patients with HHT2.1 Pulmonary AVM and cerebral AVM are more common in
HHT1, whereas gastrointestinal involvement is more common in patients with HHT2, suggesting that in the presence of pulmonary AVM, ENG should be the first gene to be tested.

Methods

A retrospective audit of patients who attended the Clinical Genetics Service at Royal Melbourne Hospital with a suspected diagnosis of HHT between 2007 and 2011 was undertaken with approval from the Melbourne Health Human Research Ethics Committee. Records of patients’ consultations and investigations as documented on the service’s database and clinic notes formed the basis of this quality assurance project.

Data on patients’ phenotypic features, investigations, HHT subtype and genetic test results were collected where available. The data were then encoded and recorded in a spreadsheet. Patients were categorised into three subtypes: HHT1, HHT2 or JP-HHT. The aim of this audit was to review the correlation between clinical subtyping, phenotype and genotype (where known), and to customise a protocol for surveillance of patients with HHT.

Results

Data were collected from 63 patients (40 females and 23 males) in 44 families referred to the Clinical Genetics Service for consideration of a diagnosis of HHT. After excluding 11 patients who did not meet a definite or possible diagnosis of HHT using the Curacao criteria, 52 patients (age range 16–82 years, 35 females and 17 males) were included in the final analysis.

Epistaxis was the most frequent clinical feature seen in our cohort, followed by telangiectasia of the skin and mucous membranes (Table 1). The most common site for AVM was the lungs, followed by the brain, liver and pancreas. Genetic test results were available for 21 patients (Table 2). Pathogenic mutations in the ENG gene were detected in four families and in the ACVRL1 gene in two families. Two families had mutations in the SMAD4 gene. Variants of unknown significance (VUS) in the ENG gene were found in one family, and two patients from one family had a VUS in the ACVRL1 gene (VUS data not shown). Further studies are being performed to assess the significance and potential clinical utility of these variants.

All three patients with mutations in the ENG gene had pulmonary AVM. Of those patients with a mutation in the ACVRL1 gene, one had severe epistaxis, the second had pulmonary AVM, and the third had hepatic AVM and developed pulmonary hypertension during pregnancy. The mother of the latter patient required liver transplantation after being diagnosed with hepatic AVM, portal hypertension and liver failure. All of the patients with a mutation in the SMAD4 gene (two families) were ascertained after the diagnosis of intestinal polyps.

Several serious complications of HHT were recorded. One patient had a TIA, one had an ischaemic stroke and another patient had a haemorrhagic stroke. One of our patients developed a pulmonary embolism requiring an inferior vena cava filter and therapy with warfarin.

Discussion

This audit presents the largest Australian cohort of patients with HHT, particularly focusing on the clinical profile of HHT patients and the correlation with genotype. The completion of the audit highlighted the need for a clinical proforma to aid in the assessment of referred patients when HHT is queried.

Progression of HHT symptoms

Epistaxis is usually the first indication of possible HHT, commencing during childhood; pulmonary AVM usually becomes apparent during puberty, although it can occur earlier. By the age of 16 years, about 70% of individuals will have some features of HHT, and this figure rises to 90% by the age of 40. Our audit also showed that
pulmonary AVM and cerebral AVM are more common in patients with HHT1, which is in agreement with published data.1

The common clinical signs documented in our audit were epistaxis, along with pulmonary, and cerebral and hepatic AVM. Individuals with mutations in the SMAD4 gene also presented with juvenile polyps. One individual had pulmonary hypertension, another individual with a pulmonary embolism, and three individuals suffered from strokes. Overall, the phenotypic features of our cohort with HHT were consistent with previously reported descriptions.2

Epistaxis
Epistaxis was the most common symptom in our cohort consistent with the reported incidence of epistaxis in the literature, which is approximately 90%. A clinical scoring system has been used to assess the effectiveness of various treatments of epistaxis.8 Treatment of epistaxis in HHT is difficult, as there is no permanent cure available to date. Individuals with epistaxis can be taught the use of haemostatic measures, including gauze, sponge or powder. Commercially available haemostatic woven textile products have been effective anecdotally.9 Medications to control epistaxis include procoagulants (tranexamic acid), antioestrogens (raloxifene and tamoxifen) and antiangiogenic drugs (bevacizumab (Avastin) and thalidomide).10,11 A recent report has demonstrated marked improvement of epistaxis with administration of either intravenous or topical Avastin.12 Another current study compares the effectiveness of potassium-titanyl-phosphate (KTP) laser therapy with and without Avastin injections for control of epistaxis in HHT.15 Laser cautery and laser ablation, in particular KTP, have gained popularity as they coagulate the telangiectasia with minimal peripheral tissue injury.14,15

Septal dermoplasty as well as endovascular therapy have a role in the management of epistaxis in HHT.16,17 In our cohort of patients, most had used local haemostatic agents, tranexamic acid and electrical/chemical cautery to stop epistaxis with varying success.

Pulmonary AVM
Consistent with the literature, four out of seven (57%) of our patients with pulmonary AVM tested had a mutation in one of the HHT genes.

Bubble echocardiograms are used to screen for pulmonary AVM, and where there is evidence of shunting computed tomography (CT) is recommended. Four patients in our cohort with pulmonary AVM required embolisation. The selection for embolisation in pulmonary AVM is based on the diameter of the feeding artery, and generally only those with 3 mm or greater diameter arteries are selected for this procedure.2 It is recommended that people with diagnosis of HHT avoid scuba diving because of risk of decompression sickness. Smoking is also strongly discouraged.

Pulmonary artery hypertension (PAH)
There is a correlation of mutations in ACVRL1 and PAH in patients with HHT.18 However, the presence of mutations in ENG gene in some patients with PAH suggests that there is an additional mechanism. One patient in our study had significant PAH during pregnancy.

Cerebral AVM
Cerebral AVM in HHT is thought to be congenital. Patients in our cohort either had a CT or magnetic resonance imaging (MRI) to screen for cerebral AVM, if they had not had a prior scan.

Hepatic AVM
Hepatic AVM is found in 30% of people with HHT;2 however, only 5% of patients with hepatic AVM are symptomatic.2 They are usually detected after finding abnormal liver enzymes or during an abdominal imaging study. In both HHT1 and HHT2, hepatic AVM is more common in females.19 The influence of environmental factors, modifier genes and hormonal factors has been suggested as a cause for this gender difference of visceral manifestations in HHT. All of our five patients with hepatic AVM were females.

Shunting between the hepatic artery and vein can lead to portal hypertension. Liver biopsy should be avoided in patients with HHT.15 Mitchell et al. used bevacizumab successfully in patients with hepatic AVM, reducing the need for liver transplantation.20

Gastrointestinal bleeding
Acute gastrointestinal bleeding in HHT is more common after 40 years of age. Telangiectasia of the gastrointestinal tract can be visualised through endoscopy.21 Three patients in our cohort were found to have telangiectasia on gastrointestinal endoscopy as a part of their work-up for unexplained anaemia. Screening of this nature, however, is not a routine recommendation.

Association between juvenile polyposis and HHT
Two families in our cohort were identified with an SMAD4 mutation; however, they were ascertained after a diagnosis of juvenile polyps. Gallione et al. have shown that 10% of HHT patients without any known history of
juvenile polyposis have mutations in the \textit{SMAD4} gene, meaning genetic testing of the \textit{SMAD4} gene should still be considered even in the absence of polyps.\textsuperscript{22}

**Pregnancy in HHT**

During pregnancy, women are at a high risk of developing complications as a result of HHT. A recent study has shown that HHT does not lead to a significant increase risk of birth defects.\textsuperscript{21} The following recommendations should, therefore, be adhered to in order to reduce maximally the risks of HHT during pregnancy (adapted from Shovlin \textit{et al.}).\textsuperscript{24}

**Pre-pregnancy**

If possible, women should undergo a thoracic CT to screen for pulmonary AVM. No routine screening or treatment is recommended during pregnancy in women with asymptomatic pulmonary AVM.

**During the pregnancy**

- A spinal MRI scan (without gadolinium) is recommended to exclude spinal AVM to allow for regional anaesthesia.
- A cranial MRI is recommended for a woman with a history of cerebral symptoms or cerebral haemorrhage.
- If cerebral AVM cannot be excluded, the second stage of labour should not be prolonged.
- Education to women about ‘red flag’ symptoms, including severe respiratory distress and haemoptysis; pregnant women should be strongly advised to immediately attend an emergency department should they experience these symptoms.

**During the childbirth**

- The use of antibiotic prophylaxis is required.
- If general anaesthesia is required during delivery, a modified induction programme using opiates should be used.

The risks of HHT during pregnancy were highlighted by one patient in our cohort. This individual with a known \textit{ACVRL1} mutation, PAH and hepatic AVM experienced significant complications during her two pregnancies. She experienced severe respiratory distress during the last trimester of her first pregnancy requiring ventilatory support. Prior to her second pregnancy, the woman was counselled regarding the risk of maternal complications and potential risks to the child. In the 28th week of her second pregnancy, she had shortness of breath. Her obstetrician gave her steroids and she was induced at 29 weeks of pregnancy. Both children were healthy following appropriate paediatric management.

In contrast, a 16-year-old woman with a clinical diagnosis of HHT who attended our service had an unplanned pregnancy. She had pulmonary AVM and was being monitored with a view to embolisation. During her pregnancy, she had regular monitoring of her oxygen saturation with a pulse oximeter, and had a spinal MRI to exclude spinal AVM.

**HHT and stroke**

Stroke is a recognised complication of HHT and occurs in 10–19\% of affected individuals.\textsuperscript{25} Stroke associated with HHT in young individuals with pulmonary AVM is most often due to paradoxical embolism. Therefore, the careful monitoring and selection of patients is required for embolisation in all patients with HHT and pulmonary AVM.\textsuperscript{26,27}

In our cohort, one patient had a pulmonary AVM and suffered a TIA. Another patient with a pulmonary AVM was also diagnosed with right-sided weakness several years previously, although there was no evidence of an infarct on his MRI scan. It was postulated that he had an ischaemic stroke and had revascularisation of the affected area of his brain. The third patient had a haemorrhagic stroke following a bleed from a cerebral AVM.

**HHT and venous thromboembolism**

There is limited literature about the association of venous thromboembolism with HHT. Shovlin \textit{et al.} demonstrated that elevated factor VIII activity in HHT is a possible explanation for increased tendency to the development of venous thromboembolism in these patients.\textsuperscript{28} A recent report has shown an association of low serum levels of iron with elevated plasma levels of coagulation factor VIII and thromboembolism in patients with HHT.\textsuperscript{29}

In our cohort, one patient experienced a severe pulmonary embolism. She was found to be heterozygous for a mutation in the prothrombin gene, which may have contributed to her pulmonary embolism.

**Screening and management of HHT**

It is recommended that individuals with suspected HHT should undertake the following screening procedures, evident in Table 3:\textsuperscript{19}

- Transthoracic contrast echocardiograms (TTCE or bubble echocardiograms) to screen for pulmonary AVM.
  - Individuals with evidence of cardiopulmonary shunting on a TTCE require follow up by CT chest.\textsuperscript{19}
  - If a pulmonary AVM of 3 mm or more in size is detected, the individual should be treated.
An individual with pulmonary AVM should have prophylactic antibiotics during any procedure (e.g. dental procedures) because of the risk of bacteraemia. Air filters need to also be fitted on intravenous lines.

• Brain MRI to screen for cerebral AVM. Repeat MRI is not recommended over the age of 18.

• In the first assessment of an adult for HHT, an MRI may provide additional benefits in the detection of infarcts and other possible central nervous system complications of HHT.

• It is recommended that management of cerebral AVM should be decided on a case-by-case basis.

We have prepared a protocol for recording clinical features and surveillance for AVM in adult patients, customised to the resources available within the Victorian health services (Supporting Information Appendices S1 and S2).

### Lifestyle recommendations

It is recommended that people with diagnosis of HHT avoid scuba diving because of risk of decompression sickness. Smoking is to be strongly discouraged.

### Things to avoid if diagnosed with HHT

It is recommended that people with HHT avoid vigorous nose blowing, electric or chemical cautery for nosebleeds, and anticoagulant and anti-inflammatory agents (including aspirin) to avoid worsening of the nose and gastrointestinal bleed. Liver biopsies should also be avoided.

### Conclusion

The management of HHT requires the involvement of a multidisciplinary team with experience in managing patients with HHT. This type of management approach will help in timely diagnosis, treatment and a streamlined follow up of these patients. Genetic testing is available, particularly where there is a request for antenatal diagnosis or pre-implantation genetic diagnosis. Genetic testing can be ‘cascaded’ in a family to determine screening requirements in relatives of a person with a known mutation in a HHT gene.

### Acknowledgements

We thank all of the specialists, Associate Professor Abe Rubinfeld (Royal Melbourne Hospital), Associate Professor Peter Mitchell (Royal Melbourne Hospital), Professor Finlay Macrae (Royal Melbourne Hospital), Dr Chris Barnes (Royal Children’s Hospital, Melbourne) for review and advice in preparing a management protocol for HHT. We also acknowledge the work done in the past by various authors for preparing similar protocols.

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Salaria et al.


Supporting information

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

Appendix S1. Proforma for Data Collection tool in HHT patients.

Appendix S2. Suggested management Protocol for our cohort of HHT patients.
Association between waist-to-height ratio and chronic kidney disease in the Taiwanese population

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Key words
obesity, waist-to-height ratio, body mass index, chronic kidney disease, predictor.

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Abstract
Background: Obesity, metabolic syndrome (MS) and chronic kidney disease (CKD) are all becoming increasingly prevalent worldwide. Body mass index (BMI) has traditionally been employed to identify overweight or obese individuals, yet multiple studies have yielded conflicting results when BMI was used to evaluate the association between obesity and CKD.

Aims: The purpose of this large, population-based, multicentre study was to evaluate the associations of BMI and waist-to-height ratio (WHtR) with CKD.

Methods: A retrospective study of 41 600 subjects who had physical examinations from January 2010 to December 2011 was performed. Data such as lifestyle and habits were collected by interviews, and systolic and diastolic blood pressure (SBP and DBP), height, body weight, waist circumference, total cholesterol (TC), high-density lipoproteins (HDL), triglycerides (TG), fasting blood glucose and creatinine levels were measured. The association of these factors with CKD was analysed by use of SPSS 15.0 software.

Results: The key findings of this study were that WHtR but not BMI was an independent predictor of CKD. Additionally, SBP was a predictor of CKD in males and females, and TG and TC were independent predictors of CKD in females. Such measures are components of MS, which may also be associated with the development of CKD.

Conclusion: WHtR appears to be a better measure of central obesity than BMI, and is an easy-to-use, noninvasive tool for identifying individuals at risk of developing obesity-related CKD, and potentially also MS-related CKD.

Introduction
Chronic kidney disease (CKD) is an important and increasingly prevalent health concern worldwide.1–3 It is currently estimated that the prevalence of CKD in the United States, Australia, Japan and Europe ranges from 6% to 11%, but Taiwan has the world’s highest incidence and prevalence of end-stage renal disease, with a prevalence of CKD of 11.9%.4,5

CKD can progress to end-stage renal disease and is associated with cardiovascular morbidity and mortality.6,10 Risk factors for CKD include diabetes mellitus, hypertension, hyperlipidaemia, cardiovascular disease, smoking, the use of herbal medicines and obesity (determined based on body mass index (BMI)).4,5,11 Of those, obesity is widely thought to be an important predictor of the development of kidney disease, which is particularly concerning because obesity has become an enormous health concern, described as one of the biggest health threats of the 21st century.3,11

Several studies have been conducted to determine the impact of obesity on CKD. Some have examined metabolic syndrome (MS) (or its components), BMI, waist-to-height ratio (WHtR) and various other anthropomorphic measurements in subjects either with or without comorbidities such as diabetes mellitus. Although some of those studies have found a clear association between BMI and CKD (i.e. patients with elevated BMIs were more likely to have/develop CKD), not all studies concurred. Further, Elsayed et al. stated that because BMI...
is affected by muscle mass, fat mass and bone, WHtR (a measure of central obesity) may be a better tool to measure obesity than BMI.²

There is currently a paucity of studies examining the association between WHtR and CKD. The purposes of this study were to explore the association between WHtR and CKD in Taiwanese adults and to compare those findings with the association between BMI and CKD. The hypothesis was that an increase in WHtR would be associated with a decline in estimated glomerular filtration rate (eGFR), and that an increased in WHtR would be positively correlated with the number of patients with CKD.

Methods

Subjects

Between January 2010 and December 2011, data from all Taiwanese individuals ≥18 years of age who underwent annual physical examinations at one of three branches of the Chang Gung Memorial Hospital (located in Linkou (in northern Taiwan), Chiayi and Kaohsiung (both in southern Taiwan)) were retrospectively collected. Subjects were excluded if they had not fasted for >12 h, if they were pregnant, if they had any chronic diseases that could significantly affect either metabolism or body composition (i.e. thyroid function abnormalities, tumour resection, chronic hepatitis, cirrhosis, pituitary disease and adrenal disease) and if the subject was currently taking pharmaceutical drugs for hypertension, diabetes mellitus or high blood lipid levels.

Data collection

Participants were interviewed using questionnaires administered by trained nurses. Information regarding demographic (e.g. age, gender), life style (e.g. historical and current smoking, drinking habits), history of illness and medication use, and physiologic status (pregnancy, fasting time) was collected.

Systolic and diastolic blood pressures (SBP and DBP) were measured using a random zero sphygmomanometer in a sitting position after a 5 min rest according to the American Heart Association and Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommendations.¹² Up to three measurements were averaged to calculate the final (reported) systolic and diastolic pressures.

Height and bodyweight was measured using an automatic scale after subjects had removed their shoes and were standing straight with their feet together, eyes looking straight ahead. BMI was calculated as weight (kg) divided by the square of height (m²). Subjects were divided into four groups according to BMI <18: underweight, BMI ≥ 18 and <25: normal, BMI ≥ 25 and <30: overweight, BMI ≥ 30: obesity.

To measure waist circumference (WC), subjects stood with their feet 25–30 cm apart. The measurement was obtained midway between the iliac crest and the lower margin of the 12th rib. Subjects were equally divided into four groups according to the 25th, 50th and 75th percentiles of WHtR. Venous blood samples were obtained between 5:30 AM and 11:00 AM after a 12-h fast. All samples were subsequently stored at 4°C until time of analysis. Total cholesterol (TC), high-density lipoproteins (HDL), triglycerides (TG), fasting blood glucose (FBG) and creatinine levels were determined for each study participant.

The eGFR was calculated using the improved Modified Diet in Renal Disease for Chinese people developed by Peking University (where Scr is serum creatinine).¹³

\[
eGFR = 175 \times \frac{Scr}{1.214} \times \frac{1}{Age^{0.219}}
\]

CKD staging was determined by eGFR and proteinuria based on the Kidney Disease Outcomes Quality Initiative definition.¹⁴ Specifically, CKD stage 1 was defined as an eGFR ≥ 90 mL/min/1.73 m² with kidney damage (proteinuria); stage 2 was an eGFR of 60–89 mL/min/1.73 m² with proteinuria; stage 3 was an eGFR of 30–59 mL/min/1.73 m²; stage 4 was an eGFR of 15–29 mL/min/1.73 m²; and stage 5 was an eGFR < 15 mL/min/1.73 m². Subjects were excluded if the eGFR was <15 mL/min/1.73 m² or classified as stage 5 (because haemodialysis could affect eGFR).

Statistical analyses

Continuous data were presented as mean and standard deviation. Categorical data were presented as count and percentage. The two independent samples t-test and the Fisher’s exact test were performed to test the differences between groups for continuous and categorical data respectively. Pearson correlation coefficients were performed to calculate correlations between either BMI or WHR and both metabolic-related measurements and eGFR. A Pearson correlation coefficient ranging from 0.0 to 0.2 indicated a very weak to negligible correlation; a correlation ranging from 0.2 to 0.4 indicated a weak or low correlation; a correlation ranging from 0.4 to 0.7 indicated a moderate correlation; a correlation ranging from 0.7 to 0.9 indicated a strong or high correlation; and a correlation ranging from 0.9 to 1.0 indicated a very strong correlation. Next, logistic regression analyses were performed to identify independent factors influencing CKD in male and female subjects. Univariate logistic
Regression analyses for all possible factors were performed first. Any factors that were statistically significant in the univariate analyses were identified, and factors with obvious collinearity were excluded. The remaining factors were stepwise included in the multivariable logistic regression model by forward conditional method. Because of the obvious collinearity in BMI versus WHtR, both BMI and WHtR were entered in two multivariable logistic regression models respectively, called model I and model II. The statistic assessments were all two sided and evaluated at the 0.05 level of significance. Statistic analyses were performed using SPSS 15.0 statistics software (SPSS Inc., Chicago, IL, USA).

**Results**

During the study period, 47 313 subjects ≥18 years of age had physical examinations conducted at one of three medical centres located in Taiwan. Of those, 5713 were excluded, and the remaining 41 600 subjects (18 494 females) were enrolled in the study (Fig. 1).

Mean subject age of the entire cohort was 37.9 years (range, 18–92 years), and the overall prevalence of stage 3 and 4 CKD in this study was 0.67% (87 females and 193 males). Mean BMI, WHtR and eGFR in all patients were 23.7 kg/m², 0.48 and 108.6 mL/min/1.73 m² respectively. In total, 63.4% of subjects had a normal BMI, including 13 381 females and 12 994 males. In addition, 3.6% of the subjects were under weight (1107 females and 384 males), and 26.9% of the subjects were overweight (including 3075 females and 8095 males). An additional 6.2% of the subjects were obese (931 females and 1633 males).

As described in Table 1, included male patients were older than females, and males had significantly lower levels of HDL and eGFRs than females. All other parameters, including SBP and DBP, TC, TG, FBG, BMI, WHtR and CKD (defined as an eGFR < 60 mL/min/1.73 m²), were significantly higher in the male subjects than females.

**Correlations between BMI, WHtR, eGFR and various metabolic-related measurements**

In both male and female subjects, eGFR decreased as BMI increased (Fig. 2A). Similarly, eGFR decreased as WHtR...

**Table 1** Summary of patient clinical demographics based on sex

<table>
<thead>
<tr>
<th></th>
<th>Female (n = 18 494)</th>
<th>Male (n = 23 106)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.8 ± 11.4</td>
<td>38.0 ± 10.6</td>
<td>0.039</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>116.6 ± 16.3</td>
<td>126.4 ± 14.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73.0 ± 10.3</td>
<td>79.0 ± 10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.69 ± 0.86</td>
<td>4.82 ± 0.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.60 ± 0.36</td>
<td>1.31 ± 0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>0.96 ± 0.64</td>
<td>1.43 ± 1.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>4.96 ± 0.87</td>
<td>5.09 ± 0.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6 ± 3.9</td>
<td>24.7 ± 3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHtR (kg/cm)</td>
<td>0.47 ± 0.06</td>
<td>0.50 ± 0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>120.9 ± 27.1</td>
<td>98.8 ± 18.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD (based on eGFR &lt; 60 mL/min/1.73 m²)</td>
<td>87 (0.47³)</td>
<td>193 (0.84³)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglyceride; SBP, systolic blood pressure; WHtR, waist-to-height ratio.

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increased, but in the female subjects the difference was only significant in the two subgroups that had larger WHtRs (i.e. 0.49–0.52 and ≥0.53) compared with the smaller groups (≤0.44 and 0.45–0.48) (all \( P < 0.001 \)). In the male subjects, the difference in WHtR was significant between all groups (all \( P < 0.001 \)) as illustrated in Figure 2B.

As described in Table 2, negative Pearson correlation coefficients were identified when comparing eGFR with either BMI or WHtR in both female and male subjects (all \( P < 0.001 \)). Note, however, that all calculated coefficients were classified as very weak, ranging from −0.126 to −0.110. In addition, negative correlations between HDL and both BMI and WHtR were observed in female and male subjects. Again, all coefficients were classified as weak, ranging from −0.328 to −0.307.

Positive correlations between both SBP and DBP versus BMI and WHtR were evident for both female and male subjects. For the females, moderate correlation coefficients were identified for SBP and DBP versus BMI and WHtR (all \( P < 0.001 \)). For the males, the correlation coefficients were also moderate for SBP and DBP versus BMI and WHtR (all \( P < 0.001 \)).

Table 2. Correlation analysis between either BMI or WHtR versus metabolic-related measurements and eGFR in male and female subjects

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.125</td>
<td>-0.129</td>
</tr>
<tr>
<td>SBP</td>
<td>-0.423</td>
<td>-0.428</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.369</td>
<td>-0.369</td>
</tr>
<tr>
<td>TG</td>
<td>0.332</td>
<td>0.326</td>
</tr>
<tr>
<td>HDL</td>
<td>0.393</td>
<td>0.397</td>
</tr>
<tr>
<td>HDL</td>
<td>0.393</td>
<td>0.397</td>
</tr>
<tr>
<td>FBG</td>
<td>0.236</td>
<td>0.260</td>
</tr>
<tr>
<td><strong>WHtR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.122</td>
<td>-0.129</td>
</tr>
<tr>
<td>SBP</td>
<td>-0.390</td>
<td>-0.390</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.362</td>
<td>-0.362</td>
</tr>
<tr>
<td>TG</td>
<td>0.354</td>
<td>0.354</td>
</tr>
<tr>
<td>HDL</td>
<td>0.317</td>
<td>0.317</td>
</tr>
<tr>
<td>HDL</td>
<td>0.317</td>
<td>0.317</td>
</tr>
<tr>
<td>FBG</td>
<td>0.271</td>
<td>0.271</td>
</tr>
</tbody>
</table>

Pearson correlation coefficients ranging from 0.0 to 0.4 indicate weak to negligible correlation; coefficients ranging from 0.5 to 0.7 indicate moderate correlation; coefficients ranging from 0.7 to 1.0 indicate very strong correlation. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WHtR, waist-to-height ratio; WBH, waist-to-hip ratio; HDL, high-density lipoprotein.
Coefficients between SBP and both BMI and WHtR were calculated, while weak correlation coefficients were noted between DBP and BMI and WHtR. For male subjects, all correlations were considered weak.

Positive correlations were also noted between the remaining factors (TC, TG and FBG) and BMI and WHtR. Coefficients between TC and BMI and WHtR were considered very weak and weak, respectively, in female subjects. In males, both coefficients were considered weak. Coefficients between TG and BMI and WHtR were both considered weak in both males and females. Finally, coefficients between FBG and BMI and WHtR were considered weak and very weak in female and male subjects respectively. All calculated \( P \) values were <0.001.

**Associations between BMI, WHtR and the prevalence of CKD**

As illustrated in Figure 3A, the prevalence of CKD in female subjects was significantly higher in the subgroup of patients classified as overweight compared with both the underweight and normal body weight subgroups (both \( P < 0.001 \)). In the male subjects, the prevalence of CKD was only significantly different between the subgroup of patients with a normal body weight and those that were overweight (\( P < 0.001 \)).

In general, the prevalence of CKD increased as the WHtR increased in both male and female subjects. In the female subjects, those with a WHtR of 0.49–0.52 had significantly higher CKD prevalence than those with a WHtR \( \leq 0.44 \) (\( P < 0.001 \)), and female subjects with a WHtR \( \geq 0.53 \) had a significantly higher prevalence of CKD than all other subgroups (all \( P < 0.001 \)). In the male subjects, only those with a WHtR \( \geq 0.53 \) had significantly higher prevalence of CKD than all other subgroups (all \( P < 0.001 \)), as illustrated in Figure 3B.

**Influence of metabolic factors, BMI and WHtR on the prevalence of CKD in male subjects**

All variables except for HDL had a significant influence on the occurrence of CKD. On multivariable analysis, DBP was excluded due to collinearity with SBP. The remaining variables except for BMI and WHtR were included stepwise into the multivariable analysis, and SBP and TC remained significant. Then BMI and WHtR were entered in two multivariable logistic regression models respectively, called model I and model II. After controlling for TC and BMI in model I, the occurrence of CKD was increased by every 1 mmHg increase in SBP; however, the influence of BMI on CKD was not significant. Unlike BMI, CKD occurrence was increased by every 0.1 unit increase in WHtR (Table 3).

**Influence of metabolic factors, BMI and WHtR on the prevalence of CKD in female subjects**

In the female subjects, all variables were significant on univariate analyses. On multivariate analysis, DBP was first excluded due to collinearity with SBP. After entering, the remaining variables (except for BMI and WHtR) stepwise into the model to identify independent predictors of CKD, SBP, TC, HDL and TG were significant. Then BMI and WHtR were entered in two multivariable logistic regression models respectively, called model I and model II. In model I, the occurrence of CKD was increased by every 1 unit increase in SBP, TC and TG (all \( P \leq 0.042 \)), and the occurrence of CKD was decreased by every 1 unit increase in HDL (\( P = 0.037 \)), but BMI did not remain significant. In model II, the occurrence of CKD was increased by every 1 unit increase in SBP, TC and TG (all \( P \leq 0.015 \)). The occurrence of CKD was increased by...
every 0.1 unit increase in WHtR ($P < 0.001$). Only HDL did not achieve statistical significance on multivariate analysis (Table 4).

**Discussion**

Obesity is a major global health concern and a risk factor for CKD, in addition to diabetes, hypertension and diabetes. Given the dearth of concrete data currently available regarding the relationship between BMI and/or WHtR on CKD, particularly in nondiabetic, nonhypertensive individuals (males and females), this study aimed to examine the association between BMI and WHtR and the prevalence of CKD. As hypothesised, WHtR rather than BMI increased as the prevalence of CKD increased. Additional key findings of this study were that of the 0.67% of the 41,600 included subjects were diagnosed with stages 3 and 4 CKD, and 13,734 subjects (33.01%) were overweight or obese. Of those, more males were overweight or obese than females. Further, as eGFR decreased, both BMI and WHtR increased regardless of gender. It is also interesting to note that other metabolic parameters related to obesity and MS were correlated with BMI and WHtR, such as HDL, SBP, DBP, TC, FBG and TC. Of those, most calculated correlations were weak or very weak, except a moderate correlation coefficient was calculated for SBP and both BMI and WHtR in female subjects. Multivariate analysis identified SBP and WHtR but not BMI as independent predictors of CKD in both males and females (as well as TC, TG, HDL in females).

The overall prevalence of CKD in this study (0.67%) was much lower than reported by Yoon et al. (3.2%), Elsayed et al. (2.3%–5.5%), Foster et al. (7.9%) with stage...
Waist-to-height ratio and kidney disease

3), Lo et al. (7%) and Shankar et al. (20.5%), which could be viewed as surprising considering that CKD is more common in Asian countries than Western nations; however, subjects included in the current study were recruited during routine health examinations and were therefore presumably healthy and free from chronic diseases.1,2,10,15,16 One third of subjects included in this study were overweight or obese (based on BMI), which is similar to other studies in this field.10,15,16

Previous research on the association between BMI and CKD has found that in certain Asian populations, such as Japan, a positive association was only noted among men.17–19 The study by Shankar et al. confirmed this observation in that a positive association between BMI and CKD in Malay men, but not women.19 In contrast, two additional studies found that WHtR but not BMI was positively associated with CKD.2,20 Those two studies confirmed the findings of the study reported herein that WHtR but not BMI was an independent predictor of CKD in both men and women. BMI, for example, does not discriminate between muscle and fat mass; therefore, an individual with an elevated muscle mass but normal fat mass could be wrongly classified as obese based on BMI alone. Various other measures of central obesity, such as WC, waist-to-hip ratio, WHtR and even the conicity index, appear to be better options than BMI for measuring central fat. As such, those alternative anthropomorphic measures would be more appropriate in studies designed to assess risk factors for CKD progression.20 Those anthropomorphic measures, inherently noninvasive, would also appear to be better choices for monitoring overweight or obese individuals at risk for developing CKD than BMI.

The current study also identified various metabolic factors as independent predictors of CKD, including SBP in both males and females and TG and TC in females. Alterations in these values are observed in individuals with MS. MS is also believed to be associated with CKD. Yoon et al. reported a significant association between MS and CKD in nondiabetic, nonhypertensive obese Korean adults, but not in the nonobese subgroup.1 This finding prompted the research group to conclude that early detection and prevention of CKD in obese subjects with MS is therefore crucial. Further, Thomas et al. published a systematic review of 11 articles and found that MS was associated with an increased incidence of subjects having an eGFR < 60 mL/min/1.73 m² and that all of the individual components of MS were also positively associated with such a decline in eGFR.21 As described in detail in the article by Tanner et al., there are several potential mechanisms that could explain the association between MS and CKD.3

One limitation of this study is that it was a retrospective, cross-sectional study. As such, no conclusions can be made regarding the causal relationship of WHtR and CKD. Further, this type of study cannot rule out the development of acute kidney injury that is unrelated to obesity. Finally, the current study examined a Taiwanese population, so the results may not apply to other populations.11

Conclusion

Despite these limitations, this is the first multicentre, large-scale, population-based study to indicate clearly that WHtR, not BMI, can identify individuals at risk of developing obesity-related CKD, and potentially also MS-related CKD. WHtR is a noninvasive tool that more precisely reflects central obesity than BMI, and can be used to help identify individuals at risk of developing CKD to ensure that the appropriate steps (e.g. lifestyle modification) are initiated as early as possible to reduce the burden of obesity, MS and CKD.

Acknowledgements

The authors would like to thank the staff of the Health Examination Centers in the Linkou, Chiayi and Kaohsiung branches of the Cheng Gung Memorial Hospital for assistance with data collection.

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2 Elsayed EF, Sarnak MJ, Tighiouart H, Griffith JL, Kurth T, Salem DN et al. Alterations in these values are observed in individuals with MS. MS is also believed to be associated with CKD. Yoon et al. reported a significant association between MS and CKD in nondiabetic, nonhypertensive obese Korean adults, but not in the nonobese subgroup.1


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Elevated mean platelet volume is associated with silent cerebral infarction

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Key words
silent cerebral infarction, mean platelet volume, atherosclerosis, platelet activation, risk factor.

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Abstract
Background: The presence of silent cerebral infarction (SCI) increases the risk of transient ischaemia attack, symptomatic stroke, cardiovascular disease and dementia. Mean platelet volume (MPV) is a surrogate marker of activated platelets and is considered a link between inflammation and thrombosis. In addition, MPV is a risk predictor for cardiovascular disease, stroke and overall vascular mortality.

Aims: The purpose of the study was to assess the MPV levels in SCI patients.

Methods: A cross-sectional study was conducted to evaluate the association between MPV and SCI in 2215 subjects (1385 men and 830 women).

Results: The participants with SCI had higher MPV levels than those without SCI (10.4 ± 1.3 fL vs. 9.2 ± 1.2 fL; P < 0.001). Moreover, the subjects with a high MPV had a higher prevalence of SCI. Multivariate logistic regression analyses revealed that the odds ratios and 95% confidence intervals for SCI according to MPV quartiles were 1.000, 2.131 (1.319–3.444), 3.015 (1.896–4.794), 7.822 (4.874–12.554) respectively (P < 0.001).

Conclusion: MPV is a novel index for SCI regardless of classical cardiovascular risk factors.

Introduction
Silent cerebral infarction (SCI) is a radiologic marker that implies the presence of cerebrovascular disease that does not show any clinical symptom. In most cases, SCI is found as a lacunar infarction caused by occlusion of small penetrating cerebral arteries. Moreover, some studies have demonstrated that the presence of SCI could be an indicator of transient ischaemia attack, clinically overt stroke, cardiovascular disease and dementia.1-3

Activated platelets play a key role in atherosclerosis. Elevated activity of platelet aggregation was observed in SCI patients.4 Moreover, treatment with anti-platelet drugs has been associated with reduced risk of developing SCI.5,6 Mean platelet volume (MPV), the most commonly used measure of platelet size, is an index of activated platelets and is available in clinical practice. Some studies have reported that MPV is a predictor of cardiovascular risk, stroke risk and overall vascular mortality.7-9

In addition, MPV is associated with worse clinical prognosis in acute myocardial infarction and acute stroke.10,11

Little research has been conducted to investigate the relationship between MPV levels and SCI. We, therefore, conducted this study to assess MPV levels in SCI patients.

Methods

Study subjects
We studied 2600 subjects who visited International Physical Examination and Healthy Center, Harbin, China, from January 2009 through December 2010 and who underwent magnetic resonance imaging (MRI) of the brain as part of their routine health check. There were 357 subjects who met the exclusion criteria and were excluded. There were 28 subjects who were excluded for having missing data for smoking status and alcohol intake. Therefore, the study population was finalised as 2215 participants. Exclusion criteria for this study included tumour, haematological disorders, autoimmune diseases, rheumatoid arthritis, infection, atrial fibrillation, transient ischaemic attacks, stroke and medical treatment with lipid-lowering agents, and anti-platelet medication. We obtained informed consent from all sub-
Clinical assessment

All the subjects underwent a clinical investigation including medical history, smoking status, alcohol intake, and physical examinations, laboratory tests and an MRI scan of the brain. Body weight was measured in light clothing, without shoes, to the nearest 0.5 kg. Height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight (kg) divided by height (m²). Blood pressure was determined using a mercury-gravity sphygmomanometer in a sitting position after a 15-min rest. Two readings were taken, with a 5-min interval between measurements. The mean of the two readings was recorded. Hypertension was diagnosed if systolic blood pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg, or as antihypertensive treatment.

Blood investigations

Fasting venous blood samples were drawn in the morning after an 8-h fast. The values included total serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and fasting plasma glucose (FPG). Diabetes mellitus (DM) was defined as fasting serum glucose was ≥ 7.0 mmol/L or non-fasting serum glucose was ≥ 11.1 mmol/L or as taking prescription medications. For the controls or the patients with impaired fasting glucose, DM was diagnosed if a 2-h post-glucose level after a 75-g oral glucose tolerance test ≥ 11.1 mmol/L. The Modification of Diet in Renal Disease (MDRD) equation was used to estimate glomerular filtration rate (eGFR). MDRD equation was: eGFR = 186.3 × (serum creatinine)−1.154 × (age)−0.203 × 0.742 if female. The assays were performed at the Laboratory of Analytical Biochemistry at the Second Hospital of Harbin Medical University, Harbin, using a biochemical analyzer (MODULAR ANALYTICS, Roche, Mannheim, German) using standard methods. Platelet count, MPV and platelet distribution width were determined with an autoanalyzer (Sysmex XE-2100, Kobe, Japan). The whole blood samples were collected in ethylenediaminetetraacetic acid-containing tubes, and all samples were processed within 30 min after blood collection.

Cerebral MRI

Brain MRI examination was performed on a 1.5-T magnetic resonance system (Achieva 1.5T, Philips, Best, The Netherlands). The scan protocol consisted of transverse relaxation time (T2)-weighted spin echo (repetition time (TR): 4800 ms, echo time (TE): 100 ms), longitudinal relaxation time (T1)-weighted spin echo (TR: 520 ms, TE: 14 ms) and fluid-attenuated inversion recovery (FLAIR; TR: 8500 ms, TE: 120 ms, inversion time: 2000 ms) imaging in axial planes at 5-mm thick slices with an interslice gap of 1.5 mm. The criteria for SCI were as follows: (i) a focal high intensity lesion (3–15 mm) in the T2 and FLAIR and low intensity in the T1 image; (ii) no corresponding symptoms in the clinical history of the patient that could be attributed to the lesion; and (iii) no history of clinical stroke. Periventricular white matter lesions were distinguished from SCI based on the high-signal intensity on FLAIR. Dilated perivascular spaces were differentiated from SCI based on their locations (along perforating or medullary arteries, often bilaterally symmetrical, usually in the lower third of the basal ganglia) and by absence of gliosis. The diagnoses were made by two independent experienced radiologists blinded to subject history and clinical status. The kappa value of agreement for SCI was 0.84. A consensus on inconsistent readings was reached through discussions.

Statistical analyses

The spss statistical software package version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. All participants were classified into quartiles by their MPV levels. Quartile 1 (Q1) was MPV ≤ 8.2 fL, quartile 2 (Q2) was MPV 8.3–9.5 fL, quartile 3 (Q3) was MPV 9.6–10.3 fL, and quartile 4 (Q4) was MPV ≥ 10.4 fL. The data were expressed as means ± standard deviation or medians (with interquartile ranges) for continuous variables or percentage for categorical variables. The Chi-squared test was used for all categorical variables. The differences of continuous variables between SCI group and non-SCI group were determined using the Student’s t-test or Mann–Whitney U-test. The differences of continuous variables according to MPV quartiles were determined using one-way analysis of variance or Kruskal–Wallis H-test. The odds ratios (OR) and 95% confidence intervals (95% CI) for SCI were calculated after adjusting for confounding variables across MPV quartiles using multivariate logistic regression analysis. A P-value of <0.05 was considered to be statistically significant.

Results

Of the 2215 participants enrolled, 830 (37.47%) were women and 1385 (62.53%) were men. The mean ages were 48.3 ± 11.1 and 49.1 ± 10.2 years respectively. There were 375 (16.93%; 242 males and 133 females) patients who presented SCI.

The clinical and laboratory characteristics of SCI and non-SCI subjects are shown in Table 1. The patients with SCI had higher serum creatinine and lower eGFR levels compared with the non-SCI subjects. The SCI group had a significantly higher prevalence of diabetes mellitus and hypertension compared with the non-SCI group. The SCI group also had higher levels of total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and lower levels of fasting glucose and hemoglobin compared with the non-SCI group. The SCI group also had a higher prevalence of smoking and alcohol intake compared with the non-SCI group. The SCI group also had a higher prevalence of hypertension compared with the non-SCI group. The SCI group also had a higher prevalence of hypertension compared with the non-SCI group.
Increased MPV is associated with SCI

SCI were older and had higher BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL, FPG, MPV, and lower HDL and eGFR levels compared with the subjects without SCI. Also, there was a higher proportion of DM and hypertension in SCI group. However, the levels of TC, TG, LDL, platelet count, white blood cell count and the proportion of gender and smoking status in two groups had no difference.

The clinical and laboratory characteristics of subjects were shown in Table 2 according to MPV quartiles. Mean age, BMI, SBP, DBP, FPG, TC, TG, LDL and the proportion of smoker, hypertension and DM increased gradually as MPV increased. However, the levels of HDL and eGFR decreased as MPV quartiles.

The prevalence of SCI is calculated by the quartiles of serum MPV level (Fig. 1). The prevalence rate (PR) of SCI in Q4 was significantly higher than that in Q1, Q2 and Q3. The PR% of SCI in Q1, Q2, Q3 and Q4 was 4.81% (31/644), 12.99% (66/508), 14.84% (81/546) and 38.10% (197/517) respectively.

The risk of SCI according to MPV quartiles are shown in Table 3. After adjusting for age, gender, BMI and smoking status, the prevalence risk of SCI for the highest quartile of MPV were 9.122 (6.051–13.751) (P < 0.001). These associations were similar after additional adjustment for SBP, DBP, FPG, TC, TG, LDL, platelet count, eGFR, DM and hypertension.

### Table 1 Baseline characteristics of the subjects according to SCI status

<table>
<thead>
<tr>
<th>Variables</th>
<th>With SCI (n = 375)</th>
<th>Without SCI (n = 1840)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.3 (10.4)</td>
<td>48.9 (10.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>242 (64.5)</td>
<td>1143 (62.1)</td>
<td>0.379</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4 (3.2)</td>
<td>24.6 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker (n, %)</td>
<td>136 (36.3)</td>
<td>589 (32.0)</td>
<td>0.109</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>133.7 (8.9)</td>
<td>125.8 (13.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.0 (7.5)</td>
<td>75.6 (8.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.11 (0.9%)</td>
<td>5.03 (1.0%)</td>
<td>0.120</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>2.04 (1.54–2.53)</td>
<td>2.04 (1.52–2.68)</td>
<td>0.563</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.49 (1.28–1.66)</td>
<td>1.52 (1.30–1.72)</td>
<td>0.035</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.95 (0.82)</td>
<td>2.65 (0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>5.59 (4.94–6.76)</td>
<td>5.28 (4.73–5.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (×10⁹/L)</td>
<td>5.5 (1.2)</td>
<td>5.4 (1.3)</td>
<td>0.134</td>
</tr>
<tr>
<td>Platelet (×10⁹/L)</td>
<td>224.1 (58.8)</td>
<td>228.2 (59.0)</td>
<td>0.219</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>10.4 (1.3)</td>
<td>9.2 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>72.8 (15.1)</td>
<td>78.9 (15.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>128 (34.1)</td>
<td>321 (17.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>93 (24.8)</td>
<td>177 (9.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are shown as mean (standard deviation) or median (interquartile range). BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MPV, mean platelet volume; SCI, silent cerebral infarction; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

### Table 2 Clinical and biochemical characteristics of subjects according to MPV quartiles

#### Quartiles of MPV

<table>
<thead>
<tr>
<th>Quartiles</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>644</td>
<td>508</td>
<td>518</td>
<td>545</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.8 (9.2)</td>
<td>48.7 (9.6)</td>
<td>51.3 (9.4)</td>
<td>53.6 (10.9)</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>351 (54.5)</td>
<td>348 (68.5)</td>
<td>366 (70.7)</td>
<td>320 (58.7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 (3.2)</td>
<td>24.7 (2.9)</td>
<td>25.1 (2.9)</td>
<td>25.2 (3.3)</td>
</tr>
<tr>
<td>Smoker (n, %)</td>
<td>236 (36.6)</td>
<td>227 (44.7)</td>
<td>274 (52.9)</td>
<td>213 (39.1)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>121.3 (12.3)</td>
<td>126.9 (14.8)</td>
<td>130.1 (11.2)</td>
<td>131.5 (12.0)</td>
</tr>
<tr>
<td>DBP (mmol/L)</td>
<td>74.4 (8.3)</td>
<td>74.2 (9.1)</td>
<td>77.6 (7.2)</td>
<td>77.9 (6.7)</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>4.83 (4.42–5.46)</td>
<td>5.34 (4.83–5.87)</td>
<td>5.30 (4.78–6.01)</td>
<td>5.87 (5.44–6.85)</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.91 (1.00)</td>
<td>5.00 (0.96)</td>
<td>5.11 (0.97)</td>
<td>5.18 (1.01)</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.96 (1.47–2.56)</td>
<td>2.06 (1.34–2.63)</td>
<td>1.98 (1.39–2.53)</td>
<td>2.16 (1.74–2.85)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.51 (1.22–1.70)</td>
<td>1.47 (1.28–1.69)</td>
<td>1.57 (1.38–1.74)</td>
<td>1.51 (1.31–1.75)</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.38 (0.83)</td>
<td>3.00 (0.74)</td>
<td>2.30 (0.73)</td>
<td>3.18 (0.70)</td>
</tr>
<tr>
<td>WBC (×10⁹/L)</td>
<td>5.5 (1.2)</td>
<td>5.4 (1.2)</td>
<td>5.4 (1.3)</td>
<td>5.5 (1.3)</td>
</tr>
<tr>
<td>Platelet (×10⁹/L)</td>
<td>227.0 (60.5)</td>
<td>232.8 (60.0)</td>
<td>224.3 (55.8)</td>
<td>226.3 (58.9)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>78.1 (16.1)</td>
<td>79.4 (16.6)</td>
<td>78.8 (16.0)</td>
<td>75.3 (14.7)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>75 (11.6)</td>
<td>125 (24.6)</td>
<td>129 (24.9)</td>
<td>120 (22.0)</td>
</tr>
<tr>
<td>DM (%)</td>
<td>42 (6.5)</td>
<td>52 (10.2)</td>
<td>44 (8.5)</td>
<td>132 (24.2)</td>
</tr>
</tbody>
</table>

Data are expressed as means (standard deviation) or median (interquartile range) or percentage. P-value was calculated by one-way analysis of variance test or Kruskal–Wallis H-test or Chi-squared test. BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MPV, mean platelet volume; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.
Discussion

In this cross-sectional study, we demonstrated that the subjects with a high MPV level have a higher prevalence of SCI. This association remained significant even after adjustment for conventional vascular risk factors. These findings suggested that platelet activation is enhanced in patients with SCI.

SCI is gaining interest of medical researchers with the introduction of modern neuroimaging techniques. Moreover, the prevalence of SCI is higher in the elderly population. Recent studies have demonstrated that SCI is linked to cognitive impairment, depression and increased risk for stroke.1,3,13 Therefore, early discovery of SCI is of great clinical importance.

Multiple mechanisms may be involved in the relationship between MPV and SCI. First, platelets with elevated MPV contain more α-granules and release more prothrombotic substances, and these substances aggravate inflammation and endothelial dysfunction.14 Recent studies demonstrated that endothelial dysfunction is involved in SCI.15 Reduced nitric oxide synthesis caused by endothelial dysfunction contributes to arterial stiffness.16 Our previous study revealed that elevated MPV is tightly associated with arterial stiffness as measured by brachial-ankle pulse wave velocity.17 Moreover, some reports confirmed brachial-ankle pulse wave velocity is independently associated with SCI.15 Second, it has been well demonstrated that low-grade chronic inflammation induces vascular damages.19 Some inflammatory markers, such as high-sensitivity C-reactive protein (CRP), CRP and interleukin-6, are reported to have positive correlation with SCI.20,21 Also, increased MPV is linked with metabolic syndrome, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease and stroke, which all are associated with chronic inflammation.8,22–26 Third, age, hypertension and reduced kidney function accelerate the development of atherosclerosis in a synergistic fashion. We confirmed that age and hypertension were related to SCI in our study. Furthermore, we revealed that decreased eGFR was also associated with SCI. The results were consistent with the fact that blood vessels in the kidney and brain are highly susceptible to fluctuations in blood pressure because the vascular beds of both kidney and brain have low resistance and are passively perfused at high-volume flow throughout systole and diastole.27

Recently, SCI has been reported to be correlated with activated platelets indicated by platelet adenosine diphosphate hyperaggregability.28 Our large sample study confirmed the result using a simple, inexpensive marker of platelet activation. In addition, consistent to other studies, our data showed that age and hypertension are the major risk factors for SCI.29

The interpretation of this study has some limitations. First, we did not detect the location of SCI. There may be an association of a specific lesion location and MPV levels. In addition, our study did not compare MPV levels in patients with single SCI with those in patients with multiple SCI. Further research is warranted to clarify whether there is a graded relationship between MPV levels and the number of SCI. Second, the study is cross-sectional, making it impossible to draw any definite

**Figure 1** The association between MPV levels and prevalence rate of SCI (%). Participants were stratified into quartiles according to their MPV levels. Quartile 1 (Q1) was MPV $\leq$ 8.2 fL, quartile 2 (Q2) was MPV 8.3–9.5 fL, quartile 3 (Q3) was MPV 9.6–10.3 fL, and quartile 4 (Q4) was MPV $\geq$ 10.4 fL. The prevalence rate of SCI in Q1, Q2, Q3 and Q4 were 4.81%, 12.99%, 14.84% and 38.10%, respectively. MPV, mean platelet volume; SCI, silent cerebral infarction.

**Table 3** Odds ratios and 95% confidence intervals for the presence of SCI risk according to MPV quartiles

<table>
<thead>
<tr>
<th>Quartiles of MPV</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>$P_{\text{value}}$</th>
</tr>
</thead>
</table>

†Model 1: adjusted for age, gender, BMI and smoking status. ‡Model 2: adjusted for age, gender, BMI, smoking status, SBP, DBP, FPG, TC, TG, HDL and LDL. §Model 3: adjusted for age, gender, BMI, smoking status, SBP, DBP, FPG, TC, TG, HDL, eGFR, hypertension, DM, platelet count and WBC. BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MPV, mean platelet volume; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SBP, systolic blood pressure; SCI, silent cerebral infarction; TC, total cholesterol; TG, triglyceride; WBC, white blood cell. © 2014 The Authors

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conclusion about the causal relationships. A prospective study is needed to clarify this point. Third, the study is lacking in information about inflammatory markers. Last, MPV levels are measured only at one time.

References


Increased MPV is associated with SCI

Conclusion

Our study showed that MPV is a novel index for SCI regardless of classical cardiovascular risk factors.
Can hospital-based doctors change their working hours? Evidence from Australia

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Centre for Health Economics Research and Evaluation (CHERE), University of Technology, Sydney, New South Wales, Australia

Key words
health workforce, doctor, Australia.

Abstract
Background and Aims: To explore factors predicting hospital-based doctors’ desire to work less, and then their success in making that change.

Methods: Consecutive waves of an Australian longitudinal survey of doctors (Medicine in Australia – Balancing Employment and Life). There were 6285 and 6337 hospital-based completers in the two waves, consisting of specialists, hospital-based non-specialists and specialist registrars.

Results: Forty-eight per cent stated a preference to reduce hours. Predictive characteristics were being female and working more than 40 h/week (both $P < 0.01$). An inverted $U$-shape relationship was observed for age, with younger and older doctors less likely to state the preference. Factors associated with not wanting to reduce working hours were being in excellent health and being satisfied with work (both $P < 0.01$). Of those who wanted to reduce working hours, only 32% successfully managed to do so in the subsequent year (defined by a reduction of at least 5 h/week). Predictors of successfully reducing hours were being older, female and working more than 40 h/week (all $P < 0.01$).

Conclusion: Several factors predict the desire of hospital-based doctors to reduce hours and then their subsequent success in doing so. Designing policies that seek to reduce attrition may alleviate some of the ongoing pressures in the Australian hospital system.

Introduction
The provision of high-quality and sustainable hospital care is a central component of health reform in Australia in the last decade. Much of the focus in recent years has concerned the role of private health insurance and the unusual application in Australia of public funding to support that.1 However, the focus has broadened to consider structural reform of the public hospital system, particularly the development of a National Health and Hospitals Network. As part of this broader focus, the National Health Reform Agreement increased the proportion of Commonwealth support to efficient growth funding of public health services, rising to 50% in 2017. Much of the motivation for the ongoing programme of reforms is the likely high rate of growth in the cost of delivering hospital care, both because of the ageing population and also the increasing costs of delivering each component of care. The issue of increasing demand for healthcare raises questions regarding the ability of the system to meet these increasing needs.

One way of strengthening the supply of doctors is to increase the number of medical school places (and also the registrar positions that are necessary to transition graduates into the labour force). This is likely to form part of the solution, but is likely to be expensive, and to contain a lag between allocating resources and having the increased staff supply in operation. An alternative, and potentially more efficient and timely strategy, is to consider ways of retaining existing staff, putting in place systems that reduce the likelihood of doctors choosing to reduce hours or leave the medical system altogether.

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Conflict of interest: None.
A doctor’s workload is likely to depend on several factors. Preferences for reducing the numbers of hours worked or for changing the type of work undertaken are likely to depend on a range of characteristics of the doctor, such as his or her age, job satisfaction and family circumstances. Additionally, it is unlikely that many doctors have complete flexibility to change their working hours, at least in the short term. This will be likely to vary based on, among other issues, seniority and speciality. Regarding the job satisfaction of Australian doctors, evidence suggests it to be correlated with good support networks, realistic expectations, self-assessed health and income, among other things. Beyond medicine, there is evidence demonstrating the link between job satisfaction and quitting. In the United States, it has been demonstrated that dissatisfaction with a medical career was a strong predictor of reducing hours per week below 20 and of retiring altogether. Recent evidence for general practice in Australia suggested that desire to reduce workload was associated with being middle-aged, being female, working more than 40 h/week, being in poor health, being dissatisfied with work and being on-call.

Thus, a better understanding of doctors’ work participation intentions and how they change their labour supply is a sound basis for developing workforce policy. We aimed to investigate two linked issues in the determination of working hours. First, by using a 2010 cross-section of an ongoing longitudinal study, we considered doctors’ stated preferences for changing working hours. Thus, what factors influence their preference for reducing their working hours? Second, we used the longitudinal nature of the data to explore whether doctors were able to change their working hours in line with their previously stated preferences. The separation of the issue into two components is valuable as it helps to identify whether changing working hours is being driven by doctor preferences or by external factors that help or impede doctors to reduce their time commitment to care delivery.

The study is reported in the following. First, a description of the dataset is provided in addition to an outline of the data manipulation undertaken prior to analysis. Second, the method for analysing the data is described. Third, the characteristics of the sample and the regression results are presented. Last, we outline some caveats to the analysis, as well as possible future steps for policymakers to consider.

**Methods**

The data sources for this analysis were the two most contemporary waves (i.e. Waves 3 and 4, collected in 2010 and 2011 respectively) of the Medicine in Australia – Balancing Employment and Life (MABEL) survey. The survey is funded by the National Health and Medical Research Council and the Department of Health and Ageing, and has been endorsed by a wide range of professional organisations. It is an increasingly widely used resource, which has been employed to explore, among other things, the determinants of earnings of doctors, of work–life balance and of junior doctors’ preferences for specialty. The Wave 1 panel of this survey consisted of a census of the 54 750 doctors from the Australasian Medical Publishing Company’s (AMPCo) Medical Directory. In subsequent waves, those who had responded to previous waves or doctors new to the AMPCo Medical Directory were invited to participate. The total number of invitations in Waves 3 and 4 was 16 327 and 15 967 respectively, yielding 9949 and 9773 responses. These were divided into four groups, namely General Practitioners, Specialists, Hospital Non-specialists and Specialist Registrars. The scope of the work presented here concerns the working hours of those doctors involved in hospital work (i.e. Specialists, Hospital Non-specialists and Specialist Registrars); the questions that MABEL asks general practitioners (GP) are sufficiently different to consider them as a distinct group, and therefore we dropped the GP observations from the dataset. Further details regarding the survey methodology are reported in the latest MABEL technical manual.

Four major modifications were made to the dataset before analysis was undertaken. These were made to ease interpretation. First, net personal income was converted into quintiles. Thus, in our analysis, there were six categories, the five quintiles and those who did not disclose income. Second, family circumstances were considered using a composite variable that included both whether the doctor had children and whether they had a partner. The composite variable took on a value representing each of the four possible combinations of these two variables. For the latter part of the analysis, this structure was simplified to two categorical variables (i.e. with/without children and with/without partner) because of sample size issues in particular subgroups. Third, to allow exploration of differences by setting, the proportion of time each doctor spent in private practice was estimated by dividing time spent per week in private hospitals or private practitioners’ room or surgery by total weekly working hours. Last, the number of hours currently worked was converted into a categorical variable, with the categories being those working less than 20 h/week, those working between 20 and 39.5, those working 40–59.5, and those working 60 h or more per week. The data are reported to the nearest half-hour, meaning that the groups described above are mutually exhaustive. One additional minor alteration to the data is that the age of
the doctor was initially reported according to 5-year bands. For the purpose of analysis, we assumed the age of each doctor was the midpoint of their band, thus allowing age to be treated as a continuous variable. As a robustness check, age was modelled as a categorical variable, but the pattern remained unchanged, so the results of this robustness check are not reported here.

Our research questions were investigated through a series of regression analyses undertaken using Stata 12.1 (Stata Corp., College Station, TX, USA). To allow subsequent exploration of whether the doctors who stated a desire to reduce their workload were able to do so, this analysis used Wave 3 data collected in 2010. For all analyses in this first step, the dependent variable was whether or not the doctor stated a desire to reduce their hours. The question in MABEL asked, ‘Would you like to change your hours of work?’, with the options being ‘No’, ‘Yes, I’d like to increase my hours’ and ‘Yes, I’d like to decrease my hours’. By specifying the dependent variable as wanting to reduce hours or not, we implicitly pooled those who stated a preference for increasing hours and those who did not want to change. The reason for doing so was that only 4% of the sample stated a willingness to increase, and the numbers of such respondents (particularly in subgroup analyses) would be too small to derive reliable inferences. A logistic regression was undertaken to reflect the binary nature of the dependent variable. Output was generated reporting both coefficients and odds ratios, and for ease of interpretation, the latter are presented here. The independent variables were age (linear and quadratic), gender, self-assessed health (on a 5-point Likert scale, including Poor, Fair, Good, Very Good and Excellent), family circumstance, job satisfaction, working hours, income quintiles and the proportion of hours spent in private practice. The odds ratios on quadratic terms on age were often statistically significant, but close to one; therefore, the quadratic variable was rescaled for ease of interpretation, dividing through by 100.

In addition to running a pooled analysis with all three subgroups of doctors (Specialists, Hospital Non-specialists, and Specialist Registrars), separate analyses were run for each group of doctors. As a further robustness test, the regression was replicated using Waves 1, 2 and 4, the results of which were similar to those for Wave 3, and are available on request.

The second part of the analysis focused on those doctors who stated a desire to reduce their hours in Wave 3, and their subsequent change in hours between Waves 3 and 4. To identify which doctors successfully reduced their hours, it was necessary to define what constitutes a reduction in hours. As a starting point, we selected a reduction in weekly working hours of five or more as the criterion, although we subsequently tested if the inferences persist if the threshold is changed to 2 or 10 h. The inferences when the threshold was set at these higher or lower values are similar, and hence not reported here (available on request from the authors). As with the analysis of the desire to reduce hours, the outcome is either yes or no, so a logistic regression was used with the same set of independent variables. However, one small adjustment was required regarding family composition. In the initial analysis, having children and/or having a partner was explored allowing for interactions between the two; in the subsequent analysis (particularly in the subgroup analyses by doctor group), the sample size was too small to allow this. Hence, family composition was represented by two binary parameters, having at least one child or not, and having a partner or not.

For all regressions, the results were P-weighted using weights included in the MABEL survey to ensure representativeness of the sample to the Australian doctor population. However, the impact of P-weighting or not was small in all cases. Therefore, while the coefficients reported here are derived through a P-weighted regression, estimates of model fit (reporting pseudo R² values) were derived from an unweighted regression.

Results

The characteristics of the pooled sample, and of the individual subgroups, are reported in Table 1. The Specialists in the analysis are older, less likely to be female, likely to be married with children, to be satisfied with their work, to have a higher personal income and to undertake a higher proportion of work in a private setting.

Of the 5698 doctors included in the analysis, 47.9% stated a desire to reduce their hours; this figure was higher for Specialists (50.1%) and Specialist Registrars (50.0%), and lower for Hospital Non-specialists (38.9%). The regression results for the pooled sample are presented in Table 2. The main effect of age is a strong positive predictor of desire to reduce hours (P < 0.01). However, the negative coefficient on age squared suggests the increased reverses in older groups. The maximum desire to reduce hours occurs for doctors in their mid-50s. Female doctors are more likely to want to reduce hours (OR:1.36; P < 0.01). Those who report excellent or very good health are less likely to want to reduce hours than those reporting good health (OR:0.70; P < 0.01, and 0.80; P = 0.027 respectively). Those who are satisfied (OR: 0.46; P < 0.01) or very satisfied (OR:0.21; P < 0.01) with their work are less likely to want to reduce hours relative to those who are neither satisfied nor dissatisfied. Working hours are a strong predictor of the desire to reduce hours; relative to someone working...
between 20 and 39.5 h, the odds ratio for a doctor working more than 60 h/week is over eight. There is a weak income effect, in that those in higher quintiles are more likely to state a desire to reduce hours, although statistical significance is only achieved for the difference between those in the third and fourth quintiles ($P = 0.041$). Working more in private settings is associated with stating a preference to reduce working hours. No statistically significant effect is observed on family circumstance.

When the analysis is run for each specialty separately, the notable age effect is driven by Specialists. This may be because, as identified in Table 1, the spread of ages in the Specialists is larger than in the other subgroups, making it easier to determine a pattern over age. The female effect is not observed for the Specialists and Hospital Non-specialists groups ($P > 0.05$ for both), but is a strong predictor of preference for Specialist Registrars ($P < 0.01$), even though age and family circumstance are controlled for. This may be because, while we have controlled for current family circumstance, the data do not allow controlling for intentions with regard to family structure. Proportion of work undertaken in a private setting is only statistically significant in the Specialists group, but the non-identification of an effect in the other groups may reflect the low rates of private sector participation for the Non-specialists subgroups in the analysis.

Of the 4584 doctors who have complete working hour intention data for both Waves 3 and 4, 2226 stated a desire to reduce their hours in Wave 3. Of those 2226, only 714 (32.1%) successfully reduced their hours by more than five per week. This figure ranged from 27% for Specialists to 44% for Specialist Registrars and 47% for Hospital Non-specialists. Some of the difference

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sample characteristics, pooled and by subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled (n = 5850)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>44.7 (12.6)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>39.6</td>
</tr>
<tr>
<td>Self-assessed health (%)</td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>38.0</td>
</tr>
<tr>
<td>Very good</td>
<td>37.2</td>
</tr>
<tr>
<td>Good</td>
<td>17.4</td>
</tr>
<tr>
<td>Fair/poor</td>
<td>5.0</td>
</tr>
<tr>
<td>Missing</td>
<td>2.4</td>
</tr>
<tr>
<td>Family circumstance (%)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>17.2</td>
</tr>
<tr>
<td>Has a partner, but no children</td>
<td>28.9</td>
</tr>
<tr>
<td>Has children, but no partner</td>
<td>2.9</td>
</tr>
<tr>
<td>Has both children and a partner</td>
<td>47.9</td>
</tr>
<tr>
<td>Work satisfaction (%)</td>
<td></td>
</tr>
<tr>
<td>Very dissatisfied</td>
<td>1.0</td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>5.8</td>
</tr>
<tr>
<td>Neither satisfied nor dissatisfied</td>
<td>4.8</td>
</tr>
<tr>
<td>Satisfied</td>
<td>54.7</td>
</tr>
<tr>
<td>Very satisfied</td>
<td>33.6</td>
</tr>
<tr>
<td>Missing satisfaction</td>
<td>0.2</td>
</tr>
<tr>
<td>Working hours (%)</td>
<td></td>
</tr>
<tr>
<td>Fewer than 20</td>
<td>4.3</td>
</tr>
<tr>
<td>20–39.5</td>
<td>21.0</td>
</tr>
<tr>
<td>40–59.5</td>
<td>58.2</td>
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<tr>
<td>60 or more</td>
<td>15.4</td>
</tr>
<tr>
<td>Missing hours</td>
<td>1.2</td>
</tr>
<tr>
<td>Personal income quintile (%)</td>
<td></td>
</tr>
<tr>
<td>First quintile</td>
<td>13.5</td>
</tr>
<tr>
<td>Second quintile</td>
<td>13.9</td>
</tr>
<tr>
<td>Third quintile</td>
<td>12.6</td>
</tr>
<tr>
<td>Fourth quintile</td>
<td>13.3</td>
</tr>
<tr>
<td>Fifth quintile</td>
<td>13.3</td>
</tr>
<tr>
<td>Missing income</td>
<td>33.4</td>
</tr>
<tr>
<td>Proportion of private work (SD) (%)</td>
<td>26.1 (36.8)</td>
</tr>
</tbody>
</table>
between Specialists and Specialist Registrars is accounted for by Specialist Registrars transitioning to another category between waves; for those who were Registrars in Wave 3 but not in Wave 4, the proportion who successfully reduced their hours by five or more was 56%. Of the 1512 who were unable to reduce their hours of work despite stating that preference, 1147 (75.9%) continued to state a desire to reduce their working hours in Wave 4, suggesting that their failure to reduce hours was not due to changing preferences, but to external factors preventing a reduction in working hours. The regression results for this analysis are reported in Table 3. The ability to reduce hours is predicted by three factors. First, younger doctors who had previously stated a desire to reduce their working hours are actually less likely to report lower working hours in the subsequent year. This is again driven by the coefficient on the quadratic term; while the coefficient on the main effect is negative, the coefficient on the quadratic term suggests the relationship is relatively flat in earlier years, then increases in older doctors. Second, female doctors are more likely to reduce hours successfully (OR: 1.61; \( P < 0.01 \)). Third, those working the longest hours are more likely to reduce hours successfully. For doctors working 60 h or more, this odds ratio relative to those working between 20 and 39.5 h is 3.71 (\( P < 0.01 \)).

**Discussion**

A major policy issue in the last decade has been the effect of reduced working hours on the availability of doctors. This study explored two linked issues that impact on doctors reducing their working hours. The first is the identification of which factors are associated with doctors wanting to work less, and the second explores the factors that appear to allow them to reduce their hours. The advantage of separating the two issues is that it allows exploration of how policy responses might impact on working hours.
Our results show that doctors stating a desire to reduce hours are generally older, female, working more than 40 h/week, and undertaking a relatively higher proportion of time working in a private setting. Conversely, those with excellent self-assessed health are less likely to state a preference to reduce hours. Similarly, those working fewer than 20 h are less likely to want to reduce, perhaps as a result of previously achieving a reduced workload. In both analyses, the relationship between responses and age should be considered in light of possible attrition bias; for the older groups of doctors, the responses in MABEL represent only a subset of those doctors who could have been in that subgroup, with an increasing proportion having retired already.

High levels of job satisfaction are strongly and negatively associated with the desire to reduce working hours. While the work presented here does not demonstrate causality (e.g. that improving job satisfaction will cause fewer doctors to reduce their hours), it is our belief that such a relationship is plausible and merits further investigation. Importantly, and unlike the other factors that are associated with high retention rates of skilled staff in the hospital setting, job satisfaction is something that might be changed by policy-makers.

Our results also show that most of the doctors who wish to reduce their working hours fail (or are unable) to do so within the next year. The key predictors of reducing hours are age, gender and current working hours. Older doctors are more likely to reduce their hours than young doctors. Female doctors are actually more likely to reduce hours if they want to do so. These results are robust to other factors, which might explain these relationships (family circumstance and income for example). This may be due to different motivations. Family constraints are more pressing for younger doctors and female doctors, while older male doctors may be contemplating moving to retirement gradually. Importantly, the variables that matter in predicting doctors’ success in reducing hours are either working hours themselves or demographic characteristics that cannot be changed through policy

| Table 3 Association between doctors reducing weekly hours by five or more, and doctor characteristics |
|---|---|---|---|---|
| | Pooled sample | Specialists | Hospital non-specialists | Specialist registrars |
| | OR (95% CI) (n = 2207) | OR (95% CI) (n = 1594) | OR (95% CI) (n = 286) | OR (95% CI) (n = 327) |
| Age | 0.87 (0.80, 0.93)** | 0.96 (0.86, 1.07) | 0.79 (0.54, 1.14) | 1.36 (0.73, 2.52) |
| Age^2/100 | 1.16 (1.07, 1.25)** | 1.05 (0.94, 1.17) | 1.29 (0.85, 1.95) | 0.61 (0.27, 1.38) |
| Female (base: male) | 1.61 (1.28, 2.02)** | 1.53 (1.14, 2.04)** | 1.33 (0.72, 2.44) | 1.72 (0.98, 3.03)* |
| Self-assessed health (base: good) | | | | |
| Excellent | 0.79 (0.59, 1.06) | 0.74 (0.52, 1.06) | 1.28 (0.58, 2.80) | 0.65 (0.33, 1.31) |
| Very good | 1.08 (0.83, 1.41) | 1.26 (0.90, 1.74) | 0.88 (0.41, 1.87) | 0.78 (0.40, 1.51) |
| Fair/poor | 1.17 (0.76, 1.81) | 1.23 (0.73, 2.07) | 0.87 (0.21, 3.51) | 1.45 (0.45, 4.68) |
| Missing | 1.55 (0.69, 3.46) | 1.54 (0.65, 3.65) | 2.72 (0.19, 39.41) | NR† |
| Children (base: no) | 0.87 (0.68, 1.12) | 0.72 (0.54, 0.96)** | 3.76 (1.65, 8.61)*** | 1.03 (0.51, 2.07) |
| Partner (base: no) | 1.12 (0.85, 1.47) | 0.98 (0.68, 1.43) | 0.86 (0.45, 1.63) | 1.59 (0.89, 2.83) |
| Work satisfaction (base: neither satisfied nor dissatisfied) | | | | |
| Very satisfied | 1.63 (0.65, 4.07) | 1.08 (0.31, 3.84) | 1.86 (0.22, 15.51) | 3.87 (0.35, 42.41) |
| Dissatisfied | 0.60 (0.36, 0.98)** | 0.78 (0.41, 1.47) | 0.31 (0.10, 0.96)** | 0.56 (0.15, 2.06) |
| Satisfied | 0.77 (0.54, 1.12) | 0.94 (0.57, 1.56) | 0.54 (0.25, 1.18) | 1.11 (0.41, 3.02) |
| Very satisfied | 0.82 (0.54, 1.24) | 0.89 (0.51, 1.52) | 0.61 (0.20, 1.92) | 1.84 (0.59, 5.67) |
| Working hours (base: 20–39.5 per week) | | | | |
| Fewer than 20 | 0.99 (0.33, 2.95) | 0.96 (0.32, 2.86) | NR† | NR† |
| 40–59.5 | 1.09 (0.76, 1.54) | 0.95 (0.64, 1.41) | 1.66 (0.50, 5.46) | 1.69 (0.47, 6.07) |
| 60 or more | 3.71 (2.54, 5.43)** | 3.15 (2.05, 4.84)** | 8.66 (2.55, 29.46)*** | 5.57 (1.44, 21.60)** |
| Personal income quintile (base: third quintile) | | | | |
| First quintile | 1.24 (0.80, 1.91) | 1.29 (0.55, 3.03) | 0.90 (0.23, 3.55) | 1.22 (0.47, 3.18) |
| Second quintile | 1.26 (0.84, 1.88) | 1.68 (0.87, 3.23) | 0.81 (0.21, 3.18) | 1.13 (0.57, 2.25) |
| Fourth quintile | 0.78 (0.52, 1.16) | 0.86 (0.54, 1.36) | 0.66 (0.09, 5.05) | NR† |
| Fifth quintile | 0.88 (0.59, 1.31) | 0.94 (0.60, 1.53) | 3.49 (0.33, 36.84) | NR† |
| Missing quintile | 1.01 (0.73, 1.40) | 1.02 (0.68, 1.53) | 1.07 (0.27, 4.23) | 1.28 (0.59, 2.77) |
| Proportion of private work | 1.36 (0.99, 1.88)* | 1.69 (1.20, 2.37)** | 0.38 (0.07, 2.18) | 0.18 (0.02, 1.54) |
| Pseudo R² | 0.077 | 0.059 | 0.141 | 0.101 |

Levels of significance: ***0.1%; **1%; *5%. †When the number of observations is fewer than five, the coefficient is not reported (NR) as it and the confidence interval are highly sensitive to single responses.
levers. The implication of this is that policy designed to retain labour supply in the health workforce should focus on the predictors of the desire to reduce hours as outlined in Table 2.

Conclusion
There is an increasing emphasis on the development of policy based on research evidence, but to date there has been little insight into doctors’ changing work patterns. The results presented here show that improved doctor job satisfaction is associated with less desire to reduce working hours. This implies that further investigation of policies that can improve doctors’ job satisfaction may well ensure improvements in the doctor supply, which are needed to meet the increasing demand for primary care into the future. However, the data demonstrate that many doctors are working very long hours, which is likely to have long-term implications for their own health, their ongoing participation in the health sector and the quality of care they can provide for patients. The balancing of meeting the needs of the population for high-quality hospital care with supporting those who provide this care represents an important balance that has to be made, and an area of ongoing challenge and opportunity.

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Family screening in hypertrophic cardiomyopathy is underperformed, but can be improved by a specialised clinic

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Key words
cardiomyopathy, hypertrophic, screening, echocardiography, phenotype.

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Abstract

Background: Hypertrophic cardiomyopathy (HCM) causes significant morbidity and sudden death. First-degree relatives (FDR) of affected patients are at risk due to autosomal dominant inheritance. Guidelines recommend clinical screening, including echocardiography, for all FDR.

Aim: We sought to determine adherence to these guidelines, and whether a specialised HCM clinic improves screening rates.

Method: This 12-month prospective follow-up study obtained family pedigrees from all patients referred to the HCM Clinic @ The Alfred. The number of living FDR was determined, and whether they had previously been assessed by echocardiography. One year after a coordinated clinic-based family screening approach was instituted, the number of additionally screened FDR was recorded.

Results: Three hundred and eight living FDR of 61 HCM patients were identified. Of these, echocardiography had previously been performed in only 80 (26%), yielding 13 (16%) additional cases of HCM. Twelve months after attendance at our clinic, 51 additional FDR were screened (64% improvement) and 8 new cases of HCM were identified.

Conclusions: Recommended family screening for HCM is underperformed, resulting in missed opportunities to detect subclinical HCM. A coordinated approach through a specialised HCM clinic improves screening rates, thus referral to such a service should be considered for all patients with HCM and their families.

Introduction

Hypertrophic cardiomyopathy (HCM) is the commonest monogenic inherited cardiac disease and is defined by the presence of otherwise unexplained thickening of the muscular wall of the left ventricle (LV). Affecting approximately 1 in 500 people, HCM contributes to significant morbidity, and is a major cause of sudden cardiac death (SCD) in both children and young athletes. Inheritance is autosomal dominant, meaning there is a 50% risk for first-degree relatives (FDR) to carry the pathogenic mutation associated with HCM in their family and are, therefore, at risk of developing HCM.

Clinical presentation of HCM is diverse. Symptoms include dyspnoea, chest pain, palpitations, dizziness and syncope. However, many remain asymptomatic and, in these patients, the first manifestation of the disease may be SCD. The annual mortality rate in HCM is up to 5% and the 6-year survival rate is 91%. This mortality risk is a major incentive for performing family screening, as individuals at high risk for sudden death can be identified and offered a prophylactic implantable cardioverter defibrillator (ICD).

Guidelines formulated by the Cardiac Society of Australia and New Zealand (CSANZ) recommend clinical screening of all FDR of HCM patients. Screening should include physical examination, electrocardiography (ECG) and echocardiography and occur regularly with a frequency determined by the age of the family relative. For example, screening every 1 to 1.5 years is recommended for those aged 11 to 20 years, a period during which phenotypic manifestations of HCM are most likely to occur, and every 3 to 5 years for those aged over 30 years.

A specialised clinic was established at our institution in 2012 to improve both the understanding and management of HCM. The ‘HCM Clinic @ The Alfred’ accepts referrals from across Australia and is staffed by a
multi-disciplinary team consisting of cardiologists, a cardiac surgeon and a genetic counsellor. Maximising the number of FDR that are properly screened for HCM is an important function of our clinic.

We sought to determine the degree of adherence to the family screening guidelines of CSANZ in the FDR of patients referred to our specialised HCM clinic. Furthermore, we sought to implement simple and practical clinic-based interventions designed to improve the overall performance of family screening for HCM.

Methods

Patient selection

All research was performed at the Alfred Hospital, Melbourne, Australia. All patients referred to the clinic with a clinical diagnosis of HCM between February 2012 and March 2013 were included in the analysis. The study was conducted in accordance with the Alfred Hospital Ethics Committee’s guidelines. Patient demographic and clinical data were collected.

Initial assessment of the pedigree

A detailed three-generation pedigree was obtained from all patients with HCM by a genetic counsellor at initial assessment. For each patient, the number of living FDR was first determined. Then, based on the patient’s knowledge, the number of these relatives who had previously undergone echocardiographic screening was ascertained. If more than one HCM patient from the same family was seen at the clinic, the number of unique FDR was calculated. Finally, the number of relatives who had been diagnosed with HCM as a result of echocardiographic screening was established. These patients were not labelled as at-risk. Patients had the opportunity, at their discretion, to contact FDR to clarify their screening status and results at a later time. FDR were also provided with contact details to provide our clinic voluntarily with the formal reports of their echocardiograms. Where there was uncertainty as to the screening status of an FDR, we assumed that screening had not been performed.

Clinic-based interventions to improve family screening

During their initial assessment, each patient was advised of the autosomal dominant pattern of inheritance of HCM and the recommendation that all FDR should be screened for HCM with a clinical assessment, ECG and echocardiogram. This was communicated to each patient during the initial assessment and subsequently through written correspondence addressed directly to the patient. The task of contacting FDR and advising them of these recommendations was made by patients, at their discretion. To facilitate this process, the patient received a letter explaining the rationale for the screening recommendations for relatives, the investigations that were necessary for screening as well as the contact details of the clinic which could be passed on directly to relatives. In circumstances where English was not a family’s preferred language, a translation of written correspondence into their preferred language was also provided. A clinical assessment was performed and referral for echocardiography was arranged for all FDR who accompanied their affected relative to the clinic. Follow-up 12 months after a patient’s initial clinic assessment, either during routine clinical follow up or through phone, was performed to record both the number of additional FDR who had been screened and new cases of HCM subsequently identified.

Analysis

Normally distributed continuous variables were presented using mean ± standard deviation. Ordinal or skewed data were presented using median (interquartile range). To calculate statistical difference, student’s t-test was used between two means, Wilcoxon–Mann–Whitney test was used between two medians, and the Chi-squared ($\chi^2$) test was used between two proportions. For all comparisons, a P-value of < 0.05 was considered significant, and all reported P-values are two-tailed. Logistic regression was used to determine univariate associations of variables such as patient demographic and clinical features that may be associated with an increase in screening rates in FDR following the first assessment. The results from the univariate regression analyses were reported as unadjusted odds ratios with 95% confidence intervals. All analyses were performed using Stata version 13.0 (Statacorp, College Station, TX, USA).

Results

Of the 66 patients referred to the clinic during its first year, 61 patients had a clinical diagnosis of HCM. This cohort consisted of 55 different families. Sixty-two per cent of patients were male and their mean age was 56 ± 15 years. One-quarter of patients had a family history of HCM. Further demographic details and clinical features are listed in Table 1.

The 61 HCM patients had a total of 308 living FDR (median 5 per patient, IQR: 2–7), with two patients
without any living FDR. A screening echocardiogram had previously been performed on only 80 (26%) of these relatives at the time of initial assessment in our clinic. Of these relatives, 13 (16%) new cases of HCM had been diagnosed as a result of screening (Fig. 1).

Twelve months after a coordinated screening approach instigated by our specialised HCM clinic, 51 additional at-risk FDR had screening performed. This represents a 64% increase (from 26% pre-clinic to 42.5% post-clinic). Prior to attending the clinic, 24 of the 53 families at risk had at least one individual screened. After attending the clinic, this number increased to 36.

Of the 51 new screened individuals, eight (16%) cases of HCM had been identified. Seven (88%) of these patients were male, with a mean age of 50.4 ± 19.2 years old. One patient underwent septal reduction therapy. By the time of follow up, no patient had received an ICD.

**Discussion**

This study of patients referred to our newly established specialised clinic for HCM demonstrates that recommended screening of FDR for this cohort is significantly underperformed. Approximately three-quarters of the at-risk relatives had not previously been screened for HCM, and nearly one-fifth of those screened were diagnosed with HCM. One year after initial assessment in our specialised clinic, which included several simple and practical interventions designed to improve overall family screening rates, screening of an additional 51 at-risk FDR had been performed, and an additional eight cases of subclinical HCM identified.

The purpose of screening FDR for HCM is to identify the condition early, thereby enabling close surveillance and the introduction of early preventative management strategies for sudden death as necessary. Since reduced mortality from HCM has been attributed to lifestyle modifications\(^{10,11}\) and implantable defibrillators,\(^{12,13}\) screening is clearly justifiable.\(^{7}\) As a widely available and relatively inexpensive imaging modality, echocardiography is the preferred imaging modality for the diagnosis of HCM.\(^{14}\) If imaging quality is poor, or if more accurate measures of LV wall thickness are required, other imaging modalities, such as cardiac magnetic resonance imaging, can be considered.\(^{15}\)

There are limited data pertaining to the adherence to local and/or international guidelines for family screening in HCM. To our knowledge, this is the first Australian study to report the screening status in FDR of patients with HCM. In a cross-sectional study emanating from the United Kingdom,\(^{16}\) that included the families of 64 HCM patients, 28.5% of FDR had previously been screened, a figure similar to our findings. A cross-sectional analysis found that 28.5% of these relatives had been screened, a
figure similar to our findings. In their tertiary heart muscle centre, which included a cardiogenetic nurse, a further 71 FDR were screened and of this cohort, 15 (21%) patients were diagnosed with HCM. Interestingly, three of the 15 (20%) patients diagnosed with HCM during family screening received an implantable defibrillator for primary prophylaxis against SCD. In our cohort, we did not experience a similarly high rate of prophylactic defibrillators, but one of the eight newly diagnosed patients underwent septal reduction therapy.

There are several possible explanations for the relatively low rates of screening among FDR of HCM patients. We observed that, before attending our clinic, many patients had an incomplete understanding of their condition, including its mode of inheritance. In some families, contact between certain family members was often absent or there was evidence of strained relationships between relatives. Finally, in FDR who were aware of the recommendation to undergo clinical screening, a lack of motivation, difficulties organising screening, concerns relating to the impact on work, as well as insurance-related concerns were all reported barriers to screening. Such barriers could be classed ‘personal preferences’, and was noted by Finch et al.16 to be the main reasons for lack of screening in 28 of their 52 unscreened FDR. In relation to barriers for genetic testing, Sivell et al.17 explain how personal traits, coping mechanisms and beliefs about risk-mitigating strategies all affect the individual’s perception of risk. The differing concerns and barriers to screening, even among family members with the same family history, therefore demand an individualised approach. The paucity of literature explaining barriers to clinical HCM screening rates necessitates inferences from other diseases, such as colonoscopies in patients with family history of colorectal cancer. Among the reasons identified are lack of symptoms, spiritual beliefs,18 fear of the screening test19 and myths or fatalistic views about the disease.18

It could be hypothesised that the number of screened FDR would increase over a 12-month period regardless of clinic attendance. This may be more likely to occur in patients who already have at least one FDR screened as they would be aware of the risk, but not yet have undergone the screening. However, the fact that we observed similar rates of screening in patients both with and without previously screened FDR supports the impact of the clinic. It also highlights that the clinic has an important role in patients who have never considered or achieved screening their FDR.

Within 12 months of attendance of the index patient at our clinic, 131 of 308 (42.5%) FDR had been screened, a figure exceeding previous reports. This reflects the value of implementing simple, but practical, clinic-based interventions both to educate patients and their families about HCM, and facilitate screening opportunities. A Sydney-based study found that positive adjustment to diagnosis and reduced psychological symptoms were experienced by patients attending a specialised HCM clinic.20 One may postulate that patients attending a multidisciplinary clinic, which addresses medical, informational and psychosocial needs, may feel more empowered to communicate with their relatives about the risk for HCM.

Since over half of at-risk relatives remained unscreened, improved methods of reaching these patients demand future research. Although we did not collect

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison between patients who had additional first-degree relatives (FDR) screened compared to those where no further screening occurred in FDR 12 months after the clinic commenced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional FDR screened</td>
<td>No change in screening of FDR</td>
</tr>
<tr>
<td>(n = 23)</td>
<td>(n = 34)</td>
</tr>
<tr>
<td><strong>Age at time of clinic</strong></td>
<td></td>
</tr>
<tr>
<td>57.5 ± 15.5</td>
<td>57.6 ± 10.7</td>
</tr>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>55.7 ± 9.2</td>
<td>53.0 ± 15.8</td>
</tr>
<tr>
<td><strong>Years since diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>2.1 ± 2.4</td>
<td>4.5 ± 6.3</td>
</tr>
<tr>
<td><strong>Gender, male (%)</strong></td>
<td></td>
</tr>
<tr>
<td>13 (56.5%)</td>
<td>22 (64.7%)</td>
</tr>
<tr>
<td><strong>Chest pain</strong></td>
<td></td>
</tr>
<tr>
<td>6 (26.1%)</td>
<td>8 (23.5%)</td>
</tr>
<tr>
<td><strong>Dyspnoea</strong></td>
<td></td>
</tr>
<tr>
<td>11 (47.8%)</td>
<td>19 (55.9%)</td>
</tr>
<tr>
<td><strong>Syncope</strong></td>
<td></td>
</tr>
<tr>
<td>2 (8.7%)</td>
<td>4 (11.8%)</td>
</tr>
<tr>
<td><strong>Palpitations</strong></td>
<td></td>
</tr>
<tr>
<td>5 (22.7%)</td>
<td>4 (11.8%)</td>
</tr>
<tr>
<td><strong>≥3 symptoms (chest pain, dyspnoea, presyncope, syncope, palpitations)</strong></td>
<td></td>
</tr>
<tr>
<td>6 (26.1%)</td>
<td>7 (20.6%)</td>
</tr>
<tr>
<td><strong>Presence of at least one FDR screened prior to attending the clinic</strong></td>
<td></td>
</tr>
<tr>
<td>11 (47.8%)</td>
<td>14 (41.2%)</td>
</tr>
<tr>
<td><strong>BMI, mean (SD)</strong></td>
<td></td>
</tr>
<tr>
<td>27.3 (4.9)</td>
<td>29.4 (6.3)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>10 (45.5%)</td>
<td>16 (47.0%)</td>
</tr>
<tr>
<td><strong>Murmur</strong></td>
<td></td>
</tr>
<tr>
<td>10 (43.5%)</td>
<td>21 (61.8%)</td>
</tr>
</tbody>
</table>

All variables were not statistically significant (i.e. P-value < 0.10). BMI, body mass index; CI, confidence interval.
data about geographic location, it is plausible that people living outside of metropolitan catchment areas are overrepresenting the vulnerable unscreened group. The HCM clinic endeavours to reach those in rural areas through liaison with rural cardiologists and rural genetic counselling services. Nevertheless, the nature of relatively rare conditions is that specialised services can only exist within large tertiary centres.

Since the first HCM-related gene was identified in 1990, hundreds of pathogenic mutations have been identified. Identifying the precise pathogenic mutation in an index patient with HCM may facilitate the exclusion of up to half of FDR from ongoing clinical surveillance. Therefore, genetic screening for HCM could be cost-effective. However in Australia, access to genetic testing and screening is limited and restricted by a large non-Medicare-funded cost. One Danish study found no genetic mutation in 149 out of 361 (41%) FDR, and thereby safely excluded these patients from ongoing screening. This has positive implications for both the relative (i.e. through reduced concerns) and the healthcare sector (i.e. through more appropriate use of resources). Future research should explore the true cost-effectiveness of genetic testing, and authorities should consider improved funding solutions.

This study has limitations. First, we were reliant on information provided by the index patients regarding their pedigree and FDR’ screening status. We attempted to minimise any false negative reports by accepting echocardiographs performed in the past, however distant, for any indication. This broad definition of ‘screened’ is likely to overestimate the number of truly screened individuals, thus making the low screening frequency even more concerning. Second, reporting of screening echocardiographic studies was made both at our specialised institution and at external sites. This might affect the true prevalence of disease. At our clinic, we use cardiac MRI for every patient to confirm the diagnosis, especially in the setting of poor quality echocardiographs. This might mean that we were able to identify more subtle LV hypertrophy than external sites. Last, our cohort was too small to detect statistical significant associations for lack of FDR screening.

Conclusion
Local guidelines for family screening in HCM are poorly adhered to in Australia. Attendance at a specialised clinic for HCM can improve the overall frequency of family screening, resulting in the detection of more cases of HCM. Improved identification of FDR with subclinical HCM can facilitate treatment strategies to prevent significant morbidity and mortality.

References


Comparison of not for resuscitation (NFR) forms across five Victorian health services

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Key words
resuscitation order, hospital communication system, decision-making, cardiopulmonary resuscitation, withholding treatment.

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Abstract

Background: Within Australian hospitals, cardiac and respiratory arrests result in a resuscitation attempt unless the patient is documented as not for resuscitation.

Aim: To examine the consistency of policies and documentation for withholding in-hospital resuscitation across health services.

Method: An observational, qualitative review of hospital policy and documentation was conducted in June 2013 in three public and two private sector hospitals in metropolitan Melbourne. Not for resuscitation (NFR) forms were evaluated for physical characteristics, content, authorisation and decision-making. Hospital policies were coded for alerts, definition of futility and burden of treatment and management of discussions and dissent.

Results: There was a lack of standardisation, with each site using its own unique NFR form and accompanying site-specific policies. Differences were found in who could authorise the decision, what was included on the form, the role of patients and families, and how discussions were managed and dissent resolved. Futility and burden of treatment were not defined independently. These inconsistencies across sites contribute to a lack of clarity regarding the decision to withhold resuscitation, and have implications for staff employed across multiple hospitals.

Conclusions: NFR forms should be reviewed and standardised so as to be clear, uniform and consistent with the legislative framework. We propose a two-stage process of documentation. Stage 1 facilitates discussion of patient-specific goals of care and consideration of limitations of treatment. Stage 2 serves to communicate a NFR order. Decisions to withhold resuscitation are inherently complex but could be aided by separating the decision-making process from the communication of the decision, resulting in improved end-of-life care.

Introduction

An attempt to resuscitate after cardiac or respiratory arrest is mandatory in Australian hospitals unless there is documentation in the patient’s notes of a decision not to attempt cardiopulmonary resuscitation (CPR). This paper explores the variation in documentation of decisions regarding CPR across five metropolitan health services.

Not for resuscitation (NFR) orders are written by treating medical officers and apply only to in-hospital arrests. As directives to withhold a medical treatment, the writing of NFR orders is influenced by the Medical Treatment Act (MTA) (1988 Vic),1 the Guardianship and Administration Act (G&A Act) (1986 Vic)2 and aspects of common law. These medical orders become more complex once capacity is lost and substitute decision-makers are involved (Levinson and Mills, unpublished data).

In Victoria, under common law a medical professional is under no obligation to provide treatment that is futile or burdensome, that being treatment that no longer offers any benefit to the patient, or where the burdens of providing the treatments outweigh the benefits.3 The Office of the Public Advocate (OPA) recognises that NFR orders reflect a clinical decision made by the medical practitioner not to attempt resuscitation because to do so would be futile or burdensome given the patient’s prognosis and consequently not in the patient’s best interests.4 The OPA policy highlights that as treatment is not being offered, patients or ‘persons responsible’ are not required to make a decision or to endorse the clinical decision not to provide CPR.

Patients or persons responsible are also not required to consent to attempted resuscitation. Emergency
procedures are defined as procedures required to save a patient’s life, to prevent serious damage to the patient’s health or to prevent the patient from suffering or continuing to suffer significant pain or distress, and are authorised in the absence of patient consent by the G & A Act. Although patients are not required to consent to resuscitation, their right to refuse is preserved where resuscitation is considered not to be futile.

To our knowledge, the only previously published review of NFR documentation and policies in Australian public hospitals was published in 2007. It found variation across hospitals in terms of standardised forms, policies (reflecting state and territory legislative differences) and patient information leaflets.

**Aim**

To review the NFR forms and associated policies of five Victorian public and private hospitals to assess alignment with the relevant policies of the OPA, the G & A Act and the MTA; to assess implied messages; and to provide a comparison of process between hospitals.

**Methodology**

The NFR documentation forms and policy documents were obtained by each site’s principal investigator as part of a larger study measuring the prevalence of NFR documentation in Melbourne public and private hospitals. The NFR forms were coded for:

- Physical characteristics
- Content
- Authorisation
- Decision

The policies underpinning each of the NFR forms were also examined and coded for:

- Alerts
- Futility and burden
- Managing discussions and dissent

The hospitals are identified by number, labelled 1 to 5. They include four private hospitals (within two branded groups) and three public health services. Hospital characteristics are displayed in Table 1 and a summary of the characteristics of the forms is shown in Table 2.

**Results**

**Physical characteristics**

Each hospital group had a standardised medical records coded NFR form identifiable by colour, as shown in Table 2. In both private groups, the form is called a ‘not for cardiopulmonary resuscitation’ form/order. The public hospital groups labelled their documentation ‘resuscitation management plan’, ‘limitation of medical treatment order’ or ‘consensus resuscitation plan’. All forms provide a designated place for the patient label and the date.

**Content**

Three forms (groups 1–3) provide a tick box for the option to withhold CPR. One of these (group 1) indicates that this refers to all of the following – chest compressions, intubation, ventilation and emergency vasoactive and antiarrhythmic drugs. Groups 4 and 5 provide an itemised checklist of components that allows for defibrillation and intubation to be itemised separately. The group 4 form also provides choice from a list of options that includes full resuscitation, resuscitation with modified Medical Emergency Team (MET) criteria, limited resuscitation or palliation.

Additional purposes served by the forms include an opt-in nomination for full resuscitation (group 4), limitations of other medical treatments (group 2), limitations to MET call or call criteria (groups 3 and 4), intensive care unit admission (groups 2, 3, 4 and 5) and transfer to an acute hospital (groups 2 and 4).

**Authorisation**

On groups 1 and 3 forms, the signed authorisation of a consultant medical officer is mandatory. In groups 2, 4 and 5, a medical officer or registrar’s signature is sufficient. It is clear the NFR is valid only for the current admission in all groups except group 2. In the latter case, the form is a limitation of treatment order that includes the option not to resuscitate.

**Decision**

Groups 1 and 2 forms have a specific section for documenting the reason for the limitation of treatment (CPR). Groups 3 and 4 forms include no reasons for the decision requested and the group 5 hospital form requests an assessment of patient status.

The group 1 form demands ownership of the decision to withhold CPR. The options provided are: medical decision; decision of the competent patient/Medical Power of Attorney (MPOA)/Guardian (Victorian Civil
Table 2 Summary of Not for resuscitation (NFR) form and hospital policy characteristics

<table>
<thead>
<tr>
<th>Form</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Coloured border</td>
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<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Coloured page</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Content</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR single entity</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR with components</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other purposes served by form</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full resuscitation preference</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limitation of medical treatment</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET call status</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission status</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authorisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registrar/medical officer</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Decision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for decision</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>Ownership of decision</td>
<td></td>
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<tr>
<td>Signature of competent patient</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discussion</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient and family</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical staff</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capacity/competency</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policy</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alerts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alerts sheet – patient history</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policy on futility and burden</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Best interests</td>
<td></td>
<td></td>
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<tr>
<td>Futility</td>
<td></td>
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<tr>
<td>Burden disproportionate to benefit</td>
<td></td>
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<tr>
<td>Non-beneficial</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Managing discussion/dissent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide CPR if requested</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>In conflict – withhold futile treatment</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>In conflict – seek second opinion</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>In conflict – advise senior staff</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>In conflict – no procedure offered</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

CPR, cardiopulmonary resuscitation; ICU, intensive care unit; MET, medical emergency team.

and Administrative Tribunal (VCAT); or decision of the family and the doctor agrees.

The group 2 form requests an assessment of competence and the availability of a substitute decision-maker (a MPOA, guardian or involuntary under the Mental Health Act). There is a section to indicate with whom the decision to withhold treatment was discussed, including competent patient, agent or guardian, family members, partners, nursing and allied health staff. If the patient is competent, there is an expectation that the patient is involved in the decision, and signs the form.

The group 3 form only requires the designation of the person with whom the decision was discussed, including the patient, and an assessment of patient competence. The group 4 form asks for the designation of persons with whom the decision was discussed, including ‘person responsible’, and a hierarchy of potential candidates to contact regarding treatment decisions. The group 5 form asks with whom the decision was discussed but does not require an assessment of patient competence.

Hospital policies and protocols

All hospital groups had a policy or protocol that supported the use of the not for attempted resuscitation decision. All stated that it was appropriate to withhold CPR if the provision of this treatment was considered futile or burdensome, and that in the case of an incompetent patient, only a person acting as MPOA or a guardian appointed by VCAT with powers to refuse treatment on behalf of the patient could refuse treatment.

Alerts

Alerts as to the presence of a NFR order vary across the hospitals, but all rely on manual systems. In group 1, coloured dots are affixed to the front of the patient’s history. In group 2, alerts are placed on the electronic medical record. In groups 3 and 5, designations are visible on the clinical alerts sheet at the front of the patient history, and in group 3, the electronic patient data system holds record of NFR status.
Protocol/policy specific to futility or burden

The groups varied in their policy definitions of and references to futility and burden. Group 1 policy states that a doctor may legally withhold CPR if it is considered futile or not in the patient’s best interests (defined as benefit of treatment outweighed by the burden), if treatment would not be successful in producing the desired effect or if it would fail to achieve important patient goals (such as survival to discharge).

The group 2 policy document provides some guidance regarding the assessment of clinically futile. It includes expectation of recovery, prognosis, expected distress and quality of life after the proposed treatment.

Groups 3 and 5 NFR policies state that NFR is appropriate on the grounds of futility (not defined) or if the medical practitioner is reasonably certain that the treatment would result in severe disability or a poor prognosis and that the ensuing distress would be disproportionate. The group 3 policy specifically refers in this situation to the frail elderly or dying patient. The group 4 policy defines futility as treatment that offers no reasonable hope of recovery or improvement or permanent long-term benefit.

Protocol/policy specific to discussion and dissent

In the event of difficulty or disagreement, all policies recommend that a second clinical opinion is sought or the matter referred to a senior nursing or medical administrator. The group 1 policy states that the clinician must take responsibility for medical decisions to limit treatment and aim to obtain agreement from the patient or family, adding obtaining agreement is not the same as consent.

Groups 2 and 3 policies state that the medical decision not to offer CPR should be discussed with the patient, when competent, and where appropriate, with family members. In the case of conflict between the clinician and the family, futile treatment should not be offered to the patient and a senior medical administrator notified.

Group 4 policy states that a specialist must refuse to provide treatment considered futile or detrimental to the patient’s health. There is no reference to a procedure for managing dissent among family members. Both groups 2 and 4 policies advise the patient or family to seek legal advice in the case of dissent.

Group 5 policy states that the decision not to offer CPR should involve the patient or patient’s MPOA, spouse, domestic partner, family and carers. It also states that if the patient requests CPR, this must be complied with. In the case of disagreement between the clinician and agent/guardian/family or friends, the medical director should be informed and comprehensive notes maintained.

Conclusion

There is a lack of standardisation of NFR documentation across these five Melbourne health services. For medical and nursing staff working across multiple sites, recognition of the presence of a NFR order is hampered by the diversity in the name, appearance and purpose of the form, the alert systems that highlight the presence of a form, its nomination and situation. We found the purpose of the forms differed across sites, with both opt-in and opt-out choices for resuscitation. The forms’ purpose is undermined by the sites that broke down the component parts of resuscitation. As in-hospital CPR usually refers to the whole of the resuscitation process (including required cardiac compressions, vasoactive drugs, bag and mask ventilation, intubation if required, and intravenous cannulation), this introduces a mixed message because CPR in the absence of the option to use intubation and defibrillation will compromise the success of the resuscitation attempt.

All hospital group policies make it clear that the doctor is not obliged to provide futile or burdensome care, yet there is no definition, medical or legal, of ‘futile’ or ‘burdensome’. Futile care is a matter of expert medical opinion given available evidence. The hospital policies provide circular guidelines on futile care by defining futility in terms of burdensome treatment, and burdensome treatment as care that is futile. Making a decision to withhold attempted CPR requires medical knowledge, and an understanding of the relevant law and clinical leadership. Only one form promotes the duality of the decision to withhold CPR as either a medical or patient-driven decision. This same form offers the option ‘decision of family and doctor agrees’, which should legally be classified as a medical decision.

All forms require completion of a section on persons with whom the decision was discussed. We believe this is commonly misinterpreted as a need for consent rather than consultation. Murphy describes the dilemma for the family of an incompetent patient when asked for consent to withhold CPR; in particular the burden that comes with the feeling of having allowed their loved one to die. We also believe that discussion with the patient of potentially withholding CPR forces both clinician and patient to acknowledge that death would not be unexpected, and this particular medical treatment has nothing to offer. This is challenging for many patients and doctors as it is contrary to the ideas that death and illness can be defeated and there is ‘always something that can be done’ associated with the feeling of having allowed their loved one to die.

In the event of dissent, the law is clear that the medical practitioner is not obliged to provide futile or burdensome care. The question surrounding futile and burdensome is
more easily clarified when the patient is competent. The more difficult situation arises when the patient is incompetent. Family members may uphold preservation of life against futile care. This may be driven by cultural factors or as a response to misapprehension that their consent is required, conferring responsibility upon them for the decision. The process for managing dissent should be clear, transparent, support the patient and family, and should recognise the treating physician’s judgement. The emotive nature of CPR discussions and the complexity created when dissent occurs can result in a reluctance to complete a NFR even when CPR is likely to be unsuccessful.

These forms send mixed messages about whether a NFR decision is a medical or a patient decision. On the one hand, it is important to preserve patient autonomy and involvement in shared decision-making. Yet if the medical officer is to be defended in the decision not to offer resuscitation on the grounds of medical judgement of futility, then freedom is required to make such a judgement.

The examined NFR forms are used both for recording the history of discussion regarding the patient’s treatment plan, goals of care and as a tool for in-hospital communication.

These considerations lead us to question the purpose of a NFR form. If it is for communication of a medical decision that resuscitation ought not to be attempted, the forms we reviewed cover too much information. It is not necessary to include reasoning behind withholding of resuscitation, patient preferences, other parties who know about and agree with this decision or which other medical treatments are not being offered.

If the form is seen as a record of a decision-making process, then the forms we reviewed cover too little information and should include aims of care, likelihood of successful treatment, patient wishes and goals, and the balance of burden and benefit of treatment.

We propose a review of NFR documentation, and advocate for a standardised two-stage process consisting of:

1. A discussion pathway that provides prompts for a discussion involving the clinician and patient/agent around goals of care and desired outcomes. It may lead to the view that limitations of medical treatment are appropriate (see Appendix S1).

2. Communication of a NFR order – a simple form containing only a tick box with date and signature of the medical officer, and reference to the patient progress notes where detail of the decision can be found (Appendix S2).

These two pieces of documentation should be uniform across state health services, unambiguous and reflect the relevant legislation. They should be filed in the same place in the medical record, have a uniform alert system, refer to competent full resuscitation and require uniformity of authorisation. We believe that such uniformity would not only improve documentation and communication of this important treatment decision, but may improve the process by which such a decision is reached.

References


Supporting information

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

Appendix S1 Discussion pathway.

Appendix S2 Not for cardiopulmonary resuscitation (CPR) order.
Prognostic value of systemic inflammation-based markers in advanced pancreatic cancer


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Key words
cancer, prognosis, biomarker, inflammation, chemotherapy, pancreas.

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Abstract

Background: The prognostic significance of various systemic inflammation-based markers has been explored in different cancers. These markers can be used to assist with decision-making in oncology clinics.

Aim: The aim of this study was to investigate the prognostic significance of three systemic inflammation-based factors: neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and modified Glasgow Prognostic Score (mGPS) in patients with advanced pancreatic cancer.

Methods: Data were collected retrospectively for advanced pancreatic cancer patients treated between 1 January 2008 and 31 December 2012 at the Royal Perth Hospital. The ratios were dichotomised as <5 versus ≥5 for NLR and <200 versus ≥200 for PLR. Modified Glasgow Prognostic Scores were scored as: mGPS ‘0’ = both C-reactive protein (CRP) and albumin normal, mGPS ‘1’ = elevated CRP < 10 mg/L and mGPS ‘2’ = both elevated CRP > 10 mg/L and albumin < 35 g/L. Univariate and multivariate analyses were carried out.

Results: Data were evaluable for 124 patients. Median survivals based on the three inflammation-based prognostic markers evaluated were: NLR <5 versus ≥5 = 8.5 months versus 2.6 months respectively (P = 0.0007; hazard ratio (HR) 1.81), PLR <200 versus ≥200 = 9.1 months versus 4 months respectively (P = 0.007; HR 1.64) and mGPS score 1, 2, 3 = 8.3 months, 9.6 months and 1.8 months respectively (P = 0.0004). Besides Eastern Cooperative Oncology Group performance status, NLR, PLR and mGPS were significant independent prognostic markers both on univariate as well as multivariate analysis.

Conclusions: Our findings suggest that the NLR, PLR and mGPS derived from routine blood tests can be used as clinically meaningful biomarkers to stratify advanced pancreatic cancer patients into different prognostic groups.

Introduction

Pancreatic cancer is the fifth most common cancer and the fourth leading cause of cancer-related mortality worldwide. Long-term outcome is poor with a median survival of 8.5–11 months for metastatic disease even with more aggressive therapy. Traditionally, the prognosis of pancreatic cancer has been correlated with various tumour characteristics including size, histological grade, lymph node metastases, vascular and perineural invasion and resectability. However, it has been increasingly recognised that progression of tumour and outcome is also influenced by a variety of host-related factors. Studies have shown that infiltration of tumour microenvironment by inflammatory cells play a crucial role in the development and progression of tumours.

A potential link between cancer and inflammation was first suspected in the ninth century on the basis of observations that tumours often arose at sites of chronic inflammation and in more recent times due to presence of inflammatory cells in tumour biopsy specimens. Chronic inflammation represents both an important etiologic factor in the development of pancreatic cancer as well as a reactionary process to pancreatic cancer. There is a proven association between pancreatic cancer and both the sporadic and hereditary forms of chronic pancreatitis. Therefore, there is great interest in evaluating the role of systemic inflammation in pancreatic cancer progression and prognosis.
The prognostic significance of a variety of systemic inflammation-based prognostic markers has been explored in different cancers such as lung, colorectal and gastro-oesophageal cancer. These include C-reactive protein (CRP) and albumin combined as the modified Glasgow Prognostic Score (mGPS),14 neutrophil-lymphocyte ratio (NLR),15,16 platelet-lymphocyte ratio (PLR),17,18 white cell count and CRP as the prognostic index (PI)19 and the combination of albumin and lymphocyte count in prognostic nutritional index (PNI).20 The aim of this study was to investigate the prognostic significance of three systemic inflammation-based factors, NLR, PLR and mGPS, in patients with advanced pancreatic cancer.

Methods

Data were collected retrospectively for advanced pancreatic cancer patients treated between 1 January 2008 and 31 December 2012 at the Royal Perth Hospital, Western Australia (WA). Information regarding baseline demographics including NLR, PLR and mGPS was collected from electronic patient records and was correlated with survival data obtained through Royal Perth Hospital Cancer Registry. Where CRP was not done at baseline, we utilised the CRP done within 3 weeks of initiation of treatment. The potential prognostic ratios were dichotomised as <5 versus ≥5 for NLR16 and <200 versus ≥200 for PLR18 as supported by literature. mGPS was scored as: mGPS ‘0’ = both CRP and albumin normal, mGPS ‘1’ = elevated CRP > 10 mg/L and mGPS ‘2’ = both elevated CRP > 10 mg/L and albumin < 35 g/L. The median cancer antigen 19-9 (CA19-9) level at initial presentation for the whole population was calculated, and results were dichotomised to less than median value compared with greater than the median to evaluate its prognostic significance.

Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death from cancer. Data censor date was 8 May 2013. Survival curves were compared using Kaplan–Meier methodology and the log–rank test. Cox regression methodology was used for univariate analysis. Variables with significant prognostic value on univariate analysis were further evaluated in the final multivariate Cox proportional hazards model. Two-sided P-values were computed. Statistical significance was defined as P < 0.05. Results of the Cox regression modelling are presented as hazard ratios (HR) and associated 95% confidence interval (CI). Statistical analyses were performed using the Stata 9.0 (StataCorp LP, College Station, TX, USA) and MedCalc Version 12.7.2 (MedCalc Software, Ostend, Belgium) statistical packages.

Results

A total of 136 patients with advanced pancreatic cancer was identified from the Royal Perth Hospital database. Data were missing for eight patients, two patients moved interstate or overseas, and two patients transferred care to a private hospital. Complete data were available for 124 patients who were included in the final analysis. Eighty-four patients (68%) had metastatic disease and 40 patients (32%) had locally advanced unresectable pancreatic cancer at time of diagnosis. The median age of the whole group was 68.5 years (range 35–90 years). Majority of the patients had a good performance status (89 (72%)) of ≤1. Adenocarcinoma was the most common histology (81%). Sixty-five patients (53%) had a pancreatic head primary. A biliary stent was inserted in 53 (43%) patients. Nearly two-thirds (78 (63%)) of patients were treated with at least one line of chemotherapy. Gemcitabine was the most commonly used chemotherapeutic agent in the first line setting. Twenty-six (21%) patients received second line chemotherapy, and 21 (17%) patients received radiotherapy for locally advanced pancreatic cancer. The median CA19-9 level at initial presentation for the whole group was 650 kU/L. Further demographic data have been summarised in Table 1.

The median follow-up time was approximately 12 months. At the time of data analysis, 114 (92%) patients had died. The median survival for the whole group was 6.1 months. Median survivals based on the three inflammation-based prognostic markers evaluated in this study along with CA19-9 were: NLR <5 versus ≥5 = 8.5 months versus 2.6 months respectively (P = 0.007; HR 1.81) (Fig. 1); PLR <200 versus ≥200 = 9.1 months versus 4 months respectively (P = 0.007; HR 1.64) (Fig. 2), mGPS score 0 or 1 versus 2 = 8.3 months, 9.6 months, 1.8 months respectively (P = 0.0004; HR 1.52) (Fig. 3) and CA19-9 < median versus > median = 7.2 months versus 3.1 months (P = 0.01; HR 1.58) (Fig. 4).

On univariate Cox regression analysis, the factors associated with significantly poor OS were: Eastern Cooperative Oncology Group (ECOG) performance status (P = 0.00; HR 1.47), absolute neutrophil count (P = 0.01; HR 1.13), NLR ≥ 5 (P = 0.001; HR 1.89), PLR ≥ 200 (P = 0.01; HR 1.68), mGPS (P = 0.001; HR 1.52), CA19-9 (> median of 650 kU/L) (P = 0.02; HR 1.53), albumin ≥ 35 g/L (P = 0.001; HR 0.42) and CRP ≥ 10 (P = 0.02; HR 1.53). Age, sex, absolute lymphocyte and platelet count were not associated with OS (Table 2). On multivariate analysis, ECOG performance status, absolute neutrophil count, NLR, PLR, mGPS, CA19-9 and albumin were found to be independent predictors of OS (Table 3). CRP was found not to be significant in the multivariate model (P = 0.15;
Patients with a NLR ≥ 5, PLR ≥ 200 or mGPS of 2 were more likely to have a poor ECOG performance status and a higher median CA19-9 level at diagnosis signifying a poor prognostic group. These patients were also less likely to receive chemotherapy compared with those with relatively lower NLR, PLR or mGPS presumably related to their poor functional status as a consequence of aggressive underlying disease biology (Table 4).

Discussion

Over the last decade, several studies have evaluated the role of various systemic inflammation-based prognostic markers in different cancers. Only a few studies have evaluated the role of NLR in pancreatic cancer. Out of these studies, three were done in patients with
operative pancreatic cancer\textsuperscript{15,17,21} and only two studies have evaluated the role of NLR in advanced pancreatic cancer patients.\textsuperscript{16,22} Our study is only the second study to evaluate the role of multiple systemic inflammation-based factors (NLR, PLR and mGPS) derived from routine blood tests in advanced pancreatic cancer patients. We also evaluated the prognostic significance of an elevated CA19-9 level at baseline. In our study, we found that patients with a NLR $\geq 5$ had a significantly worse OS (2.6 months) compared with patients with a NLR $< 5$ (8.5 months). Researchers have utilised different cut-off values for NLR, but a cut-off of 5 has been the most commonly used in medical literature evaluating cancer-related inflammation and different prognostic markers.\textsuperscript{16,16}

It is now widely recognised that outcomes in cancer patients are not merely dependent on tumour characteristics, but several host-related factors play an important role as well. Cancer-associated inflammation is a key determinant of cancer progression and survival.\textsuperscript{23} The exact pathogenesis of this is unclear but a marked systemic-inflammatory response is associated with patients’ nutritional, functional and immunological decline. Systemic-inflammatory response is also associated with alterations in circulating white blood cells including neutrophilia and relative lymphopenia.\textsuperscript{24,25} Elevated neutrophil count may aid in cancer progression by providing favourable environment for tumour growth. They are also involved in the release of various cytokines and chemokines including tumour necrosis

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**Table 2** Univariate analysis for overall survival

<table>
<thead>
<tr>
<th>Prognostic variables</th>
<th>P-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA19-9 &lt; median vs. &gt; median</td>
<td>0.02</td>
<td>1.53 (1.05–2.22)</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>$&lt;0.001$</td>
<td>1.13 (1.08–1.17)</td>
</tr>
<tr>
<td>Absolute lymphocyte count</td>
<td>0.11</td>
<td>0.82 (0.64–1.05)</td>
</tr>
<tr>
<td>Platelet count ($&lt;400$ vs. $\geq 400$)</td>
<td>0.68</td>
<td>0.91 (0.57–1.44)</td>
</tr>
<tr>
<td>NLR $&lt; 5$ vs. $\geq 5$</td>
<td>$&lt;0.001$</td>
<td>1.89 (1.30–2.76)</td>
</tr>
<tr>
<td>PLR $&lt;200$ vs. $\geq 200$</td>
<td>0.01</td>
<td>1.68 (1.14–2.46)</td>
</tr>
<tr>
<td>mGPS $0$, $1$, $2$</td>
<td>$&lt;0.001$</td>
<td>1.52 (1.21–1.90)</td>
</tr>
<tr>
<td>Albumin $&lt;35$ vs. $&gt;35$</td>
<td>$&lt;0.001$</td>
<td>0.42 (0.29–0.62)</td>
</tr>
<tr>
<td>CRP</td>
<td>0.02</td>
<td>1.53 (1.04–2.24)</td>
</tr>
<tr>
<td>ECOG</td>
<td>$&lt;0.001$</td>
<td>1.47 (1.18–1.82)</td>
</tr>
<tr>
<td>Age</td>
<td>0.77</td>
<td>1.00 (0.64–1.38)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.66</td>
<td>1.34 (0.98–1.82)</td>
</tr>
</tbody>
</table>

CA19-9, cancer antigen 19-9; CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; mGPS, HR, hazard ratio; modified Glasgow Prognostic Score; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.

**Table 3** Multivariate analysis for overall survival

<table>
<thead>
<tr>
<th>Prognostic variables</th>
<th>P-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA19-9 &lt; median vs. &gt; median</td>
<td>0.04</td>
<td>1.43 (1.01–2.16)</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>$&lt;0.001$</td>
<td>1.12 (1.08–1.17)</td>
</tr>
<tr>
<td>NLR $&lt; 5$ vs. $\geq 5$</td>
<td>0.02</td>
<td>1.60 (1.07–2.40)</td>
</tr>
<tr>
<td>PLR $&lt;200$ vs. $\geq 200$</td>
<td>0.02</td>
<td>1.58 (1.07–2.33)</td>
</tr>
<tr>
<td>mGPS $0$, $1$, $2$</td>
<td>0.01</td>
<td>1.41 (1.10–1.80)</td>
</tr>
<tr>
<td>Albumin $&lt;35$ vs. $&gt;35$</td>
<td>$&lt;0.001$</td>
<td>0.47 (0.31–0.72)</td>
</tr>
<tr>
<td>CRP $&lt;10$ vs. $\geq 10$</td>
<td>0.15</td>
<td>1.42 (0.89–2.01)</td>
</tr>
<tr>
<td>ECOG</td>
<td>0.002</td>
<td>1.43 (1.13–1.81)</td>
</tr>
</tbody>
</table>

CA19-9, cancer antigen 19-9; CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; mGPS, HR, hazard ratio; modified Glasgow Prognostic Score; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.
factor, interleukin (IL)-1 and 6 and pro-angiogenic factors like vascular endothelial growth factor (VEGF). An elevated NLR has also been associated with an increase in IL-17 and peritumoral macrophage infiltration. These findings suggest that an elevated NLR at least in part reflect an upregulated innate immune response.

An elevated NLR could also be as a consequence of relative lymphopenia rather than neutrophilia. Fogar et al. found that the levels of cluster of differentiation (CD)8+ suppressor T-lymphocytes were higher with relatively lower CD4+ helper T-cell levels in pancreatic cancer patients compared with controls and patients with chronic pancreatitis. Pancreatic cancer is also associated with a decrease in lymphocyte count through inhibitory cytokines including IL-10 and transforming growth factor beta (TGF-ß). Pancreatic adenocarcinoma is thought to be associated with the most significant lymphopenia compared with other gastrointestinal tumours. These findings suggest that dysregulation in lymphocyte-mediated immune response may also contribute to tumour progression and poor prognosis. However, in our study, it was the neutrophil count and not the lymphocyte count, which had a strong prognostic impact on OS as suggested by the Cox regression models. When NLR was used as a continuous variable and not dichotomised, it was only the neutrophil count that was consistently significant on multivariate analysis rather than the lymphocyte count and continuous NLR.

Thrombocytosis is caused by the stimulation of megakaryocytes secondary to release of pro-inflammatory mediators (mainly IL-1, IL-2 and IL-6). It is associated with poor prognosis potentially reflecting a higher platelet count as an indirect indication of exaggerated systemic-inflammatory response. Similar to neutrophils, platelets can release various growth factors like platelet-derived growth factor, platelet factor 4, TGF-ß, VEGF and thrombospondin. These growth factors can function as potent mitogens and stimulate tumour cells proliferation and adhesion to other cells leading to tumour growth and metastases. The prognostic significance of PLR in pancreatic cancer has been evaluated in only two studies where the preoperative PLR represents a significant independent prognostic marker in patients with resected pancreatic cancer. We found PLR to be an independent predictor of OS in advanced pancreatic cancer patients on both univariate and multivariate analyses.

Acute-phase proteins including CRP and albumin are sensitive and reliable markers of systemic-inflammatory response in cancer patients. The mGPS based on the combination of CRP and albumin is a well-established prognostic marker that has been evaluated and validated in over 60 studies involving both operable and inoperable cancers. In our study, we found that patient who had a low mGPS score of either 0 or 1 had a significantly better OS (8.3 months and 9.6 months respectively) compared with patients with a mGPS score of 2 (1.8 months; P = 0.0004, HR 1.52).

Pancreatic cancer has a poor prognosis and only a limited number of patients benefit from chemotherapy. Majority of the patients are over 60 years of age and have a poor functional status because of cancer-related cachexia and other symptoms related to tumour burden or secondary infective and inflammatory complications. It will be prudent to identify the group of patients who are least likely to benefit from systemic anticancer therapy so that they receive symptom-focussed care through early palliative care involvement and thereby avoiding them chemotherapy-related toxicity. The three prognostic factors that we investigated can be generated through routine blood tests with minimal costs involved and can assist clinicians with better prognostication and stratification of patients and help facilitate decision-making regarding systemic therapy. There is also emerging evidence that normalisation of NLR after first cycle of chemotherapy can be used as an early predictor of response to treatment. Manipulation of systemic inflammatory response through IL-6 blocking antibodies can be a potential therapeutic target in future in an attempt to dampen the exaggerated systemic-inflammatory response associated with certain cancers including pancreatic cancer.

There are several limitations of our study. This is a single institution retrospective analysis of a relatively small number of patients. Both CRP and neutrophils are markers of acute inflammation and can be elevated secondary to acute infection, which is relatively frequent in pancreatic cancer patients requiring stent insertion and are at potential risk of biliary sepsis. Having said that, all these patients were assessed by their treating clinicians before treatment, and it is assumed that they had no

### Table 4 Age, median CA19-9 at diagnosis and chemotherapy rates in advanced pancreatic patients according to NLR, PLR and mGPS subgroups

<table>
<thead>
<tr>
<th></th>
<th>NLR</th>
<th>PLR</th>
<th>mGPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>68</td>
<td>68.5</td>
<td>67</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1</td>
<td>35%</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>≥2</td>
<td>17%</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>80%</td>
<td>55%</td>
<td>70%</td>
</tr>
<tr>
<td>Median CA19-9</td>
<td>395</td>
<td>2350</td>
<td>560</td>
</tr>
</tbody>
</table>

CA19-9, cancer antigen 19-9; ECOG, Eastern Cooperative Oncology Group; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil-lymphocyte ratio, PLR, platelet-lymphocyte ratio.
evidence of active infection pre-chemotherapy. Steroids are routinely used in management of cancer-related cachexia, which is common in pancreatic cancer patients and this can lead to neutrophilia thereby confounding the results. It should also be noted that the univariate and multivariate models considered patients with locally advanced and metastatic pancreatic cancer as a single group.

Relatively poorer outcomes of patients with a higher NLR, PLR or mGPS could be related to lesser systemic therapy but it can be argued that they had rapidly progressive disease resulting in a poor functional status, hence a decision of not treating them with cytotoxic agents was made by their treating oncologists. An interesting point worth mentioning here is whether the high-risk patients (those with an elevated NLR, PLR and/or mGPS) should be treated with more aggressive therapy with newer treatment options including FOLFIRINOX (fluorouracil, folinic acid, irinotecan, oxaliplatin) and a combination of gemcitabine/abraxane compared with gemcitabine alone in order to improve potentially their outcomes. However, in our study, this group of patients seemed to have aggressive disease biology reflected by their poor performance status and elevated CA19-9 making their tolerability of these toxic regimens less likely. We also do not know at this point how accurately these inflammatory markers correlate with inflammation in tumour micro-environment at cellular level.

Conclusion

Our findings suggest that the NLR, PLR and mGPS derived from routine blood tests can be used as clinically meaningful biomarkers along with ECOG performance status to stratify advanced pancreatic cancer patients into different prognostic groups and assist with decision-making regarding systemic anticancer therapy. Further prospective evaluation of these prognostic markers is needed through clinical trials in order to validate our findings. The predictive value of normalisation of NLR and PLR after first cycle of chemotherapy in pancreatic cancer patients will be evaluated in future.

References


Outcomes of allogeneic haemopoietic stem cell transplants at a small New Zealand centre: does size matter?
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Key words
allogeneic haemopoietic stem cell transplant, survival, conditioning, reduced intensity transplantation.

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Abstract
Background: Reduced intensity conditioning (RIC) protocols for allogeneic haemopoietic cell transplants (HCT) have become commonplace treatments for patients with haematological disease, extending allogeneic HCT to older and less fit patients. There is a perception that centres treating larger numbers of patients have improved outcomes.
Aims: We wanted to examine whether outcomes for adult allogeneic HCT patients from our smaller centre were equivalent to those expected at larger centres internationally.
Methods: Clinical and laboratory data were collected on all patients who received allogeneic HCT during 2000–2012. Outcomes, including overall survival (OS) and progression-free survival, were compared between patients receiving myeloablative conditioning (MAC) and RIC protocols.
Results: One hundred and eighteen adult patients underwent allogeneic HCT with MAC (n = 51) or RIC (n = 67). The mean age of patients receiving MAC (35.8 years, range 18–56) was lower than those receiving RIC (48.4 years, range 19–64). Two-year OS was similar for MAC and RIC patients (66% vs 62%, P = 0.17), whereas 2-year progression-free survival was superior in MAC patients (63% vs 50%, P = 0.01) due to fewer relapses. OS was reduced in older patients irrespective of conditioning. Patients with chronic graft-versus-host disease had improved survival due to fewer relapses. OS was unaffected by HCT comorbidity index, donor, cell source or patient/donor cytomegalovirus status.
Conclusion: RIC protocols have resulted in long-term survival in many patients ineligible for MAC protocols. In our smaller centre, patient age but not conditioning intensity influenced survival, which was equivalent to reports from larger centres.

Introduction
Recent developments in allogeneic haemopoietic stem cell transplant practice have included the use of less myelosuppressive and/or immunosuppressive pre-transplant conditioning such that allogeneic transplants can now be offered to older and less fit patients. When introduced, it was hoped that such reduced intensity conditioned (RIC) allografts would retain the anti-leukaemic effect from graft-versus-leukaemia properties, that patients would have less early toxicity from the reduced conditioning, and that this would result in improved non-relapse mortality. General conclusions drawn are that RIC transplants can provide long-term survival and cure, and that a population of older patients, ineligible for myeloablative conditioned (MAC) allografts, can indeed cope with such conditioning. Graft-versus-leukaemia and graft-versus-host effects are both maintained.

Allogeneic transplantation is a complex procedure, and reported outcomes vary between studies due to heterogeneity in patient populations and conditioning schedules. As the field of transplantation has progressed, allografting centres have looked for consistency and good practice by reporting results to international registries. An increasingly sophisticated and costly accreditation process that includes quality management has been developed by the Foundation for the Accreditation of Cellular Therapy (FACT, www.factwebsite.org), which mandates minimum standards and undertakes inspection of centres providing this therapy to ensure adherence to these standards. One requirement for accreditation is that centres perform a minimum of 10 allogeneic transplants per year, although evidence is lacking whether smaller centres are less effective than larger centres. Treatment decisions are often based on estimates of outcomes from international registries and large single-centre series, but really what doctors and patients want to know is what they can expect in the centre where treatment is undertaken. To address these questions, we reviewed all adult patients who had received a first allograft from April 2000 to May 2012 at
our single centre, which is in the process of obtaining FACT accreditation.

Methods

Data collection

Christchurch Hospital is the referral centre for all patients receiving allogeneic transplant in the South Island of New Zealand. All patients who received a first allogeneic transplant at Christchurch Hospital between April 2000 and May 2012 were identified using an institutional database. Information on patient characteristics, diagnosis, treatment and treatment outcomes was obtained from electronic and written hospital records, and used to calculate the European Bone Marrow Transplant (EBMT) Group risk score, and the haemopoietic cell transplant comorbidity index (HCT-CI). All patients were followed up until December 2012. The number of patients receiving transplants in Australia between 2006 and 2011 was obtained from the Australasian Bone Marrow Transplant Recipient Registry, which has recorded more than 95% of all HCT activity in Australia since 1992 and in New Zealand since 1998.

Treatment and evaluation of response

Patients were selected for transplant and were treated according to EBMT Group and other relevant guidelines where available. Conditioning regimens were defined, according to published consensus criteria, as myeloablative, reduced intensity or non-myeloablative. For this analysis, the latter two groups were combined and were both termed RIC. Post-transplant graft-versus-host disease (GVHD) prophylaxis was with a calcineurin inhibitor and a short course of methotrexate or mycophenolate in the majority of patients. Patient outcomes, including all-cause mortality, non-relapse mortality, relapse incidence, and occurrence of acute or chronic GVHD requiring treatment, were measured. Overall survival (OS) was calculated from the date of transplant until death or last follow-up. The non-relapse mortality rate (NRM) and relapse incidence were calculated from the date of transplant until death in remission or relapse respectively. Progression-free survival (PFS) was calculated from the date of transplant until the date of relapse or death from any cause.

Statistical analysis

Patients were analysed according to the intensity of the conditioning regimen. Other comparisons were made between groups based upon age or other pre- or post-transplant variables, including donor type, source of stem cells, EBMT score, HCT-CI, cytomegalovirus (CMV) risk status and occurrence of chronic GVHD. Statistical comparisons of continuous and categorical variables between groups were made with Student’s t-test and chi-squared test respectively. Time-dependent outcomes, including OS, PFS, relapse incidence and NRM rate, were estimated using the Kaplan–Meier method. The log–rank test and a Cox’s model were used for analysis of risk factors for time-to-event variables. Hazard ratio and 95% confidence interval were reported. Differences were considered to be statistically significant if the corresponding P-value was ≤0.05. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA)

Results

Patient characteristics and treatment received

One hundred and eighteen patients received a first allogeneic transplant during the study period of 2000–2012. The South Island is home to one million people, thus the allogeneic transplant rate was 1 per 100,000, significantly lower than the allogeneic transplant rate in Australia over the same period, which was approximately 2.1 per 100,000 (P < 0.01). Characteristics of patients receiving MAC and RIC conditioning regimens are summarised in Table 1. The median age of patients who received allogeneic HCT was 46 years. As a generalisation, RIC was preferred for older (>45 years) or previously autografted patients. Therefore, the mean age of patients was lower in the MAC than RIC group (35.8 vs 48.4 years; P < 0.01), and since age is included as a component of the EBMT score, that score was lower in MAC patients (2.35 vs 3.45; P < 0.01). Seven (6%) of all patients were older than 60 years. A programme of tandem autologous and RIC allogeneic transplant for patients with myeloma in first response who had matched sibling donors (MSIB) was active during this period, and this is reflected in the different diagnoses seen within the two treatment groups. The source of haemopoietic stem cells was more commonly bone marrow as opposed to peripheral blood stem cells (PBSC) for MAC patients than for RIC patients. Both groups of patients were equally likely to receive haemopoietic stem cells from matched unrelated donors (MUD), all of whom were 8/8 high-resolution matched with their recipient at HLA-A, HLA-B, HLA-C and HLA-DRB1. Three patients had transplants from umbilical cord blood or haploidentical donors. MAC most commonly consisted of cyclophosphamide and total body irradiation, or busulphan and cyclophosphamide. RIC consisted of fludarabine and melphalan with or without alemtuzumab, or particularly for patients with myeloma, fludarabine and low-dose total body irradiation, or for patients with aplastic anaemia, cyclophosphamide only.
GVHD prophylaxis was usually cyclosporine and methotrexate in MAC patients but was more varied in RIC patients, for whom tacrolimus and mycophenolate were also used, particularly in the myeloma treatment protocol. One or more donor lymphocyte infusions were administered for incomplete chimaerism or relapse to one MAC patient and 22 (33%) RIC patients.

### Outcome of treatment by patient and transplant characteristics

The median times to neutrophil (neutrophils >0.5 × 10^9/L) and platelet engraftment (platelets >20 × 10^9/L) were 16 days (range 0–29) and 11 days (range 0–143) respectively. Neutrophil and platelet engraftment were significantly delayed (P = 0.01) in patients receiving BM when compared with PBSC.

OS, PFS, relapse incidence and non-relapse mortality (NRM) rates for patients who received MAC or RIC are shown in Figure 1. The relationships between type of conditioning, donor and transplant characteristics, and OS and PFS, are presented in Table 2. OS of patients receiving MAC and RIC was not different (2-year OS 66% vs 62%, P = 0.17) (Fig. 1a), but PFS was poorer in those who had RIC (2-year PFS 63% vs 50%; P = 0.01) (Fig. 1b), due to a higher incidence of relapse (2-year relapse incidence 21% vs 38%, P < 0.01) (Fig. 1c). NRM at 2 years was 19% in patients who received either MAC or RIC (Fig. 1d). There was no statistically significant difference between patients treated with MAC or RIC in either acute GVHD (MAC 61% vs RIC 43%) or chronic GVHD (MAC 59% vs RIC 64%) requiring treatment. Furthermore, there was no difference in incidence of acute or chronic GVHD between those patients who received PBSC or bone marrow grafts.

In order to examine the effect of age on outcome, patients were divided into age terciles (>36 years, 36–50 years, >50 years). Patients in the younger and intermediate age terciles had similar outcomes with significantly better OS than patients in the older tercile (Fig. 2a). In addition, increasing age adversely influenced PFS, as did increasing EBMT score, as shown in Table 2. In contrast, HCT-CI, CMV risk, type of donor and source of stem cells had no significant effect on OS or PFS. Patients who developed chronic GVHD requiring treatment had significantly improved OS and PFS (Table 2).

### Outcome of treatment depending on interaction among conditioning, age and diagnosis

Older patients tended to receive RIC (Table 1). In order to explore the effect of age independent of conditioning intensity, transplant outcome was examined for each age
tercile in each conditioning group. Patients in the youngest age tercile, who mainly had MAC (72% MAC, 28% RIC), had equivalent OS irrespective of conditioning intensity (Fig. 2b). Patients in the middle age tercile, which contained similar proportions of MAC and RIC patients (45% MAC, 55% RIC), also had no difference in OS (Fig. 2c). Patients in the oldest tercile, which mainly comprised RIC patients (13% MAC, 87% RIC), had poorer OS than either of the other two terciles, which was not different for MAC or RIC (Fig. 2d). In the same way, when PFS and relapse incidence were examined within each age tercile according to intensity of conditioning, there was no difference in outcome between patients of the same age tercile who received either MAC or RIC (data not shown).

Diagnoses between conditioning groups were varied (Table 1), and in general there were insufficient patients with the same diagnosis in each conditioning group to

Table 2  Influence of patient and transplant characteristics on OS and PFS

<table>
<thead>
<tr>
<th>Prognostic factors for OS</th>
<th>Prognostic factors for PFS</th>
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<tbody>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td><strong>Hazard ratio (95% CI)</strong></td>
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<tr>
<td><strong>P-value</strong></td>
<td><strong>P-value</strong></td>
</tr>
<tr>
<td>Age (&lt;50 years vs &gt;50 years)†‡</td>
<td>0.36 (0.20–0.62)</td>
</tr>
<tr>
<td>EBMT score (≤3 vs &gt;3)§</td>
<td>0.53 (0.30–0.94)</td>
</tr>
<tr>
<td>HCT-CI score (≤2 vs &gt;2¶)</td>
<td>0.77 (0.44–1.35)</td>
</tr>
<tr>
<td>CMV risk (negative vs positive)</td>
<td>1.32 (0.76–2.31)</td>
</tr>
<tr>
<td>Conditioning (MAC vs RIC)</td>
<td>0.66 (0.37–1.19)</td>
</tr>
<tr>
<td>Donor (MSIB vs MUD)‡</td>
<td>0.78 (0.42–1.47)</td>
</tr>
<tr>
<td>Cell source (bone marrow vs PBSC)</td>
<td>0.66 (0.32–1.39)</td>
</tr>
<tr>
<td>Chronic GVHD (no treatment vs treatment)</td>
<td>2.20 (1.19–4.07)</td>
</tr>
</tbody>
</table>

†Hazard ratios greater than or less than 1.0 indicate higher or lower risk, respectively, for death (OS) or relapse or death (PFS), for the first category listed. ‡79 patients ≤50 years, 39 patients >50 years. §83 patients EBMT score ≤3, 34 patients EBMT score >3. ¶74 patients HCT-CI score ≤2, 44 patients HCT-CI score >2. CI, confidence interval; GVHD, graft-versus-host disease; MAC, myeloablative conditioning; MSIB, matched sibling donor; MUD, matched unrelated donor; OS, overall survival; PBSC, peripheral blood stem cell; PFS, progression-free survival; RIC, reduced intensity conditioning.

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compare their outcomes by conditioning. The most frequent diagnosis in both groups was acute myeloid leukaemia (AML) in first remission (13 such patients treated with MAC, 9 with RIC). For patients with this diagnosis, irrespective of conditioning group, there was no difference in 2-year PFS (69% vs 55%, respectively, \( P = 0.64 \)). The group of patients who received RIC contained many with myeloma who have been reported previously. They received allogeneic HCT as part of first-line therapy, and on relapse often responded well to further lines of therapy with prolonged survival, to the extent that they may have favourably influenced OS for the whole group of RIC patients. This possibility was explored by repeating the analyses for OS and PFS having excluded patients with myeloma. Patients who received MAC now had an improved 2-year OS over those who received RIC, of borderline significance (66% vs 49%; \( P = 0.06 \)), because although the relapse rate was unchanged (21% vs 44%, \( P = 0.02 \)), relapsed patients (without myeloma) had short post-relapse survival.

**Discussion**

Publication of standards in cellular therapy by FACT has emphasised the importance of annual transplant numbers in maintaining expertise in larger centres. The fifth standard, which requires a minimum of 10 allogeneic transplants per year for accreditation, has been developed in highly populated parts of Europe and North America, and may be more difficult to achieve in Australasia without providing treatment exclusively in large centres far from a patient’s home. For example, our centre provides all haemopoietic transplant services for a population of 1 million living in an area larger than England – where there are over 40 centres – from a city with a population smaller than that of any in Australia where allogeneic HCT provision is located. Our centre just meets the current FACT activity standard. Thus, while seeking FACT accreditation, we wanted to confirm as far as possible that our patients’ outcomes have been as satisfactory as those that might have been predicted – information of equal or greater importance to patients and ourselves than simple compliance with FACT standards. In this study, we report the outcomes of adult patients from a single institution who underwent their first allogeneic stem cell transplant since RIC protocols were introduced in 2000, focusing on any differences between myeloablative and reduced intensity conditioning.

Allograft conditioning intensity has been examined in large, multicentre studies and our finding that there was no difference in OS between patients receiving either conditioning approach is in keeping with such studies and
confirms that older, frailer patients can benefit from RIC allogeneic transplantation. Nonetheless, age remained the major prognostic factor, with our patients in the upper age tercile having the poorest outcomes despite most receiving RIC. In the mid-tercile, patients were equally likely to receive MAC or RIC, but there was no difference between either conditioning regimen for OS, which was identical with that seen in patients from the younger tercile. These findings suggest that for many malignant haematological diseases, the graft-versus-malignancy effect is of equal or greater importance for disease control, rather than the cytotoxic effect provided by conditioning.

We are following international trends and using an increased proportion of unrelated donors. When first introduced, results of allogeneic HCT from unrelated donors were distinctly poorer than those from matched sibling donors. With time, and with better matching, results of MUD transplant have improved and appear equivalent for most diagnoses, with any increased non-relapse mortality being offset by increased graft-versus-malignancy effect. All our MUD were HLA 8/8 or better matches. We found no correlation between outcome and whether the donor was an HLA identical sibling or well matched but unrelated. Over time, there has also been a shift to increasing use of PBSC as donor cell source because neutrophil and platelet recovery are accelerated, and there may be more graft-versus-malignancy effect and consequently reduced relapse incidence. We found quicker recovery of cell counts in our patients who received PBSC, but otherwise there was no change in outcome. This is in keeping with a recent large randomised study in which increased GVHD in PBSC recipients was matched by increased graft failure in bone marrow recipients. In the past, CMV has been a major cause of morbidity and mortality after allogeneic HCT.

In our patients, CMV PCR was used to monitor serially at-risk patients and treatment with ganciclovir was started early. This approach would seem to have been effective in that CMV status was not a statistically significant prognostic factor for OS.

The outcome of transplantation for any individual patient will clearly depend on patient, disease and transplant factors. Several schemes are in use to predict outcome of transplant. EBMT score combines patient age, disease aspects (time since diagnosis, disease stage) and transplant aspects (donor type, donor–recipient gender combination). This scoring system is easy to use and predicted OS in 56,000 patients with a broad range of haematological disorders treated with MAC or RIC before 2005. Our patients as a whole, with an average EBMT score of 2.35–3.45, had similar or better outcomes than those reported for patients with EBMT score 3 in that study who had 2-year OS and NRM of around 55% and 30% respectively. We found that high EBMT score, >4, predicted for a poorer outcome. HCT-CI captures and grades patient comorbidities, and has been shown to be valuable in predicting outcome mainly by an effect on NRM. In proposing this index, the authors showed that 2-year OS and NRM of patients with HCT-CI scores 1–2 were 60% and 21%, which is similar to outcomes for all our patients, who had a mean HCT-CI score of 1.86. We were not able to demonstrate any significant difference in outcome according to HCT-CI scores, perhaps because of small numbers of patients with higher scores. Our patients had heterogeneous diagnoses, which clearly made any attempt to correlate outcome to disease impossible. Recently, a prognostic system that defines four groups based on disease diagnosis and disease status has been shown to be useful and applicable for patients with a wide range of diagnoses irrespective of transplant procedure.

We did not have sufficient data, specifically cytogenetic data, to apply this classification to our patients, but note that our patients’ 2-year OS was equivalent to patients of intermediate risk in this scheme. Whereas it is well recognised that outcomes following MAC HCT are improved in larger centres, the efficacy of reduced intensity transplants in smaller centres is less clear, but centre size effects have been described. Thus, in a recent EBMT report, centres undertaking fewer than 15 RIC procedures between 2001 and 2007 reported, for patients with AML in first complete remission, a significantly lower PFS of 43% vs 55% for those centres undertaking more. Our centre would qualify as a larger centre according to this study, and the corresponding PFS among our patients with AML in first remission was also 55%.

Non-relapse mortality was low and possibly reflects a conservative approach to patient selection and avoidance of very high-risk patients. For example, although the age of patients receiving transplants has increased dramatically through the use of RIC programmes, none of our patients transplanted from unrelated donors was older than 60 years and their median age was 43 years compared with international figures during 2003–2006 of 12% and 47 years respectively. Transplant activity in the South Island of New Zealand is low compared with that elsewhere in Australasia. The reasons for this cannot be determined from the present study. The New Zealand transplant programme is publicly funded through taxation and is free at the point of care. In a public health system with finite resources, there is likely to be targeting of resources where they are most likely to be effective.

There are unavoidable limitations in any study such as this, which has sought simple and useful predictors of outcome by examining a modest number of patients of all ages in different states of health, with heterogeneous diagnoses at various stages, treated with allogeneic HCT.
after a great (perhaps too great) variety of treatment regimens for conditioning and GVHD prophylaxis. Nevertheless, we believe that we have acquired useful information that will inform local practice, and provides reassurance to our patients that, although our centre is small, the results of allogeneic transplantation are as good as those that can be expected elsewhere.

**Conclusion**

RIC protocols have enabled us to extend allogeneic HCT to older patients who would not have been fit enough to receive MAC protocols. The choice of protocol did not influence the outcome in our patients, whereas age >50 years remained the most important determinant of poorer PFS. These results are equivalent to those reported from large transplant centres.

**Acknowledgements**

The authors thank their colleagues in the haematology units in the South Island of New Zealand for their constant care of patients receiving allogeneic haemopoietic stem cell transplants.

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**BRIEF COMMUNICATIONS**

**Rhabdomyolysis in association with simvastatin and dosage increment in clarithromycin**

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**Key words**
drug interaction, clarithromycin, simvastatin, rhabdomyolysis, troponin.

**Abstract**

Clarithromycin is the most documented cytochrome P450 3A4 (CYP3A4) inhibitor to cause an adverse interaction with simvastatin. This particular case is of interest as rhabdomyolysis only occurred after an increase in the dose of clarithromycin. The patient developed raised cardiac biomarkers without any obvious cardiac issues, a phenomenon that has been linked to rhabdomyolysis previously. To date, there has been no reported effect of rhabdomyolysis on the structure and function of cardiac muscle. Clinicians need to be aware of prescribing concomitant medications that increase the risk of myopathy or inhibit the CYP3A4 enzyme. Our case suggests that troponin elevation could be associated with statin induced rhabdomyolysis, which may warrant further studies.

An 83-year-old Caucasian woman presented as an emergency admission with a short history of diffuse muscle pain and bilateral leg weakness. She had been started on clarithromycin 250 mg Twice a day (BD) by her respiratory physician for 3 months for recurrent chest infections as well as for the treatment of asthma, and 1 month prior to admission the dosage was increased to 500 mg BD. The week prior to admission she felt unwell and complained of muscle ache and developed leg weakness. Her myopathy progressed to the point where she was unable to move without assistance and eventually became bedridden 3 days prior to admission.

The patient’s medical history included severe chronic obstructive pulmonary disease on home oxygen, cardiac bypass surgery, acute coronary syndrome, iron deficiency anaemia and hyperparathyroidism. Her medications prior to admission included simvastatin 80 mg + ezetimibe 10 mg and clarithromycin 500 mg BD; the other medications were aspirin, seretide 250 inhaler, ventolin inhaler, tiotropium, propylthiouracil, metoprolol, ramipril and nitrolingual spray.

On admission, her vital signs were normal and pertinent findings on physical examination included mild end expiratory wheeze and bilateral ankle oedema with tenderness over the right flank with no bony tenderness. The patient demonstrated difficulty sitting to stand, with a 3/5 bilateral hip flexor motor strength and a 3/5 motor strength in shoulder and elbow flexor muscle groups.

Significant laboratory findings included serum creatine kinase 20 268 U/L (ref range 30–150), high-sensitive troponin T 158 ng/L (ref range <14), urea 9.3 mmol/L (ref range 3.5–10.0), creatinine 96 umol/L (ref range 45–95), potassium 3.4 mmol/L (ref range 3.5–5.5), sodium 139 mmol/L (ref range 135–145), alanine transaminase 328 U/L (ref range 135–145), gamma glutamyl transpeptidase 328 U/L (ref range 5–30), gamma glutamyl transpeptidase 70 U/L (ref range 5–35), calcium 2.25 mmol/L (ref range 2.20–2.60), phosphate 0.67 mmol/L (0.8–1.5 mmol/L) and magnesium 0.73 mmol/L (ref range 0.70–1.10). The patient’s urine was red/brown in colour, and myoglobin was detected. Her creatinine clearance was estimated at 40 mL/min.

On hospitalisation, the clarithromycin was reduced to 250 mg BD and the simvastatin was ceased, which she had been taking regularly for the past 5 years. The patient was treated with intravenous fluids, and a strict fluid balance was kept. She had daily electrolytes monitoring and replacement. An autoantibody screen (Extractable nuclear antigen including Anti Jo-1, Anti-nuclear antibody, Anti-neutrophil cytoplasmic antibody, Rheumatoid factor) detected no abnormality. The patient’s serum
Creatine kinase (CK) continued to rise and peaked at 23,246 U/L on day 5 and the high sensitivity troponin T continued to be elevated despite having no cardiovascular symptoms, electrocardiogram or echocardiogram changes (see Fig. 1). The patient’s renal function remained within normal limits throughout her admission, and she only required potassium replacement to maximise muscle recovery and function.

A Tc-99m Methylene-diphosphonate (MDP) nuclear scan was performed to assess the extent of rhabdomyolysis and specific area of uptake, which showed prominent soft tissue radiotracer uptake in the lower limbs, particularly in the hamstring muscles and the right shoulder girdle (see Fig. 2).

On day 8, the serum CK fell below 1000 U/L, and we decided not to do a muscle biopsy. Physiotherapy treatment was provided, and the patient regained most of her premorbid functions. She was therefore discharged home 15 days after hospital admission.

The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors are widely used for management of dyslipidaemia as well as in primary and secondary prophylaxis of cardiovascular and cerebrovascular events. Although well tolerated, they are associated with a small risk of rhabdomyolysis (0.2 per 1000 person-years). The risks of rhabdomyolysis are increased by other factors, for example high dosing, impaired renal or hepatic function, diabetes, hypothyroidism, advanced age and recent surgery.

The HMG-CoA reductase inhibitors are at risk of potential interaction with concurrent use of cytochrome P450 inhibitors. The risk for interaction is highest for statins metabolised by CYP3A4, the most abundant isoenzyme, which metabolises most drugs undergoing the cytochrome P450 pathway. The interaction between clarithromycin and simvastatin is the most documented of any of the potential CYP3A4 inhibitors. In our patient, most of the less common causes of myopathy had been excluded, and there was a high probability that it was related to the interaction of the simvastatin and clarithromycin, especially given the insidious onset. The use of the Naranjo probability scale indicated that the myositis was probably the result of an interaction between simvastatin and higher dose of clarithromycin in our patient.

The importance of this case and its uniqueness is the fact that the patient has already been on simvastatin and low-dose clarithromycin for 3 months without any adverse event. It was only when the dose of clarithromycin was increased to 500 mg BD, which caused interaction with simvastatin. This observation has not been reported in the literature previously.

From the reports, patients’ CK results normalised (median 17 days) after simvastatin was ceased and intravenous hydration given. Other treatment options discussed were two patients had haemofiltration and sodium bicarbonate and one patient had mannitol. One patient died subsequently following admission for rhabdomyolysis as a result of severe hypocalcaemia and then had a ventricular tachycardia/respiratory arrest, leading to anoxic brain injury, and he eventually died of a hospital-acquired infection. Based on our review of the literature, we suggest that conservative treatment with intravenous hydration seems to be the most effective treatment without the risk of infection (with haemofiltration) or hypocalcaemia (given sodium bicarbonate).

Studies have shown that the incidence and severity of myopathy is dose related with each type of HMG-CoA reductase inhibitor, as cases with simvastatin are at higher maintenance dose (e.g. 80 mg) compared with lovastatin (40 mg) when adverse effects have been documented, such as rhabdomyolysis. There has been recent evidence from meta-analyses that suggest that 80% of the lipid-lowering effect of statins occurs at half the maximal statin dose. The Food and Drug Administration in USA has warned that the maximum dose of...
Simvastatin should be 40 mg – without any concomitant therapies that may reduce clearance. Alternatives to simvastatin such as pravastatin/fluvasatin that avoid phase 1 metabolism through CYP3A4 enzyme would be a good substitute if a patient requires indefinite treatment with a CYP3A4 inhibitor or in high-risk patients, for example, renal transplant patient.

In our patient we found a troponin (cTnT) rise with no clear clinical cardiovascular signs that pointed to an acute coronary syndrome. A few studies have indicated that the phenomenon of cTnT increases in the absence of cardiovascular disease can occur. This may challenge the specificity of the TnT test in patients with myopathies and may confound detection of patients with true cardiovascular disease. Clinicians need to keep this in mind when evaluating patients for cardiovascular disease who may have underlying skeletal myopathy, albeit subtle, especially when their clinical presentations are atypical and where increases of cTnT seem to stand alone indicating cardiovascular involvement. Some authors have thought that the re-elevations of TnT levels in the sub-acute phase of rhabdomyolysis relate to the re-expression of TnT isoform during the regeneration of skeletal muscle. This expression is perhaps triggered by inflammatory changes or severe damage occurring within the skeletal muscle. There has, to date, been no report on the specific effect of rhabdomyolysis on cardiac muscle and the function of cardiac muscle. Our case suggests that troponin elevation could be associated with statin induced rhabdomyolysis.

The exposure to higher doses of statins or higher potency statins does not increase their effectiveness in older patients, but does increase the risk of adverse effects, such as myopathy and cognitive impairment. Applying the evidence for statins to older individuals requires frequent review by prescribers, pharmacists and nurses, and there needs to be a careful balanced approach for therapeutic goals and the deciding of potential benefits and harms. A suggestion for consideration is a mandate for a lower dose of simvastatin in the elderly.

Figure 2  Tc-99m MDP nuclear scan in our patient with rhabdomyolysis showing increased uptake in the hamstring muscles and right shoulder girdle (arrows).
that is safer to avoid adverse effects. This case highlights the difficulty of avoiding adverse drug reactions especially an interaction that is so well known. For this patient, we consulted a pharmacist to review the medication with a plan to update the patient records and notify the general practitioner and community pharmacy. For future prescribers, there may need to be more education required and safer electronic systems put in place to avoid adverse events and highlight specific drug alerts.

Rhabdomyolysis is a rare but significant adverse effect that causes high morbidity and mortality particularly in older patients with multiple co-morbidities. We reported a case of rhabdomyolysis associated with increased dose of clarithromycin in a patient who had tolerated high-dose simvastatin with low-dose clarithromycin. It is important that clinicians recognise the risk associated with the interaction between simvastatin and clarithromycin. If only a short course of CYP3A4 inhibitor is required, then we recommend to briefly interrupting HMG-CoA reductase inhibitor therapy. Our patient had a non-specific troponin rise in the context of rhabdomyolysis; in our review of the literature, we could not find any report or study that commented on the effect of rhabdomyolysis on cardiac muscle specifically. Given that skeletal muscle and cardiac muscle share similar molecular properties, the effect of HMG-CoA reductase on cardiac muscle might be similar to skeletal muscle. Further studies to examine this relationship might be useful.

References
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening multi-system disorder characterised by the delayed onset of fever, rash and internal organ involvement following the administration of a drug.1 Drugs associated with DRESS syndrome include aromatic anticonvulsants, sulfonamides, minocycline, antiretrovirals (nevirapine and abacavir in particular), lamotrigine and allopurinol.2 We report three definite cases of vancomycin-associated DRESS syndrome occurring and review the literature regarding this syndrome.

Patient 1 was a 24-year-old man who presented with Corynebacterium jeikeium septic arthritis and was commenced on vancomycin. After 3 weeks, he developed a generalised pruritic maculopapular rash, involving his face, trunk and limbs with associated arthralgias, fever up to 40°C and deranged liver function tests (LFT), which peaked with an alanine aminotransferase (ALT) of 270 U/L and a gamma-glutamyl transpeptidase (γGT) of 255 U/L (Table 1). There was mucosal involvement with sore throat, mouth ulceration and desquamation of his lips. He also developed cervical lymphadenopathy with significant facial oedema. He had a peripheral eosinophilia that peaked at 2.9 × 10⁹/L. Vancomycin was ceased and changed to daptomycin. Additionally, he was treated with intravenous and topical corticosteroids and antihistamines. His intravenous steroids were converted to a tapering dose of prednisolone. He experienced significant resolution of his symptoms, but after a rapid wean of steroid therapy, he re-presented with a rash, associated with recurrence of his eosinophilia, which peaked at 1.2 × 10⁹/L. He was re-treated with intravenous steroids for 24 h, followed by a much slower taper of his oral corticosteroids.

Patient 2 was a 48-year-old woman treated for L5/S1 osteomyelitis with vancomycin. Two weeks into therapy, she developed a pruritic maculopapular rash, spreading from her face to arms, legs and torso. She also developed pronounced facial angioedema, with odynophagia, fevers and chills but no lymphadenopathy. She presented to the emergency department and was noted to have a temperature of 39.8°C. A patchy purpuric rash was noted on the limbs with confluent erythema over the torso. A peripheral blood eosinophilia was measured at 2.9 × 10⁹/L, which later peaked at 6.0 × 10⁹/L. Abnormal LFT were noted, with an ALT 337 U/L, aspartate aminotransferase (ALT) of 270 U/L and a gamma-glutamyl transpeptidase (γGT) of 255 U/L (Table 1). There was mucosal involvement with sore throat, mouth ulceration and desquamation of his lips. He also developed cervical lymphadenopathy with significant facial oedema. He had a peripheral eosinophilia that peaked at 2.9 × 10⁹/L. Vancomycin was ceased and changed to daptomycin. Additionally, he was treated with intravenous and topical corticosteroids and antihistamines. His intravenous steroids were converted to a tapering dose of prednisolone. He experienced significant resolution of his symptoms, but after a rapid wean of steroid therapy, he re-presented with a rash, associated with recurrence of his eosinophilia, which peaked at 1.2 × 10⁹/L. He was re-treated with intravenous steroids for 24 h, followed by a much slower taper of his oral corticosteroids.

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significantly improved. Oral steroids were gradually weaned in the outpatient clinic.

Patient 3 was a 59-year-old man with a methicillin-resistant Staphylococcus aureus (MRSA) wound infection on his right leg, treated with vancomycin for 3 weeks then converted to rifampicin and fusidic acid. Within 1 day of commencing the oral antibiotics, he presented with fevers, facial angioedema and an itchy erythematous rash affecting his face, arms and torso. The rash had appeared on his scalp during vancomycin therapy but had not been reported. Following re-admission to hospital, the eosinophil count peaked at 10.4 $\times$ $10^9$/L. Atypical lymphocytosis was noted on peripheral blood smear. LFT were abnormal with an elevated ALT of 113 U/L. Treatment consisted of oral and topical corticosteroids with antihistamines for control of his severe pruritus.

For all three patients, molecular testing for HLA alleles was performed, but no common HLA alleles were identified to suggest an association, but patient numbers were small.

DRESS syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), was first described in 1996. The liver, kidneys, heart and lung are most commonly affected and mortality rates of up to 10% have been reported. The rash is usually diffuse and maculopapular, although other presentations, such as vesicles, bullae, pustules, cheilitis, purpura, target lesions and erythroderma have also been described. Facial angioedema may be striking. Peripheral blood eosinophilia is usually present, and atypical lymphocytosis may be seen. Lymphadenopathy may be present. Hepatic involvement may range from asymptomatic and mild transaminitis to fulminant liver failure. Other manifestations include myocarditis/pericarditis, nephritis, acute respiratory distress syndrome, colitis and encephalitis. The pathogenesis of this condition is not well understood, but the delayed onset and skin test/RAST negativity suggest that it is not IgE mediated. However, in support of an immune mechanism several drugs that cause DRESS syndrome have been linked with HLA haplotypes: allopurinol with HLA-B*5801; carbamazepine with HLA-A*3101 in Japanese and European patients; and abacavir with HLA-B*5701. There may also be a link between HLA alleles and DRESS syndrome secondary to vancomycin, but larger cohorts of patients with this syndrome would need to be tested.

Many of the features of DRESS syndrome also resemble a viral infection, particularly the rash, fever, lymphadenopathy and the presence of atypical lymphocytes on the blood smear. It has been proposed that reactivation of human herpesvirus 6 infection (HHV6) may be a significant factor in the pathogenesis of DRESS syndrome.

The most important step in managing patients with DRESS syndrome is to identify the triggering drug and stop it. This can be difficult as hospital patients are often on multiple agents, the onset of symptoms is often delayed, and there is no validated diagnostic test. To date, 19 cases

<table>
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<th>Patient</th>
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<tr>
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<td>03, 68</td>
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<td>04</td>
<td>06, 14</td>
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</table>

RegiSCAR score: Final score < 2 no case; final score 2–3 possible case; final score 4–5 probable case; final score > 5 definite case DRESS syndrome. ANA, anti-nuclear antibody; ANCA, anti-neutrophilic cytoplasmic antibody; CRP, C-reactive protein; DRESS, drug reaction with eosinophilia and systemic symptoms; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen.
of DRESS syndrome secondary to vancomycin have been reported,12-26 but there has been a recent sharp increase in reported cases (nine cases since 2012), perhaps due to the increased use following the emergence of MRSA, or a trend towards using continuous intravenous infusions leading to higher trough levels and higher total dosages of vancomycin. Symptoms typically respond to cessation of the drug and introduction of steroids, but relapses have been reported (similar to Patient 1) as steroids are weaned; from our experience, a taper over several weeks is required. However, perhaps due to the rarity of the syndrome, no controlled trials have proven the benefit of using systemic glucocorticoids over and above drug cessation. We present these three cases to highlight vancomycin-induced DRESS is an important and potentially life-threatening syndrome in the hospital setting.

References

El trombopag for resistant immune thrombocytopenia secondary to chronic lymphocytic leukaemia

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Key words
el trombopag, thrombopoietin receptor agonist, immune thrombocytopenia, chronic lymphocytic leukaemia.

Abstract
Autoimmune manifestations are a common occurrence with chronic lymphocytic leukaemia (CLL). We describe a case of CLL-associated immune thrombocytopenia (ITP) that had a loss of response to standard treatment for ITP. The thrombopoietin receptor agonist, el trombopag, was successfully used preoperatively to increase the platelet count to a safer level, in this instance to facilitate laparoscopic splenectomy.

A 61-year-old man with a 6-year history of stage A chronic lymphocytic leukaemia (CLL) under active surveillance but who had received no previous treatment, presented with a week-long history of epistaxis. Over the preceding 3 months, he had begun to experience night sweats but had not experienced fevers or weight loss. On examination he had enlarged lymphadenopathy in the cervical, axilla and inguinal regions but no hepatosplenomegaly.

A full blood count revealed a haemoglobin of 99 g/L, platelet count of $5 \times 10^9/L$, white cell count of $178 \times 10^9/L$ and neutrophil count of $5.3 \times 10^9/L$. Bone marrow biopsy revealed a normocellular marrow with a diffuse infiltrate of small mature lymphocytes and numerous megakaryocytes, consistent with peripheral platelet destruction as the cause of the thrombocytopenia. Flow cytometry confirmed a clonal population of B lymphocytes with the immunophenotype: CD5+ (dim), CD19+ (dim), CD20+ (dim), CD10-, CD22-, CD23+, FMC7-, CD38-, CD79b- consistent with CLL.

Investigations revealed a history of hepatitis B exposure, anti-HBs 297 IU/L, anti-HBc positive, HBsAg negative and HBeAg negative. Hepatitis C and HIV serology were negative. Computed tomography (CT) of the abdomen revealed a large number of small mesenteric and retroperitoneal lymph nodes, which were not pathologically enlarged. The spleen was not enlarged, measuring approximately 12 cm in its longest dimension.

A diagnosis of immune thrombocytopenia (ITP) was made. The patient commenced oral prednisone at a dose of 1 mg/kg and he received 2 g/kg of intravenous immunoglobulin in two divided doses. The platelet count remained $<10 \times 10^9/L$. In an attempt to reduce the B cell clone, the patient commenced our standard chemoimmunotherapy regimen of fludarabine, cyclophosphamide and rituximab (FCR). Prednisone was tapered and continued at a dose of 5 mg. After the second cycle of FCR, the platelet count was still $<10 \times 10^9/L$ and splenectomy was considered.

The patient received a trial of high-dose methylprednisolone with the intention of improving the platelet count sufficiently to undergo splenectomy safely. The patient received two doses of 1 g of methylprednisolone and on day 13 the platelet count had improved to $15 \times 10^9/L$. The following day the platelet count had fallen to $<10 \times 10^9/L$ and the patient was admitted with progressive breathlessness and hypoxia. CT chest revealed bilateral ground glass and interstitial changes consistent with atypical infection. The platelet count improved from day 17 and peaked at $74 \times 10^9/L$ on day 25. Induced sputum confirmed Pneumocystis jirovecii pneumonia on day 22 and he commenced high-dose treatment.
co-trimoxazole. Prednisone was increased to 40 mg, then tapered and continued at 5 mg. Unfortunately, the patient was unfit for splenectomy and the window of opportunity passed; by day 34 the platelet count had fallen to <10 × 10^9/L.

In a further attempt to improve the platelet count prior to splenectomy, eltrombopag, a thrombopoietin (TPO) receptor agonist, was trialled. Prior to eltrombopag, full blood count revealed haemoglobin 107 g/L, platelet count 4 × 10^9/L, white cell count 15 × 10^9/L and neutrophil count 1.7 × 10^9/L. The patient was commenced on 50 mg once a day. The platelet count responded increasing to 32 × 10^9/L by day 10, but then unexpectedly fell to <10 × 10^9/L on day 14. Eltrombopag was increased to 75 mg with an excellent response in platelet count to 139 × 10^9/L on day 6 of the higher dose. Laparoscopic splenectomy was performed the following day with minimal blood loss and no complications. Ertrombopag was stopped on day 1 post splenectomy. An expected rebound in platelet counts occurred, peaking at 768 × 10^9/L. Of relevance, no side-effects were experienced by the patient during the period eltrombopag was administered.

Discussion

Autoimmune manifestations are a common occurrence with CLL. The incidence of ITP is approximately 2–5% of the CLL population. ITP is characterised by increased destruction and impaired production of platelets caused by autoantibodies directed against the platelets and megakaryocytes.

ITP poses particular diagnostic difficulties. Thrombocytopenia in CLL is more commonly due to splenomegaly and bone marrow failure secondary to infiltration by disease. Thrombocytopenia in a patient with CLL can be considered immune-mediated when there is a sudden large fall in platelets (>50% fall to a platelet count of <100 × 10^9/L) in the absence of splenomegaly, infection or chemotherapy and with plentiful megakaryocytes in the bone marrow.

Due to the risk of bleeding, it has been recommended to initiate therapy in those patients with a platelet count of <30 × 10^9/L. Conventional therapies of ITP focused on decreasing the rate of platelet destruction based on the hypothesis that ITP is a disease caused by autoantibody-mediated platelet destruction. However, there is increasing evidence that ITP is also a disease of impaired platelet production due to the direct effect of autoantibodies on the megakaryocytes.

This case highlights the difficulty of treating the autoimmune manifestations associated with CLL. Response to ITP treatment can be defined as a platelet count >30 × 10^9/L and at least a two-fold increase the baseline count and an absence of bleeding. Most patients respond to the conventional therapy of corticosteroids and immunosuppression. In patients with resistant ITP, the most effective treatment is that directed at the underlying CLL. The patient we described did not respond to conventional therapy of corticosteroids, intravenous immunoglobulin or a CLL-targeted chemoimmunotherapy regimen including rituximab.

A trial of high-dose methylprednisolone appeared unsuccessful. It resulted in a transient improvement in platelet count, which did not meet response criteria. Platelet count peaked at 15 × 10^9/L on day 13 and had fallen to <10 × 10^9/L the following day when the patient was admitted with P. jirovecii pneumonia. Without further intervention and before treatment directed at P. jirovecii was initiated, the platelet count improved, peaking at 74 × 10^9/L on day 25 before falling to <10 × 10^9/L. The improvement in platelet count may have been an effect of previous treatments, including prednisone, rituximab, cyclophosphamide or a delayed response to the methylprednisolone. Patients with idiopathic ITP treated with high-dose methylprednisolone (30 mg/kg/day) respond more rapidly compared with conventional dose corticosteroids, and may respond even if a prior trial of conventional dose steroids was unsuccessful. Response to high-dose methylprednisolone (4.7 days) occurred more rapidly compared with standard prednisone (8.4 days), and with a higher response rate (80% compared with 52.7%).

Splenectomy remains an effective treatment, particularly for ITP. Eighty percent of patients respond to splenectomy, and response is sustained in 66% with no additional therapy for at least 5 years. While it is possible to perform laparoscopic splenectomy safely with extremely low platelet counts, the morbidity rate associated with surgery correlates with the degree of thrombocytopenia, so effort should be made either to elevate the platelet count preoperatively to achieve platelet counts of >50 × 10^9/L or transfuse platelets in selected cases.

Novel approaches were sought that would enable splenectomy to be performed safely. TPO receptor agonists, such as romiplostim and eltrombopag, represent a new approach in the treatment of ITP. Ertrombopag is an oral nonpeptide TPO receptor agonist. It increases platelet production by binding to the transmembrane domain of the TPO receptor and inducing proliferation and differentiation of bone marrow progenitor cells in the megakaryocyte lineage. Response to romiplostim and eltrombopag can be expected within 5–14 and 7–28 days respectively. A dose finding, randomised controlled trial demonstrated that patients receiving 50 mg or 75 mg of eltrombopag achieved a platelet count >50 × 10^9/L at 6 weeks in 70% and 81% respectively, compared with 11% of placebo patients.
The effect of TPO receptor agonists is transient, and platelet counts usually return to baseline within 2 weeks unless treatment is continued. TPO receptor agonists need to be taken indefinitely to maintain response, and although they have the advantage of not being immunosuppressive, their long-term effects are unknown. Common side-effects include nausea, myalgia and hepatic transaminits. A potential association of TPO receptor agonists and an increase in bone marrow reticulin fibrosis is a concern.

Eltrombopag is approved by the Federal Drug Agency for chronic idiopathic ITP unresponsive to corticosteroids, intravenous immunoglobulins or splenectomy. However, there is little published data on the use of TPO receptor agonists for ITP secondary to CLL. Case reports have shown that both romiplostim and eltrombopag effectively and rapidly increase the platelet count in refractory ITP. However, neither patient responded. The third patient initially responded but lost response after 9 months of therapy.

In summary, this case provides further evidence that the TPO receptor agonist eltrombopag is effective in patients with ITP secondary to CLL who have had a loss of response to standard treatment for ITP. TPO receptor agonists can be used preoperatively to increase the platelet count to a safer level, in this instance to facilitate laparoscopic splenectomy.

References
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Novel finding of carbamazepine induced gall bladder granulomatous vasculitis

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Key words
carbamazepine, vasculitis, gall bladder, eosinophilia, cholecystitis.

Abstract
We report a 63-year-old male patient who presented with eosinophilic granulomatous vasculitis of the gall bladder secondary to carbamazepine drug therapy. Following commencement of carbamazepine for treatment of partial seizures, the patient developed an allergic cutaneous drug rash. He continued to take carbamazepine postdischarge despite cessation by the treating team. He represented 7 weeks later with acute pancreatitis and cholecystitis. Gall bladder histopathology showed a granulomatous vasculitis.

Drug rash with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening syndrome and is associated with aromatic anticonvulsants, such as carbamazepine or phenytoin. It typically occurs within 12 weeks of commencing the medication and resolves with cessation of the offending drug. We describe a case that expands the spectrum of this disorder.

A 63-year-old male patient of Middle Eastern origin with a background of pontine haemorrhage 15 years prior to presentation, coronary artery disease with coronary artery bypass grafting (CABG), hypertension, diabetes, Von Willebrand disease and previous alcohol abuse presented to hospital with a complex partial seizure following a traumatic head injury. Imaging revealed a small traumatic subarachnoid haemorrhage over the right frontal lobe. He was admitted for observation. Following further seizures over the subsequent 48 h, he was commenced on carbamazepine 200 mg twice a day and was discharged home.

Five weeks later, the patient represented with atypical chest pain and was evaluated for acute coronary syndrome, which was excluded. During his admission, he was noted to have a maculopapular rash and significantly deranged liver function tests (LFT), which were not present on previous laboratory testing. A presumptive diagnosis of carbamazepine-related adverse drug reaction was made. Carbamazepine was ceased and levetiracetam was started. Despite this advice and unknown to the family or medical team, he failed to fill his prescription for levetiracetam and continued on his old stock of carbamazepine on discharge.

He represented a week later with fever, epigastric pain and altered LFT, including an elevated lipase suggestive of acute pancreatitis. Abdominal ultrasound revealed an oedematous heterogeneous pancreas consistent with pancreatitis. There were multiple immobile gallstones with no sonographic evidence of cholecystitis, and the liver was normal in echotexture with no intrahepatic or extrahepatic biliary duct dilation. Despite conservative treatment, his LFT and lipase remained elevated, a cholecystectomy was performed and he was subsequently discharged home.

Three weeks later, he represented with delirium, fever and raised inflammatory markers without any focal source of infection. Review of gall bladder histology revealed a granulomatous vasculitis without evidence of cholecystitis (Fig. 1). Given his history of carbamazepine allergy-causing hepatitis, a carbamazepine drug level was tested confirming his ongoing ingestion of the drug. A review of blood counts during this period showed that his eosinophil count was intermittently raised (Fig. 2). An extensive workup looking for a vasculitic or infective cause of his presentation was negative. Over the next 2 weeks, he returned to his baseline and he was discharged home. Both he and his family were counselled regarding his carbamazepine allergy.
along with discarding the remaining tablets in the house. He has had no further presentations related to vasculitis, and there has been no evidence of ongoing disease activity on follow up.

Discussion

Our case highlights two important clinical lessons. First, it exemplifies the common problem of poor patient compliance with medication changes made during hospitalisation and the resulting adverse consequences. Second, it emphasises the broad spectrum of allergic reactions to carbamazepine, including our novel finding of gall bladder granulomatous vasculitis.

Patients often take medications that are not prescribed and commonly fail to adjust regimens appropriately on discharge when changes are made in hospital. The recently published DISCHARGE study found that two-thirds of patients above 65 years of age did not understand intended medication changes on discharge from hospital.1 In our case, failure to recognise this delayed the diagnosis in what was otherwise a typical manifestation of carbamazepine hypersensitivity. This example reminds us that clear communication of important discharge, and follow-up information to patients and families is critical.

The manifestations of carbamazepine hypersensitivity are protean and necessitate immediate drug cessation. Carbamazepine may trigger multiorgan hypersensitivity reactions, which can affect the skin, liver, haemopoietic organs and lymphatic system. Anticonvulsant hypersensitivity syndrome (AHS) is characterised by fever, skin rashes and involvement of the internal organs, and

Figure 1  Sections show multiple arteries within the subserosal and submucosal layer displaying a perivascular inflammatory cell infiltrate consisting of lymphocytes, eosinophils, histiocytes and multinucleated giant cells (A). Some histiocytes and giant cells are seen to aggregate forming non-necrotising granulomas within the submucosamucosal and subserosal layers (B) as well as in a perivascular location (C). Slide D shows inflammatory cells infiltrating the arterial wall with associated intimal hyperplasia, concentric media thickening and luminal narrowing of the vessels. Histocytes; multinucleated giant cells; granuloma.
includes both Stevens–Johnson syndrome and DRESS.\textsuperscript{2} AHS has been estimated to occur in between 1 in 1000 and 1 in 10 000 drug exposures, and the pathophysiological process is not fully understood.\textsuperscript{3}

The term DRESS was first proposed by Bocquet H. \textit{et al.} in 1996 to describe the clinical manifestations of extensive mucocutaneous rash, fever, lymphadenopathy, hepatitis, haematologic abnormalities with eosinophilia and atypical lymphocytosis.\textsuperscript{4} The pathogenesis of DRESS is associated with both herpes virus reactivation and a drug-specific hypersensitivity reaction, although the exact mechanism is not clearly understood. Human herpes virus 6 (HHV-6) has been implicated in approximately 60\% of DRESS cases using anti-HHV-6 immunoglobulin G titres, and HHV-6 DNA is found in serum in approximately 30\% of cases, suggesting active viral proliferation.\textsuperscript{5} Patients with detected viral reactivation had worse outcomes.\textsuperscript{5} HHV-7 and Epstein–Barr virus have also been identified in DRESS patients in association with activated CD8\textsuperscript{+} T lymphocytes directed against virus found in skin, liver and serum.\textsuperscript{6}

The initial manifestations include a morbilliform eruption evolving to a confluent rash affecting the face, extremities and upper trunk. There is often an associated febrile illness, malaise and a diffuse, tender lymphadenopathy, although not all features are always present.\textsuperscript{7} Blood workup reveals leucocytosis with eosinophilia and elevated LFT often present. Systemic involvement occurs with eosinophilic infiltration of several organs, especially the kidneys, heart, lungs and pancreas.\textsuperscript{8} The multisystem involvement differentiates DRESS from other skin reactions to drugs. Another feature of this syndrome is its late presentation in relation to the introduction of the culprit drug, which tends to occur from 3 weeks to 3 months after the time of drug introduction and may persist or worsen despite withdrawal of the offending drug. Although symptoms usually regress gradually over weeks to months after cessation of the causal medication, relapses can occur.\textsuperscript{5}

DRESS has also been reported in association with lamotrigine, phenytoin, phenobarbital, allopurinol and less frequently with sulfonamides, dapsone, vancomycin and minocycline.\textsuperscript{9} Human leukocyte antigen (HLA) haplotype influences susceptibility to DRESS. In South-East Asian populations, the HLA-A*3101 allele is associated with hypersensitivity syndrome due to carbamazepine,\textsuperscript{10} and the HLA-B*1502 allele with Stevens–Johnson syndrome associated with carbamazepine. The HLA-B*5801 is a marker for allopurinol induced DRESS or hypersensitivity syndromes in both Asian and European populations.\textsuperscript{11}

Carbamazepine-induced granulomatous reactions have been reported in skin, liver and kidneys, but not in gall bladder. Superficial granulomatous dermatitis has
been described in association with persistent antigenic stimulation from continued carbamazepine ingestion in a case report of a 26-year-old woman. She developed rash, fever, pruritis and deranged LFT 6 weeks after the commencement of carbamazepine. In another case report, cutaneous granulomatous reactions were observed around the hair follicles and vessels in a 69-year-old female 12 weeks after treatment with carbamazepine for postherpetic neuralgia.13 Hepatotoxic reactions associated with carbamazepine therapy have also been described, including a granulomatous hepatitis.14

Carbamazepine-induced granulomatous necrotising angiitis has been reported in kidneys.15 This was described in a 42-year-old man treated with carbamazepine who developed a skin eruption followed by acute renal failure. A renal biopsy disclosed granulomatous necrotising angiitis, which was different from classic periarteritis nodosa and hypersensitivity angiitis. The treating team stopped all medications immediately, and his kidney function improved gradually. Provocation testing utilising carbamazepine was positive, and he was diagnosed with carbamazepine-induced granulomatous necrotising angiitis. Our findings of a granulomatous vasculitis affecting the gall bladder have not been reported previously. The extensive and severe changes seen in our case could reflect the repeated and prolonged exposures over a 4-month period despite established drug hypersensitivity. Typically, with the current heightened awareness of the spectrum of DRESS, carbamazepine is ceased early, which is the definitive treatment.

We present a case of carbamazepine-induced drug reaction with gall bladder granulomatous vasculitis, which has not been previously described in the literature and is the second histopathologically documented case of carbamazepine-induced vasculitis. Our case also draws attention to the need for a thorough and accurate drug history particularly when faced with an unusual or unexplained clinical presentation.

References


PERSONAL VIEWPOINT

Clinical judgement and the emotions

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Key words
Consciousness, emotions, intuition, reason, clinical judgement, diagnosis.

Abstract
The basic emotions are more important in decision making than we think. So we need to be aware of them and look not just for rationality in our clinical judgements but rational judgements that ‘feel’ right.

It is now quite clear from neuroscience studies that consciousness is late on the scene of brain activity, actually lagging behind it by half a second or more.1,2 So though we may be consciously aware of what we do, we do not actually do anything consciously. Hard to believe I know, but true. Conscious awareness of incoming sensory information likewise, although the situation there is a little more complicated.3

We therefore need to ask just what other mechanism might be in control of brain function, and, more specifically, if consciousness is so passive, how does the brain actually make its decisions? On reflection, I have gradually come to the somewhat strange conclusion4 that there is no better candidate for this than the risk/reward system that resides in ‘emotional brain’,5 and essentially within its subcortical mesolimbic aspect.6 There, over the billions of years, evolution has produced an increasingly sophisticated and now highly refined mechanism to facilitate life survival decisions extremely well.6

This risk/reward system has been shown to put the incoming sensory information into a ‘common currency’,7,8 take into account the prevailing context9,9 and then give each datum a ‘relative subjective value’,10,11 so that it is poised ready for the process of ‘reward harvesting’.8 The mechanism has now become highly sophisticated, quantitatively calculating not just potential risks and rewards,6 in what I have called ‘emotion scores’,4 but also evaluating the risk prediction errors from past experiences, from which it is continually learning through reinforcement feedback.8

With this as background, my additional suggestion has been that when multiple emotion-score options present themselves over changing times and contexts, the risk/reward system acts as a ‘winner-take-all’ mechanism to compare and assess the available options and choose the one with the highest emotion score relevant to life survival in the prevailing setting.4 This then, I suggest, becomes the system’s ‘output decision’. At higher cortical levels, there are areas that contribute further to risk/reward evaluation,12 including the orbitofrontal cortex (value/evaluation)12 and the anterior cingulate gyrus (cost/benefit of any calculated action),12 but I want to emphasise here that the subcortical mesolimbic system has the ability to achieve an appropriate risk/reward outcome by best option selection in the absence of any cortical input.

Thus, the basic brain risk/reward system is seen as being focused to attention whenever some new situation arises and poised ready for action when something presents of potential cost or benefit. Just watch a little honey-eater on the edge of a bird bath constantly and automatically evaluating the environment for rewards.
and threats relevant to its survival: eternally vigilant! Importantly, such rapid and basic evaluation of the incoming information is just as true in humans.\textsuperscript{13,14}

This is all consistent with evidence for the involvement of the emotional brain in human decision making\textsuperscript{6,8,10,11} and has been brought to our attention not so much by conventional neuroscience as by neuroeconomics.\textsuperscript{6,8,11}

You will no doubt say that while this might provide an evolutionary basis for survival decisions in animals, and some foundation for life and death emotional decisions in humans, it could hardly explain the logical basis on which humans thrive so well. Well, I am not so sure. I have proposed that rationality does indeed get a look in but only when the individual’s experience within society has given such rational options sufficiently high emotion scores to allow them to compete with other more intuitive alternatives.\textsuperscript{4}

In essence:

Rational options are chosen if, and only if, the emotion-score values they evoke from the evaluative risk/reward system of the emotional brain are high enough to out-compete their more intuitive rivals.\textsuperscript{4}

You may say that such a system would not, in any event, be up to making the complex rational decisions of which the human brain is capable. However, at least in some aspects, the problem-solving ability of the human brain is not nearly as sophisticated as we like to think. For example, in the area of probabilities, it often serves us somewhat poorly, as shown in the following:

1. You see a woman in a train reading the Financial Review.

Which of the following is more probable about the stranger?

a. She has a PhD
b. She does not have a university degree.

Answer: See footnote\textsuperscript{4} (adapted from Kahneman\textsuperscript{13}).

2. Suppose Rafael Nadal reaches the next Open Tennis final.

Rank in order the following outcomes from most to least likely.

a. Nadal will win the match
b. Nadal will lose the first set
c. Nadal will lose the first set but win the match
d. Nadal will lose the match

Answer: See footnote\textsuperscript{b} (adapted from Kahneman\textsuperscript{13}).

3. As De Neys and Glumicic have shown well, we can even err profoundly when asked to draw conclusions about two simple and only very superficially conflicting pieces of information.\textsuperscript{16}

It should be noted that the views expressed here on the emotions and brain function are quite different from those of Damasio.\textsuperscript{17} In another important approach, Kahneman, has proposed that the brain has two quite contrasting mechanisms for making decisions.\textsuperscript{18}

System 1. This operates automatically and quickly, with no sense of voluntary control.

System 2. This allocates mental effort to solve complex problems and is associated with a sense of agency, choice, and concentration.

System 1 is usually thought of as including heuristic rules of thumb. Such heuristics are certainly rapidly available and quickly retrieved, but I would argue that they nonetheless belong in system 2 because they are essentially analogies learned from previous experience rather than primarily deriving from instinctive or emotional aspects of brain function.

Importantly, I am not saying that you – or your brain – should not take the time to search for a logical answer – quite the reverse. We must always strive for that.\textsuperscript{19} It is just that to be successful, such logical options must have sufficient emotional appeal to allow them to out-compete more intuitive rivals within the risk/reward system of the basic emotional brain. Of course, in the end, if you cannot find anything rational that ‘feels’ emotionally right, then you should probably just go with the emotional/intuitive. In this circumstance, it is probably right.

That is how I see the brain working in light of the fact that consciousness has turned out to be a passive epiphenomenon. Hard to swallow? Well, you are not the only one. But there it is: this is my synthesis based on the evidence.\textsuperscript{4}

The relevance to clinical diagnosis is that if you have a strong intuition that X is correct, then \textit{in the absence of any appealing rational option striving to override it}, just go with that. Those fingernail bases do have abnormal capillaries, and because the patient gets Raynaud phenomenon, her dyspnoea might well be due to chronic pulmonary fibrosis secondary to systemic sclerosis. On the other hand, do not allow yourself to be persuaded by your first intuition that the patient has, say, multiple sclerosis if the neurological episode before you came on over a period of a few minutes. Your more considered rational view that this is probably a vascular event of some sort is much more appealing and should be pursued accordingly.

Just as importantly, in a world of medicine beset by increasing information, even within individual patients, we will soon need a way to guide us through the maze.
The present approach might then help: look not just for rational solutions but for rational solutions that ‘feel’ emotionally right.

References

LETTERS TO THE EDITOR

Clinical-scientific notes

Severe haemosiderin pigmentation after intravenous iron infusion

Haemosiderin pigmentation is a known cosmetically disfiguring complication of intramuscular (IM) iron injections. It results from leakage of iron into subcutaneous tissues, generally from reflux of solution through the injection site and is more common with poor technique. Some clinicians consider that pigmentation after intravenous (IV) infusions is either trivial or does not occur, a view often cited in preferring the IV over the IM route. The side-effect may be underestimated when guiding IV procedural protocol and is underreported in literature. Our literature review encompassed searches of Medline, Scopus, Google Scholar and iron formulation product information. MeSH terms were: hemosiderin/haemosiderin or iron and pigmentation, hemosiderin/haemosiderin or iron and staining, iron and skin and/or pigmentation, iron and cutaneous, IM and iron, IV and infusion and iron, iron and ‘side-effects’. We ascertained only a single case of pigmentation after IV administration, this case report being limited in detail and documented within a wider IM series. We therefore report a case of severe, persistent and distressing...
haemosiderin pigmentation occurring over a significant skin surface area after a single IV iron infusion to highlight the importance of recognising that this disfiguring effect can occur with IV as well as IM iron administration.

A 78-year-old Arabic woman presented with severe iron deficiency anaemia due to blood loss. She complained of right-sided chest pain and had melaena on admission. She was haemodynamically stable and examination was otherwise unremarkable. Her haemoglobin was 76 g/L and iron studies confirmed iron deficiency with iron 2 μmol/L (reference range (RR): 8–30 μmol/L) and ferritin 6 μg/L (RR: 15–250 μg/L). The source of bleeding was from angiodysplasia of the colon and possibly from a Cameron erosion resulting from a large hiatus hernia.

Our patient was treated according to hospital guidelines with one unit of red blood cells followed by an iron polymaltose infusion (1800 mg in 500 mL normal saline). This was the patient’s first and only iron infusion, and no other iron supplement was given. Dosing was based on total body weight. The infusion was run through an IV cannula in the dorsum of the right hand, at a rate of 40 mL/h for the first 75 min, then at 120 mL/h for the remainder of the infusion. Blood pressure and pulse were monitored every 2 min for the first 10 min, then half-hourly thereafter, with no abnormalities detected. Approximately 2 h after infusion commencement the patient developed a fever of 37.9°C. The infusion was continued under observation and fever resolved after the infusion was complete. When the infusion was almost complete, nursing staff noted that the patient’s hand was swollen and the IV cannula was no longer functioning, suggesting leakage of the infusion into tissue at the hand. The nurse performing observations an hour earlier confirmed that swelling was not present at this time and the cannula was functioning, suggesting total leakage of <120 mL. Iron studies 8 months after infusion showed iron 12 μmol/L (RR: 8–30 μmol/L) and ferritin 90 μg/L (RR: 15–250 μg/L), indicating adequate iron replacement despite the leakage.

Two days after the infusion, the patient developed brown pigmentation over a large area of skin including the dorsal aspect of her right hand (infusion site) and dorsal and volar aspects of her right forearm. The staining has, according to the patient, darkened with time and is still present 8 months post-infusion (Fig. 1). Punch biopsy confirmed cutaneous iron deposition, showing a dermal and subcutaneous infiltrate of pigment-laden macrophages with a positive Perls’ stain (Fig. 2). The cosmetic effects of the infusion have been distressing for this patient. The patient consented to publication of de-identified images and details of her case.

Skin pigmentation after parenteral iron therapy results from deposition of metallic salts in connective tissue of the dermis.1 While only eight cases are, to our knowledge, reported in literature, the side-effect is generally considered frequent enough after IM iron to warrant
informing patients and to recommend the option of IV administration as an alternative. Many practitioners do not consider that this potentially distressing side-effect can also occur with the IV route. Our report suggests that the side-effect should be highlighted when deciding and advising on iron administration protocols.

The pigmentation in our case appears similar in mechanism to previously reported cases but was more extensive. A review and case series by Raulin and Greve report four cases of IM iron administration causing grey-brown skin pigmentation, describing circumscribed lesions of 2–30 cm² in size and discusses four further similar previous cases. The area of staining in our case was approximately 300 cm². Iron preparations used in previously reported cases are mostly undocumented, but one patient in Raulin and Greve’s series received iron polymaltose (the preparation used for our patient). Six of the eight cases reported had skin biopsies confirming haemosiderin pigmentation demonstrated by Prussian blue staining in all layers of the dermis, similar to biopsy findings in our patient.1,2

The single-recorded case of pigmentation occurring with IV iron administration reported within Raulin and Greve’s series was localised in the right forearm and was only 4 cm² in size. Raulin and Greve’s patient experienced 6 months of unresolved staining after eight administrations (presumably all IV, preparation unknown). Infusion events and photos were not provided. It is presumed that the pigmentation resulted from paravenous leakage as described in our case, with a mechanism similar to the IM cases.

Haemosiderin pigmentation after parenteral iron administration is often difficult to treat. Most reported cases document persistent staining for 6 months to several years. Two cases reported regression without treatment.1 Raulin and Greve reported partially successful treatment, with all five subjects in their case series responding with lightening of staining after laser treatment with either Q-switched ruby or Nd : YAG laser.1 Complete resolution of staining was not achieved.1 We are unaware of any other literature reports of successful treatment. Given that total removal of pigmentation is not possible with current treatments, it is important to recognise that IV iron administration also carries risk of haemosiderin skin pigmentation and can potentially cause large, persistent areas of severely disfiguring staining. When using IV iron, practitioners should take measures to minimise the risk of paravenous leakage by incorporating into protocols regular monitoring of the IV site during the infusion and careful withdrawal of the IV cannula post infusion. These practice changes should reduce the risk that incidence of this disfiguring complication will increase with the widening use of IV iron therapy.

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References


A novel hepatitis B virus S gene insertion associated with reduced humoral immunity and diagnostic escape

A 37-year-old Asian woman was referred for assessment of abnormal liver function following a needle-stick injury. She was asymptomatic. Liver function testing revealed albumin 40 g/L, alkaline phosphatase 62 IU/L, alanine aminotransferase 43 IU/L and bilirubin 23 μmol/L. Serum hepatitis B surface antigen (HBsAg) testing was negative using the Roche Cobas assay (Roche Elecsys platform, Roche Diagnostics, IN, USA), and anti-HBs titre was 616 IU/mL (Roche Elecsys). Standard serology for antibodies to hepatitis C virus and HIV was negative, as was testing for autoimmune and metabolic liver diseases. She was clinically well and taking no regular medication. The patient was a primary care doctor (general practitioner). The needle-stick injury occurred to the patient when vaccinating an infant. The patient was noted to be anti-HBs positive at the time of the needle-stick injury, and the infant (donor) was hepatitis B virus (HBV) negative. There were no prior recognised occupational exposures to HBV. The patient's mother was born in Hong Kong and was confirmed to have chronic hepatitis B infection with detectable serum HBsAg and HBV DNA. The patient was born in the UK, but did not receive immunoprophylaxis at the time. She received a complete course of HBV vaccine as a teenager. In 1991, HBsAg testing was negative, with a low positive anti-HBs titre, and subsequently three booster doses of vaccine were administered. Anti-HBs levels were >100 IU/mL in 1994. She received a booster vaccine in 1999, and serum HBsAg was again negative in 2003.

Further testing at presentation showed that serum was positive for antibodies directed against the core protein of HBV (anti-HBc). The HBV precore protein (or hepatitis B ‘e’ antigen) was also detectable in serum, at a level of 133 Paul-Ehrlich IU/mL (Roche Cobas Assay). Serum HBV DNA level was 134 488 IU/mL (Roche Cobas AmpliPrep-Taqman HBV Test v2.0, Roche Diagnostics). Sequencing of the HBV genome was performed and identified genotype C HBV with a four amino acid (aa) repeat insertion at position 115 in the surface protein (Fig. 1).

We present an unusual case of a HBV diagnostic escape variant, where the standard HBsAg immunoassay was negative despite persistent viraemia and active hepatitis. The standard diagnostic assay for HBV infection is an enzyme immunoassay for detection of HBsAg. The assay relies on antigenic interaction between HBsAg and antibodies directed against HBsAg (anti-HBs). Most commercial assays use a panel of monoclonal antibodies directed against antigenic determinants (epitopes) between aa99 and aa169. HBsAg is a transmembrane protein, and this region exists as a large and exposed hydrophilic segment containing multiple cysteine residues and likely stabilised by the formation of numerous disulphide bonds, with the antigenic determinants being highly conformation dependent.1–4 The major antigenic determinant lies between aa121 and 149 (the protective immunity conferred by HBsAg vaccination is associated with neutralising antibody against this ‘a’ determinant).1–4 Structural variations in this region (Fig. 1), including substitutions and insertions, may alter the conformation of the region, disrupt antibody binding and result in diagnostic escape and/or vaccine escape (e.g. G154R vaccine escape mutation).1–4 We believe that this is the first description of an insertion at aa115 leading to diagnostic failure.

Routine testing for HBV infection should always include serology for HBsAg and anti-HBs, as well as anti-HBc. Although HBsAg diagnostic escape is uncommon using modern immunoassays, this case demonstrates the importance of maintaining an index of suspicion in high-risk individuals, particularly with a family history of chronic hepatitis B. In such a setting, nucleic acid testing for serum HBV DNA is required.

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Acute viral encephalitis co-existing with fulminant hepatitis caused by Epstein–Barr virus

Epstein–Barr virus (EBV) infection often causes a fever, sore throat and adenopathy, referred to as infectious mononucleosis, which is usually a benign and self-limiting disease. Gastrointestinal manifestations are frequently present, characterised by elevation in transaminases, abdominal pain, hepato-splenomegaly and less commonly acute fulminant hepatitis.1–4 In rare cases, neurological complications associated with EBV have been described involving encephalitis, transverse myelitis and cranial neuropathy.4–6 However, the simultaneous involvement of encephalitis and hepatitis by the EBV has not been documented to our knowledge. Therefore, we describe a patient who presented with EBV encephalitis involving the splenium of the corpus callosum and concomitant fulminant hepatitis.

A 20-year-old man presented with fever, general myalgia and headache since 5 days ago. On admission to the hospital, his temperature was 37.1°C and blood pressure 110/70 mmHg. Initial laboratory studies yielded aspartate transaminase: 2787 U/L (upper limit normal (ULN): 40 U/L); alanine transaminase: 2390 U/L (ULN: 40 U/L); lactate dehydrogenase: 2601 U/L (ULN: 200 U/L); alkaline phosphatase: 280 U/L (ULN: 338 U/L); ceruloplasmin: 39 mg/dL (ULN: 60 mg/dL); prothrombin time: 13.0 s (ULN: 12.5 s); and gamma-glutamyl transpeptidase: 166 U/L (ULN: 55 U/L). Total bilirubin was 0.7 mg/dL (ULN: 1.3 mg/dL), and direct bilirubin was 0.4 mg/dL (ULN: 0.4 mg/dL). Serum electrolyte test showed a low plasma sodium level of 132 mEq/L (ULN: 135 mEq/L). The white blood cell count was 12 630 with 57% neutrophils and 29% lymphocytes. Common virological tests were negative for hepatitis B surface antigen, hepatitis B surface antibody, IgM antibody against hepatitis B core antigen, hepatitis C virus (HCV) antibody, HCV RNA, hepatitis A virus IgM antibody and human immunodeficiency virus antibody. An abdominal dynamic computed tomography revealed mild hepatosplenomegaly with fatty infiltration and minimal periperal lucency.

Interestingly, the serological response to EBV was positive for specific antibodies to viral capsid antigen (VCA-IgM); however, anti-Epstein–Barr nuclear antigen Ab and EBV(VCA)-IgG were negative. The EBV DNA detected by polymerase chain reaction (PCR) was positive in peripheral mononuclear cells, and consequently, the patient was diagnosed as a primary EBV infection. Other virological and serological examinations including antinuclear Ab, smooth muscle Ab, anti-Sjögren’s syndrome A (SSA, Ro) Ab, anti-Sjögren’s syndrome B (SSB, La) Ab, anti-Jo1 Ab, cytomegalovirus-IgM, herpes simplex virus-IgM, Hantann virus, scrub typhus, leptospirosis and murine typhus were negative.

On 3 days after admission, he complained of severe headache, dizziness, nausea and behavioral disturbances including right-arm shaking and confusion, and suddenly showed repetitive facial convulsive movements followed by decreased mentality. Brain magnetic resonance imaging (MRI) of the patient revealed a high signal lesion in the splenium of the corpus callosum (Fig. 1a). Cerebrospinal fluid (CSF) analysis that showed lymphocytic pleocytosis (35/mm³) and EBV PCR performed by CSF centrifugation, EBV DNA extraction, qualitative assay and EBV-DNA concentration identified by PCR band was positively compatible with EBV infection. Previously, our patient had not received any immunosuppressive treatment or cancer chemotherapy and had no malignancy history that may have caused immunosuppression. In conclusion, he was diagnosed with a primary EBV infection presenting encephalitis and concomitant hepatitis, and then managed with conservative treatment and anti-epileptic drugs without steroid or antiviral medications. On day 20, the patient’s

References


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liver function was normalised and EBV VCA-IgM was declined (<0.2), and on day 21, the brain MRI was remarkably improved (Fig. 1b).

Most EBV infections are asymptomatic and acquired in childhood, while symptomatic disease typically occurs among adolescents or adults who were not exposed during childhood. The diagnosis of EBV hepatitis is suggested by the appropriate clinical symptoms and laboratory findings and confirmed by a positive EBV IgM antibody and heterophile antibody test. Occasionally, serological tests are unremarkable, and the diagnosis must be established by the use of PCR assay. In our case, the diagnosis of EBV infection is ascertained by the detection of EBV PCR and a positive VCA-IgM in the serum and CSF.

Interestingly, our case of EBV encephalitis was remarkably similar to the MRI feature of mild encephalitis with a reversible splenial lesion with reduced diffusion and apparent diffusion coefficient values in the corpus callosum, especially in the splenium, sometimes related to symmetrical white-matter lesions. Viral and bacterial infections implicated in MERS have been reported, and most common pathogens are influenza virus A/B and the mumps virus. Recently, EBV was documented in the pathogenesis of MERS, however, a case of primary EBV infection presenting as both MERS and fulminant hepatitis has not yet been reported. Accordingly, it is noteworthy that the hepatitis and encephalitis of MERS could be simultaneously caused by primary EBV infection or the fulminant hepatitis by EBV could have influence on the splenial lesion of MERS.

To the best of our knowledge, this is the first documented case describing both acute encephalitis and fulminant hepatitis induced by EBV; therefore, possible EBV should be evaluated in the event of simultaneous encephalitis and acute hepatitis.

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Successful pregnancy in ventilatory failure due to campomelic dysplasia with severe kyphoscoliosis

Pregnancy places additional stress on the mothers’ cardio-respiratory system. We present successful management of a pregnancy in a mother with pre-existing ventilatory failure. The mother was first referred for ventilatory support assessment at the age of 23 years in the setting of severe kyphoscoliosis and resultant severely restricted ventilatory capacity (Table 1). She was diagnosed with campomelic dysplasia given a constellation of unusual conditions (including bilateral conductive hearing impairment, cleft palate with micrognathia, congenital club foot deformity) and the associated chromosomal abnormality (gene translocation located close to SOX9 gene, 46,XX, t(2;17)(p11.1;q24.2). There was no developmental delay during her childhood. She subsequently developed

Table 1 Blood gas analysis, respiratory rate and spirometry values measured at baseline, during pregnancy and puerperium

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2011</th>
<th>December 2012 (week 26)</th>
<th>March 2013 (week 33)</th>
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<tr>
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<td>FEV1 (L)</td>
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FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.
daytime somnolence with elevated arterial carbon dioxide level of 48 mmHg. Nocturnal non-invasive ventilation (NIV) was implemented with a relatively high-pressure support of 12-cm H₂O given her weight of 35 kg. She remained clinically stable over the subsequent 6 years.

She was reviewed by our obstetric and ventilatory failure services 12 weeks after falling pregnant. After genetic counseling about the potential gene inheritance, she decided to continue her pregnancy. Serial transthoracic echocardiogram did not identify any signs of pulmonary hypertension. A sleep study in the second trimester demonstrated good control of nocturnal hypopnea. At 33-week gestation, she developed progressive tachypnoea from 18–20 breaths per minute to 30 breaths per minute with a borderline fall in vital capacity to 25% of predicted. Due to the risk of developing overt ventilatory failure with continuing the pregnancy and the attendant risks associated with emergency delivery, she proceeded with a planned semi-elective caesarean section delivery under general anesthesia at 34-week gestation. Post-intubation, her ventilatory pressures were very high at 45-cm H₂O, falling dramatically to less than 25-cm H₂O post-delivery. She was extubated and weaned successfully to nocturnal NIV only within 24 h. Postnatal examination of the newborn was normal and chromosome analysis confirmed that she did not carry the translocation.

Campomelic dysplasia is a rare autosomal dominant disorder with different phenotypes characterised by skeletal dysplasia, including kyphoscoliosis, and developmental abnormalities due to mutations of SOX9 gene located on chromosome 17. Respiratory failure is common in severe kyphoscoliosis. It can usually be successfully managed with nocturnal NIV. Pregnancy reduces ventilatory reserve, putting those with pre-existing ventilatory failure at risk of deterioration at a time when ventilation normally increases. Patients with kyphoscoliosis can develop ventilatory failure during pregnancy with beneficial therapeutic effects from NIV use. Successful pregnancy has been reported in a patient with campomelic dysplasia, but without respiratory involvement. This is the first documented case of a campomelic dysplasia adult with chronic ventilatory failure on NIV due to severe kyphoscoliosis having an uncomplicated delivery of an unaffected baby. Regular observation enabled timely delivery prior to developing overt ventilatory failure. In summary, this case supports the presence of a subgroup of campomelic dysplasia with milder phenotype and better survival. In mothers with severe kyphoscoliosis and pre-existing ventilatory failure, NIV can assist in maintaining respiratory stability during pregnancy with close observation for consideration of early delivery to avoid overt ventilatory failure.

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References
General correspondence

Flawed peer-review process

Since the introduction of digital imaging, clinicians have unprecedented access to medical images and this has enabled them to incorporate images into articles. However, clinicians are not experts at image interpretation; they may select incorrect images and may mislabel them. This was demonstrated in an article published in the March edition of Internal Medicine Journal (IMJ) by Blanchard et al.1 The adrenal lesion in question is poorly visualised because of the phase selected and is also most likely incorrectly labelled. The arrows on the lateral part of the ‘cystic adrenal mass’ are pointing at what looks like a normal gallbladder. It would be highly unusual for any adrenal mass to be in this position. Certainly this ‘cyst’ bears little relationship to the photograph of the resected specimen. This raises an important issue. First, authors are potentially misleading readers by using incorrect/suboptimal images and labels, and reviewers are not selected appropriately to be able to detect these errors. This issue was first raised in 2010 by Stuckey2 following another IMJ article with misleading images. A radiologist should be involved in the review process to detect errors and ensure the image supports the findings of the text. The failure of specialist peer review has the potential to contaminate the literature with misleading articles and degrades the scientific process and knowledge transfer. As this is a serious recurrent issue, does the editorial board of IMJ have a plan to rectify this problem?

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References

Author reply

We thank Sutherland1 for his observation regarding the erroneous placement of arrows in our case of the reported adrenal lymphangioma.2 We completely agree that radiologists should be involved in the review process of case reports where imaging is presented, to ensure accuracy. Perhaps, as is standard in the review process, the pro-bono and after-hours expertise and participation of experienced radiologists could be invited. Sutherland makes a valid point about the importance of radiographic accuracy.

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References

EDITOR’S NOTE

Medical journal editors face some unexpected hurdles in the course of performing their duties. One of these is raising the angst of expert readers when errors are made. In the case described here, a scan was mislabelled, and this was missed. Fortunately, we have the means of correcting such errors, and I am not distressed that any meaningful
harm was done. Another potential area of concern might be statistical interpretation in complex analyses. Let the reader be assured that we have now taken steps to try to minimise these errors in the future, but I cannot guarantee that they will not happen again. The Letters pages are always available to you if you spot something, and corrigenda will be published where appropriate.

Jeff Szer
Editor-in-Chief
Instructions for Authors

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