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This Issue of the Journal

Temporal trends of acute nephrolithiasis in Auckland, New Zealand
Jason Du, Richard Johnston, Michael Rice

Over the last 10 years an increasing number of people in the Auckland region are presenting to hospitals with kidney stone disease. This trend was observed in all ethnic groups apart from the Middle Eastern population who are known to have high rates of kidney stone disease. A greater proportion of patients were female compared to 10 years ago.

Transient ischaemic attack services in New Zealand
Wallace J Brownlee, Lucy Fergus, Patricia Bennett, John Gommans, John Fink, P Alan Barber

Most strokes occur when an artery supplying blood to part of the brain blocks and the brain downstream stops functioning and then dies. Stroke is the third most common cause of death after heart disease and all cancers combined. One-third of people with stroke will die in the year following their stroke and another third will be dependent on others for their everyday activities. Transient ischaemic attacks (TIAs) as defined as stroke symptoms that disappear within 24 hours, usually before any permanent brain damage has developed, and occur as a warning before about one quarter of strokes. This is a significant proportion of the eight thousand strokes seen in New Zealand every year.

The good news is that up to 80% of the strokes that follow TIAs can be prevented. This is done by introducing therapy to thin the blood, lower blood pressure and cholesterol, and ensure good blood flow to the brain. However, this survey has found that few if any DHBs are able to provide a sufficiently prompt and efficient service to prevent many of the strokes that follow a TIA. Major regional discrepancies between services provided in different DHBs are seen. This failure to provide appropriate services represents a lost opportunity to prevent stroke and reduce the burden of this devastating disease.

Hospital stay and early complication rates following joint replacement: is there any ethnic difference in New Zealand?
Pai Vasu, Vishal Pai, Sophie Wrighton

It is clear that there is no benefit in considering the ethnic origin of a patient when preparing for surgery. Instead, each patient should be considered in turn, taking their comorbidities and lifestyle into account. Assessment before the operation is vital to enable recognition and treatment of any existing medical conditions thus ensuring optimal fitness of the patient prior to surgery. It is also of financial and medical benefit to minimise waiting time prior to surgery.
Dietary supplement use in the prevention of age-related macular degeneration progression
Aparna Raniga, Mark J Elder

The Age Related Eye Disease Study Group (AREDS) has found high-dose vitamin and mineral supplementation may have a role in preventing the progression of age-related macular degeneration. This study found that dietary intakes in New Zealand, Australia, United Kingdom, and United States are insufficient in achieving the AREDS nutrient intake recommendations. Hence, dietary supplements are required and this may be achieved by using any combination of multivitamin and individual supplement preparations available. Comprehensive tables have been constructed to guide New Zealand ophthalmologists in the process of recommending appropriate levels of supplementation.
Contrast-induced nephropathy: does it really exist?

Tim M Buckenham

In contemporary hospital practice there is increasing reliance on sophisticated diagnostic imaging—its efficacy is significantly reduced without the administration of intravascular iodinated contrast media.

In this issue of the Journal, Dr Tarek Darwish summarises the evidence for the existence of contrast-induced nephropathy (CIN) and the strategies commonly used to minimise the nephrotoxicity of iodinated contrast. His article poses an important question as to the existence of CIN as an entity and refers to recent evidence suggesting iodinated contrast medial (ICM) administration may not be necessary to induce nephropathy in hospitalised patients undergoing enhanced imaging.

The possibility of CIN being over-estimated has important ramifications. Most radiology departments have developed protocols aimed at identifying those at risk of CIN prior to imaging, usually by measuring serum creatinine and/or glomerular filtration rate (GFR). Patients at risk, e.g., those with pre-existing renal failure and/or diabetes, may either be offered alternative imaging that does not use ICM or be pre-hydrated.

The problem with these protocols is they create other risks for the patient, in particular the alternative imaging strategy may be less efficacious leading to under-diagnosis, and if that modality is gadolinium-enhanced magnetic resonance imaging (MRI), we are selecting the subgroup at highest risk of developing nephrogenic systemic fibrosis and exposing them to paramagnetic contrast media.

What is the evidence that CIN has been over-estimated and is it sufficient to relax the stringent protocols that are currently in place?

The general consensus that intravascular administration of iodinated contrast media is a significant cause of iatrogenic nephropathy has recently been challenged.

Newhouse and colleagues, in a recent article entitled Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity, suggest that the creatinine rise that occurs in many hospitalised patients has not been taken into account (“background noise”) and may have led to the over-estimation of creatinine rises secondary to iodinated contrast media.

Other investigators have produced similar findings, with Bruce and Pozniak reviewing 15,357 patient observations, with 6533 patients receiving intravenous iodinated contrast and 8824 unmatched controls receiving no contrast. There was no difference in the rate of renal dysfunction between the two groups (as defined as an increase in creatinine of 25% over baseline).
In the subgroup with pre-existing renal dysfunction (creatinine of 1.0–2.5 mg/dL), 22% of those who had iodinated contrast media developed CIN, compared with 11% in the non-contrast group.

This paper raises the multifactorial aetiology of CIN and suggests the concept of hospital-induced nephropathy (HIN) reflects the multifactorial aetiology of renal dysfunction in hospitalised patients undergoing enhanced imaging.

**Where does this new research leave us?**

Newhouse and colleagues have alerted us to the complexity of assessing the role of ICM in causing renal dysfunction in patients undergoing enhanced imaging. However, due to the absence of matched patients, it is not possible to reduce or dismantle the current protocols surrounding the intravascular administration of contrast media, particularly as these protocols are often set up to allow the responsibility for contrast administration to be devolved to trained nursing staff who rely on robust guidelines as they are often not in a position to make individual clinical-based decisions which require the advice of a radiologist.

**Will the question of CIN’s existence ever be resolved?**

This is unlikely, unless new studies randomise patient groups between contrast and no contrast, or select an appropriate matched patient group. Both these options are impractical and are unlikely to occur.

In the meantime, we need to give thought to how we manage those patients perceived to be at risk of CIN and, in the light of Newhouse’s study, have an enhanced consciousness of the risk/benefit ratio of offering patients alternative imaging that may be less effective at making the diagnosis or puts them at risk of other conditions such as nephrogenic systemic fibrosis.⁴

**Competing interests:** None known.

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**References:**

Vector-borne disease prevention: the need for a joint South Pacific approach

José G B Derraik, David Slaney, Edwin R Nye, Philip Weinstein

There seems to be a growing potential for widespread outbreaks or the introduction of vector-borne diseases in the South Pacific region, particularly those that are mosquito-borne. New Zealand for example, is at risk from the introduction and subsequent vector-borne disease outbreaks. Exotic mosquito vectors are established in the country (Aedes notoscriptus, Aedes camptorhynchus, and Culex quinquefasciatus) and other exotic species are regularly intercepted at New Zealand borders, including the Asian tiger mosquito Aedes albopictus. In addition, an increasing number of people are travelling between New Zealand and countries where vector-borne diseases are endemic, which leads to a regular influx of viraemic travellers. For instance, in the past few years there have been numerous outbreaks of dengue in the South Pacific whose impact reached New Zealand, where a significant increase in the number of cases of imported dengue was observed.

In 2007, of the 114 notified imported dengue cases, the most common countries travelled to during the incubation period were the Cook Islands (65.8% of cases) and Samoa (9.6% of cases). Such human pathogens could be passed, under favourable conditions, to local or future introduced vectors. The potential hazards to New Zealand are no different from those in other Pacific countries, with certain arboviruses being of particular significance and therefore concern, such as West Nile virus (WNV), Ross River virus (RRV), and more recently Chikungunya virus (CHIKV). An outbreak of CHIKV in the Réunion Island in 2005–6, in which Ae. albopictus was incriminated as the vector, led to an estimated 255,000 cases (affecting over 30% of the population), including 77 deaths. More recently, approximately 200 cases of CHIKV infection occurred in northern Italy, in which Ae. albopictus was again the likely vector involved. CHIKV has consequently been identified as an emerging pathogen, which poses a risk to other temperate areas, including New Zealand and Australia, should a vector such as Ae. albopictus become established.

For the Pacific Islands the risk of a CHIKV outbreak is greater as another vector (Aedes polynesiensis) is widespread in the region, and Ae. albopictus is also established in Cook Islands, Fiji, French Polynesia, Guam, New Caledonia, Papua New Guinea, Samoa, Seychelles, Solomon Islands, Tonga, Tuvalu, Vanuatu, and Wallis and Futuna. In addition, arboviruses can mutate rapidly to adapt to new locally available vectors, as also demonstrated recently by CHIKV. The authors acknowledge that no locally-acquired cases of RRV have been reported in New Zealand 11 years after Ae. camptorhynchus was first recorded in the country. This may be a result of limited known distribution of the species, low human population densities, an ongoing surveillance programme, and a multi-million dollar investment.
in an eradication campaign. These two programmes in particular, would not likely be possible in less wealthy countries in the South Pacific, which would consequently be at a greater risk of a disease outbreak following the arrival of a new vector or pathogen.

West Nile virus is another mosquito-borne pathogen that could potentially arrive in the South Pacific.\textsuperscript{12} For New Zealand, it has been proposed that the distribution of WNV would be most likely determined by the distribution of suitable vectors,\textsuperscript{13} which is potentially limited as the only known WNV vector in the country is \textit{Cx. quinquefasciatus}.\textsuperscript{14} However, recent mosquito collection and surveillance data indicate this species is distributed further afield than previously thought and it seems to have been spreading southwards.\textsuperscript{15} Furthermore, since the majority of native mosquitoes in New Zealand are most likely ornithophilic (primarily bird-feeders) and some appear to occasionally feed on humans,\textsuperscript{16} their potential role as WNV vectors certainly needs investigation.\textsuperscript{12}

The establishment of \textit{Ae. albopictus} would increase the likelihood of a WNV outbreak occurring as well,\textsuperscript{17} since this species has been found to be a very efficient laboratory vector of WNV,\textsuperscript{18} and it may be implicated in the ecology of the disease due to the isolation of the virus from this species in nature.\textsuperscript{14} More recent studies have highlighted the potential role of \textit{Ae. albopictus} as a bridge vector of WNV.\textsuperscript{34} Furthermore, it is important to point out that although these ecological limitations exist in New Zealand, the same would not apply to other South Pacific areas, as potential WNV vectors are present in all Pacific Islands.\textsuperscript{32}

Compounding the threat to the South Pacific region (especially to the more temperature areas) global warming will have a bearing on the wider situation as it would likely induce habitat changes and wider temperature fluctuations, which would favour viral replication in local hosts.\textsuperscript{19,20} New Zealand can again be used as an example, where a temperature increase of approximately 0.9°C has been recorded over the past 100 years, as well as reduced frost frequency over most of the country since the 1970s, and a continued retreat of major South Island glaciers.\textsuperscript{33}

South Pacific nations due to their close proximity, frequent exchange of goods and high flow of travellers are not independent from each other in regards to infectious diseases. We contend, therefore, that it is becoming increasingly important to support a collaborative integrated approach in the South Pacific for monitoring changes in species distributions and population dynamics of mosquitoes that could constitute a threat to public health, for tracking habitat and climatic changes, and to detect the occurrence of vector-borne diseases. This knowledge could be used to aid intervention strategies and to improve eradication and control programmes.

Essentially everywhere in the world there is an unfortunate reluctance to invest proactively in vector surveillance and prophylactic mosquito control measures in the absence of recognised disease outbreaks. Given the single most important factor determining the scale of an outbreak appears to be community awareness of and involvement in mosquito control,\textsuperscript{2} we suggest that a coordinated campaign be initiated in the South Pacific areas most at risk. In New Zealand for instance, it has been estimated that the public health costs from a RRV epidemic in the Auckland region could be tens to hundreds of millions of dollars.\textsuperscript{5}
The 2004 tsunami in Southeast Asia illustrates the need for collaborative regional hazard surveillance. Because the area of impact of a tsunami cannot be predetermined, it is necessary to have a surveillance network capable of giving any member country advanced warning. This situation is very similar to that of an introduction of exotic mosquitoes or other arthropod vectors, and of vector-borne disease outbreaks.

A practical example of an effective system is the WHO’s Global Influenza Programme, through which an international influenza surveillance system works to reduce the number of people affected by that disease annually and to prepare for future pandemics. Another example is the Global Alliance to Eradicate Lymphatic Filariasis, a multinational and multi-institutional partnership established to prevent parasite transmission, while alleviating the suffering and disability caused by it. In the South Pacific, apart from avoiding human suffering, the prevention of mosquito-borne disease outbreaks would also safeguard the tourism industry in the region, which underpins the economy of many nations.

The costs of programmes to prevent mosquito-borne diseases are relatively small when compared with the human suffering and the human, political and financial costs of the epidemics themselves, and the attendant vector control and other public health measures an epidemic necessitates. Many issues need to be addressed in the interest of the individual and of the common good. For example, New Zealand’s lack of confirmatory arboviral testing facilities is reason for concern, as it means that such tests for the South Pacific are currently only available in Australia—although New Caledonia and Fiji both have testing capability for some viruses.

This need is starting to be addressed through the development of confirmatory assays for arboviruses in New Zealand at the National Centre for Biosecurity and Infectious Disease (NCBID). The establishment of such capability in New Zealand would not only address its own testing requirements, but it would provide an important support facility for many Pacific nations in need of arboviral testing facilities, but which are much less able to afford it.

Such an approach is also consistent with developments in international public health policy, where there is a realisation that to decrease the public health risk to their own populations, higher income countries need to invest in protecting the health of more vulnerable populations in developing tropical countries that can act as sources of emerging infectious diseases.

A recent report from the United Kingdom’s House of Lords Select Committee on Intergovernmental Organisations have appropriately recognized the importance of transnational collaborations to tackle outbreaks of infectious diseases.

The report’s foreword adequately acknowledges that

…though Britain and many other countries have effective surveillance systems and though WHO operates a competent international surveillance network, many developing countries are seriously deficient in this respect. On the basis that a chain is as strong as its weakest link, there is a need to direct greater investment into this vital area of global disease control (p.5).

We believe that this statement is applicable to the situation in the South Pacific, and the support of such an approach would greatly strengthen the ability to reduce potential morbidity and mortality from vector-borne disease across the region.
We therefore encourage that extended support is given to the Pacific Public Health Surveillance Network. This will require continued and extended collaboration and funding support between epidemiologists, medical entomologists, non-government organisations and public health departments in New Zealand, Australia, and other South Pacific nations. Such collaboration should also link to international aid eradication programmes being developed in the South Pacific.

The adoption of transnational anti-vector measures in the region is also necessary. Furthermore, New Zealand should boost its commitment to establish its own diagnostic reference centre, capable of carrying out all necessary laboratory tests for detection and confirmation of arboviral infections.

Competing interests: None known.

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Temporal trends of acute nephrolithiasis in Auckland, New Zealand

Jason Du, Richard Johnston, Michael Rice

Abstract

Aim An increasing amount of evidence suggests that the occurrence of kidney stone disease has increased over the last 50 years. No data analysis on temporal trends in Auckland, New Zealand has ever been performed. The aim of this study was to investigate the changing pattern by age, ethnicity, and gender on stone incidence over a 10-year period.

Methods Demographic data was collected on all patients who presented with renal colic. Population numbers were provided by the New Zealand ministry of statistics using regular census data. The analysis was performed using Pearson's correlation coefficients and a Poisson regression model.

Results From 1997 to 2007, 17,532 new stones were coded as nephrolithiasis with an age range of 1–97. Disease incidence amongst Auckland residents was greater in 2007 than 1997 (0.131% or 131 per 100,000 population vs 0.102% or 102 per 100,000 population. p=0.012). The male to female ratio changed over time with a greater proportion of females presenting in 2007 than 1997 (0.47 vs 0.41, p<0.05). Pacific, Asian, and Māori incidence increased faster compared to European whilst those from the Middle East were the only group to have a stable rate (0.26% or 260/100,000 per year) over the 10-year period.

Conclusions Incidence of kidney stone disease in the Auckland region has increased significantly from 1997 to 2007. Different ethnic groups had different rates of change, but all groups showed an increasing incidence over time, with the exception of those from the Middle East. A greater proportion of patients are female than 10 years ago.

Numerous studies have suggested that the incidence and prevalence of kidney stone disease has been rising over the last few decades.1–3 However, no epidemiological data exist in New Zealand. Ureteric stones are not usually silent,4 typically causing patients considerable pain and suffering. In addition, costs for the diagnosis and treatment of kidney stone disease are not trivial,5 resulting in a substantial financial burden. Better knowledge about the epidemiology of kidney stone disease could contribute to improved disease prevention and financial planning.

Previous epidemiologic investigations of kidney stones have shown that the disease is more common in males than in females; Europeans are more affected than Asians and Africans. The disease incidence in men increases with age, peaking in the age group of those 40 to 59 years old.6–8 Ecological studies have suggested factors such as higher average temperature, greater sun exposure, increased water hardness, higher dietary calcium, protein, salt and low dietary fibre are associated with formation of kidney stones.7,9–11
Auckland has an ethnically diverse population which allows analysis of ethnic subgroups with variables such as weather, tap water hardness, and other environmental confounders being controlled for to some degree.

The primary aim of this study is to estimate the incidence of kidney stone disease in the Auckland, New Zealand population over 1997–2007. Secondary aims are to evaluate the association of kidney stones with gender, age, and ethnicity.

**Methods**

The greater Auckland region includes a population of over 1,300,000, which represents nearly 37% of the total population of New Zealand. Auckland also has the largest Polynesian population of any city in the world, as well as substantial European, Asian, Māori, and Middle Eastern populations.

The details of all renal and ureteric calculi within this population presenting to public hospitals in Auckland acutely between 1997 to 2007 were collected using clinical coding searches ICD-10-AM: N13.2 (*Hydronephrosis with renal and ureteral calculus obstruction*) and N20.0-9 (*Calculus of kidney and ureter*). Confirmation of kidney stones was done using CT scanning in the majority followed by conventional X-ray and ultrasound. All acute cases presenting to public hospitals in Auckland with renal and ureteric calculi were included.

Clinical data was linked with ethnicity data provided on hospital admission forms. These forms have a single check box for ethnicity, and are completed at the time of presentation. Population demographics data were obtained from the Ministries of Statistics and Health of New Zealand. This data is derived based on regular census activity. From 1997, the NZ Census Bureau allowed multiple ethnic grouping, in this study we used the “first choice” ethnic category.

Incidence and standard errors were computed for the Auckland region. For subpopulation comparisons, incidence estimates were adjusted to age range in keeping with the 1997, 2002 and 2006 Census population data for ages below 20 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and greater than 70 years. Assessment of temporal changes in incidence of kidney stone disease was based on 95% confidence interval (CI) estimates of the difference between time-period incidence estimates.

A Poisson regression analysis was used. Categorical independent terms included in the model were age, ethnicity and gender. All statistical analyses were performed using SAS statistical software.

**Results**

17,532 patients identified with nephrolithiasis from 1997 to 2007 in Auckland, New Zealand. Age ranged from 1 to 97 years old with a mean of 48.6 years for men and 47.5 years for women.

The incidence of nephrolithiasis amongst the population of Auckland significantly increased from 0.102% or 102 per 100,000 per year (±0.013% 95%CI) in 1997 to 0.131% or 131 per 100,000 per year (±0.013% 95%CI) in 2007 (p =0.039). See Table 1 and Figure 1.

Incidence of nephrolithiasis was greater in 2007 than 1997 for every decade of age. However there was no significant change in the average age at presentation over the study period, with the range being 46.7–47.9. Similarly the incidence increased in every decade in a relatively uniform manner, meaning that the age distribution showed no significant change.

The male to female ratio of patients with nephrolithiasis in Auckland also changed significantly from 1997 to 2007 with a greater proportion of females in 2007. In 1997, 41% (±0.029 95%CI) of patients were female compared with 47% (±0.024 95%CI) in
2007 (p<0.05). The population male to female (M:F) ratio remained constant over the study period at 49:51. See Figure 2.

Table 1. Nephrolithiasis incidence estimates by year with 95% confidence intervals

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>0.102 % or 102/100,000</td>
<td>± 0.013 %</td>
</tr>
<tr>
<td>1998</td>
<td>0.109 % or 109/100,000</td>
<td>± 0.013 %</td>
</tr>
<tr>
<td>1999</td>
<td>0.111 % or 111/100,000</td>
<td>± 0.013 %</td>
</tr>
<tr>
<td>2000</td>
<td>0.109 % or 109/100,000</td>
<td>± 0.013 %</td>
</tr>
<tr>
<td>2001</td>
<td>0.116 % or 116/100,000</td>
<td>± 0.013 %</td>
</tr>
<tr>
<td>2002</td>
<td>0.113 % or 113/100,000</td>
<td>± 0.013 %</td>
</tr>
<tr>
<td>2003</td>
<td>0.124 % or 124/100,000</td>
<td>± 0.013 %</td>
</tr>
<tr>
<td>2004</td>
<td>0.121 % or 121/100,000</td>
<td>± 0.013 %</td>
</tr>
<tr>
<td>2005</td>
<td>0.127 % or 127/100,000</td>
<td>± 0.012 %</td>
</tr>
<tr>
<td>2006</td>
<td>0.132 % or 132/100,000</td>
<td>± 0.012 %</td>
</tr>
<tr>
<td>2007</td>
<td>0.131 % or 131/100,000</td>
<td>± 0.012 %</td>
</tr>
</tbody>
</table>

Figure 1. Incidence of nephrolithiasis over the study period with trend line
In 2007 the Middle Eastern population in Auckland had the highest incidence of nephrolithiasis amongst all ethnic groups (0.254% or 254/100,000±0.064%). This is followed by European (0.142% or 142/100,000±0.015%), Pacific Island (0.131% or 131/100,000±0.022%) and Māori (0.089% or 89/100,000±0.019%) populations with the Asian population having the lowest incidence of nephrolithiasis (0.073% or 73/100,000±0.024%). See Table 2.

Table 2. Incidence of nephrolithiasis by ethnicity over the study period

<table>
<thead>
<tr>
<th>Year</th>
<th>European</th>
<th>Māori</th>
<th>Pacific</th>
<th>Asian</th>
<th>Middle East</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>0.109%</td>
<td>0.073%</td>
<td>0.112%</td>
<td>0.057%</td>
<td>0.220%</td>
</tr>
<tr>
<td>1998</td>
<td>0.110%</td>
<td>0.102%</td>
<td>0.103%</td>
<td>0.062%</td>
<td>0.256%</td>
</tr>
<tr>
<td>1999</td>
<td>0.119%</td>
<td>0.070%</td>
<td>0.101%</td>
<td>0.070%</td>
<td>0.210%</td>
</tr>
<tr>
<td>2000</td>
<td>0.118%</td>
<td>0.069%</td>
<td>0.126%</td>
<td>0.065%</td>
<td>0.230%</td>
</tr>
<tr>
<td>2001</td>
<td>0.120%</td>
<td>0.078%</td>
<td>0.112%</td>
<td>0.066%</td>
<td>0.211%</td>
</tr>
<tr>
<td>2002</td>
<td>0.125%</td>
<td>0.079%</td>
<td>0.120%</td>
<td>0.071%</td>
<td>0.263%</td>
</tr>
<tr>
<td>2003</td>
<td>0.131%</td>
<td>0.085%</td>
<td>0.130%</td>
<td>0.071%</td>
<td>0.251%</td>
</tr>
<tr>
<td>2004</td>
<td>0.132%</td>
<td>0.079%</td>
<td>0.125%</td>
<td>0.072%</td>
<td>0.211%</td>
</tr>
<tr>
<td>2005</td>
<td>0.132%</td>
<td>0.088%</td>
<td>0.129%</td>
<td>0.075%</td>
<td>0.243%</td>
</tr>
<tr>
<td>2006</td>
<td>0.137%</td>
<td>0.093%</td>
<td>0.125%</td>
<td>0.076%</td>
<td>0.255%</td>
</tr>
<tr>
<td>2007</td>
<td>0.142%</td>
<td>0.089%</td>
<td>0.131%</td>
<td>0.073%</td>
<td>0.254%</td>
</tr>
</tbody>
</table>

The variation in incidence over the study period by different ethnic groups is represented in Figure 3. Although the Middle Eastern population had a higher incidence compared to other ethnic groups, their incidence over the study period remained stable with no positive or negative correlation. However, in all other ethnic
groups (European, Pacific Island, Māori, and Asian) there was a positive correlation in the incidence over the study period. When analysed with the Poisson regression model, only the European population had a statistically significant rise (p=0.032) between 1997–2007.

**Figure 3. Variation in incidence of nephrolithiasis by different ethnic groups over the study period**

<table>
<thead>
<tr>
<th>Year</th>
<th>European</th>
<th>Māori</th>
<th>Asian</th>
<th>Pacific</th>
<th>Middle East</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>0.102%</td>
<td>0.102%</td>
<td>0.102%</td>
<td>0.102%</td>
<td>0.102%</td>
</tr>
<tr>
<td>1998</td>
<td>0.200%</td>
<td>0.200%</td>
<td>0.200%</td>
<td>0.200%</td>
<td>0.200%</td>
</tr>
<tr>
<td>1999</td>
<td>0.300%</td>
<td>0.300%</td>
<td>0.300%</td>
<td>0.300%</td>
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**Discussion**

This is the only study to analyse and describe the temporal trends of kidney stone disease incidence in the population of Auckland. The incidence of kidney stone disease among the population of Auckland, New Zealand increased significantly from 0.102% (102/100,000) to 0.131% (131/100,000) from 1997 to 2007.

Gender analysis revealed a statistically significant increase in the proportion of females presenting in 2007 (47%) compared with that of 1997 (41%) consistent with overseas evidence. According to the national census, the population male to female ratio in Auckland did not change significantly over that period, indicating the increase in incidence of females with kidney stone disease observed in the population of Auckland is true, rather than apparent, secondary to an increase in the female population.

Speculations for this increase in female incidence include dietary and lifestyle changes. For example, declining consumption of calcium-rich dairy products among younger women has been correlated with increased risk of stone formation. Although the exact reasons for this increase remain to be investigated.
Ethnicity analysis revealed that in the Auckland population, the European population had a significant change in incidence from 0.109% or 109/100,000 to 0.142% or 142/100,000 over the study period. Pacific Island (0.112% or 112/100,000 to 0.131% or 131/100,000), Māori (0.073% or 73/100,000 to 0.089% or 89/100,000), and Asian (0.057% or 57/100,000 to 0.073% or 73/100,000) showed a similar significant trend to increasing incidence.

The reduced incidence of stone disease in the Asian population compared with other ethnic groups is consistent with previous analyses done on Asian populations in other areas. Of note, the Middle Eastern population were the only subgroup to show no increase in incidence over the study period. Despite this, they had the highest average incidence of kidney stone disease (0.237% or 237/100,000). This high incidence is consistent with previous studies done on Middle Eastern populations in other areas.

The Middle Eastern population in Auckland is characterised by a large number of recent immigrants, therefore, there was no way to accurately determine whether their stones were formed in Auckland during the study period or if they had pre-existing stones when they emigrated. In addition, the incidence of kidney stone disease in the Middle Eastern population was the most variable compared with other ethnic subgroups during the study period. We think this could be attributed to the relatively small population and stone event numbers.

Our results clearly showed an increase in incidence in the Asian, Pacific Island, Māori and European populations. Previous studies conducted in other countries have demonstrated an increase in frequency of kidney stone disease in European and Asian populations. No temporal trend data was available in the Polynesian and Māori populations.

The different incidence between these subgroups could well be attributable to differing aspects of lifestyle. However, the general increase in incidence observed over the study period would probably suggest the presence of an etiological factor affecting the entire population in Auckland.

Overseas studies have suggested numerous factors which may contribute to increasing risk of kidney stone disease including sunlight and heat, water hardness, dietary consumption of animal protein, salt, alcohol, and certain comorbid conditions. Possible mechanisms involving several of these factors have been advanced to explain why people of different ethnic origin living in different areas confer different risks of stone formation. However, we compared the population of Auckland over 1997–2007 only, and according to the New Zealand National Institute of Weather and Atmospheric Research (NIWA) the annual average temperature and sunshine hours in Auckland has not changed over the study period. Therefore, this is less likely to be a factor in the observed increasing kidney stone disease incidence.

Other factors may have also contributed to these observed changes. Perhaps the most likely reason for the observed increase in disease over the study period is due to changes in health-related behaviours such as increased modified protein, saturated fats, salt, alcohol, and caffeine intakes, and decreased fibre and vegetables intakes.

Total diet surveys for New Zealand have been conducted in 1996/7 and 2002/3. This showed clearly that average calcium intake, energy intake, percentage protein and
percentage fat in diet amongst all age ranges has increased. The surveys also showed that dietary fibre and vegetables have decreased over the study period. Indeed, these factors may be the driving force in the change in incidence of kidney stone disease.

Interestingly, previous reports have suggested that an inverse relationship between the frequency of kidney stones and indicators of socioeconomic levels exist. In the Auckland population, Māori and Pacific Island populations are generally of lower socioeconomic levels and yet, their kidney stone incidence were not of the highest when compared to other ethnic subgroups.

We were limited in our ability to examine all hypothesised associations mentioned above. We did not collect information regarding dietary consumption, water hardness and other comorbidities. It should be noted that a previous study of women residents of three communities in the United States with differing mineral content of their water supplies reported that residence in the high-calcium water community was not associated with a higher prevalence of kidney stones. Auckland’s water supply has been constant over the study period, with minimal variations in water mineral content and hardness.

Conclusion

The incidence of kidney stones in the population of Auckland, New Zealand was significantly greater in 2007 compared to 1997. Moreover a significantly greater proportion of females had kidney stones in 2007 compared to 1997. Disease incidence varied between different ethnicity groups and the rate of increase also varied.

The fact that all ethnic groups showed an increase in incidence, except that of the Middle Eastern population, suggests that both genetic and environmental factors such as dietary changes are influential in kidney stone disease.

Further studies should target environmental risk factors such as dietary consumption of modified protein, saturated fats, water hardness and sunlight exposure with a goal to devise primary stone prevention strategies to reduce kidney stone disease burden in the population.

Competing interests: None known.

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References:

Abstract

Background We conducted an audit of transient ischaemic attack (TIA) services in New Zealand to determine how current practice compares to best practice recommendations.

Methods A brief written questionnaire was sent to all district health boards (DHBs) concerning service provision, clinical management and clinical audit activity related to patients with TIA.

Results Questionnaires were completed by all 21 DHBs. In 18 of 21 (71%) DHBs, most TIA patients were managed by acute services; 3 (14%) DHBs routinely admit most patients and 15 (72%) see most patients in hospital emergency departments or acute assessment units. Three (14%) DHBs see most TIA patients in outpatient clinics, with a usual wait to be seen of more than 1 week. Delays of more than a week were common for carotid ultrasound scans (10 DHBs, 48%) and carotid endarterectomy when indicated (16 DHBs, 76%). Only 4 (19%) DHBs had audited TIA management at a patient level and 3 (14%) at a service level.

Conclusions There are major discrepancies between current management of TIA patients and best practice recommendations in national and international guidelines. Significant regional variations in models of care and access to investigations exist. The provision of dedicated appropriately resourced TIA services within an organised stroke service should be seen as a priority.

Transient ischaemic attack (TIA) is defined as symptoms of stroke that resolve within 24 hours. In recent years it has become clear that the risk of stroke following TIA is higher than previously thought. In the population-based OXVASC study, stroke risk was 8% at 1 week, 11.5% at 1 month, and 18.2% at 3 months following a TIA. In a hospital-based study, the stroke risk was 10.5% in the three months following a TIA. Approximately 85% of the strokes that follow a TIA are fatal or disabling.

Early intervention following TIA may reduce the risk of stroke by up to 80%. However, half of the strokes that follow a TIA occur in the first 48 hours, so that the time window for intervention is brief. New Zealand guidelines recommend that TIA patients at high-stroke-risk be assessed by a specialist and all investigations completed within 24 hours.

We conducted an audit of TIA services provided in New Zealand to determine how current TIA management compares with national and international guidelines.

Methods

In August 2008 a postal questionnaire was sent to the director of medical services or physicians known to have an interest in stroke and TIA at all 21 district health boards (DHBs) in New Zealand. The
questionnaire was designed by the authors, focused on the organisation of TIA services provided by the DHB and could be completed in less than 10 minutes. The questionnaire concluded with a free text section for respondents to identify particular areas of concern relevant to their DHB. After 6 weeks, clinicians from DHBs that had not returned the questionnaire were contacted directly by email and telephone.

Results

Responses were obtained from all 21 DHBs. Thirteen of 21 (62%) respondents were clinicians with an interest in stroke/TIA; 12 (57%) were a physician who took overall responsibility for stroke/TIA services at their DHB (5 neurologists, 4 “stroke physicians”, 2 general physicians, and 1 geriatrician), and one was a nurse specialist who coordinated local stroke/TIA services (Table). Respondents in the remaining eight DHBs were three general physicians, three geriatricians, a visiting neurologist and a medical officer.

Eighteen of 21 (86%) DHBs indicated that most patients with TIA are managed by acute services; 3 (14%) DHBs routinely admit all patients and 15 (72%) DHBs see patients in the emergency department or acute assessment units. Three (14%) DHBs indicated that most patients with TIA are managed in the outpatient setting. The usual time from referral to specialist assessment in these three DHBs was 72 hours to a week in one DHB and a week or more in the other two DHBs.

Six of 21 (29%) DHBs provide a “TIA clinic” i.e. a dedicated outpatient service for the assessment and management of patients with TIA. This service was available 1–4 days/week and the waiting time to be seen was 3–7 days in two DHBs and more than a week in the other 4 DHBs.

TIA patients who required admission to hospital for further investigation and management were admitted to general medical wards or short stay units in 18 (86%) DHBs and stroke units in 3 (14%) DHBs. Follow-up of TIA patients was routine in 4 (19%) DHBs. General practitioners (GPs) could request follow up in all 21 DHBs and patients could self-refer for an outpatient review in 3 (14%) DHBs.

Brain imaging was obtained in all TIA patients in nine (43%) DHBs and in “most patients” in the remaining 12 (57%) DHBs. CT brain scans were available 24 hours per day in 17 (81%) DHBs, days and evenings in three (14%) DHBs and working hours in one (5%) DHB. The usual waiting time for brain imaging was same day or within 24 hours in 13 (62%) DHBs, between 24 hours and 1 week in 5 (24%) DHBs, and more than 1 week in three (14%) DHBs. The usual wait for carotid ultrasound scans, where indicated, was within 1 week in 11 (52%) DHBs, between 1 week and 1 month in 9 (43%) DHBs and more than 1 month in one (5%) DHB.

For patients with significant internal carotid artery (ICA) stenosis the usual wait for carotid endarterectomy, where this was indicated, was within 1 week in 5 (24%) DHBs, between 1 week and 1 month in 12 (57%) DHBs and more than 1 month in 4 (19%) DHBs. Three (14%) DHBs indicated that the usual wait for carotid endarterectomy was more than 6 months.
Table 1. Results by District Health Board population

<table>
<thead>
<tr>
<th>Population served by DHB</th>
<th>&lt;80,000 (n=5)</th>
<th>80–180,000 (n=9)</th>
<th>&gt; 180,000 (n=7)</th>
<th>Total (%) (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA Clinician</td>
<td>1</td>
<td>5</td>
<td>7</td>
<td>13 (62)</td>
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<tr>
<td>Location most patients managed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED/Acute assessment</td>
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<td>7</td>
<td>5</td>
<td>15 (72)</td>
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<tr>
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<td>3 (14)</td>
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<td>3 (14)</td>
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<td>1</td>
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<tr>
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<td>0</td>
<td>3</td>
<td>3 (14)</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Within 1 week</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>11 (52)</td>
</tr>
<tr>
<td>1 week to 1 month</td>
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<td>4 (19)</td>
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<tr>
<td>At service level</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3 (14)</td>
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Thirteen of 21 (62%) DHBs had local guidelines for the management of TIA patients. Local guidelines incorporated the ABCD² score in nine of 13 (43%) DHBs, recommended investigations in 11 (52%) and secondary prevention strategies in 11 (52%) DHBs. Five (21%) DHBs used a clinical pathway for the assessment and management of TIA. Routine audit of TIA services was carried out in only 4 (19%) DHBs at the patient level, and only 3 (14%) DHBs at the service level.

Nineteen of 21 (90%) respondents identified areas they would most like to improve in their region. These included the development of specialised TIA clinics (7 of 19 DHBs, 37%), reduced waiting times for investigations (7 DHBs, 37%), improved staff and patient education (6 DHBs, 32%), development of clinical pathways (5 DHBs, 26%) and appointment of a stroke specialist (4, 21%).

Discussion

This survey has demonstrated discrepancies between the management of TIA patients in New Zealand and best practice recommendations in national and international guidelines. Significant regional variations in models of care also exist. There are unacceptable delays in almost all DHBs for specialist assessment of patients. Once patients are seen, there are further delays in obtaining investigations such as carotid ultrasound and interventions such as carotid endarterectomy, where indicated.
Almost 40% of DHBs have no TIA guidelines suggesting the management of TIA may be provided on an ad hoc basis. Few DHBs have audited TIA services resulting in a missed opportunity improve services at a patient and service level.

In patients presenting with TIA there is a one in 20 risk of a completed stroke in the next seven days. Furthermore, about one in five strokes that follow TIAs are fatal and a further two thirds are disabling. This represents a much worse prognosis for TIA patients than for those presenting with chest pain.

In a study of 212 patients with unstable angina admitted to a chest pain unit and thought to be at intermediate risk for cardiovascular events, adverse events occurred in only three percent of patients (5 myocardial infarctions, 1 death from cardiovascular causes and 1 case of congestive heart failure). Nevertheless, chest pain is treated as an emergency and people are advised to call emergency services so they can be transported immediately to hospital.

Most patients are monitored for between 6 and 24 hours in the emergency department, a chest pain observation unit or an inpatient bed and those with high risk features are admitted to coronary care units. Given the reasonably high risk of stroke in the days following a TIA, patients presenting with transient neurological symptoms should be managed as seriously as those with chest pain.

Tools are now available for the rapid risk stratification of patients presenting with a TIA. The 7-point ABCD² score incorporates Age (≥60 years), Blood pressure (≥140/90 at first assessment), Clinical features (unilateral limb weakness 2 points, speech disturbance without weakness, 1 point), Duration of symptoms (10–59 minutes, 1 point and ≥60 minutes, 2 points), and Diabetes requiring treatment. Patients can be stratified into low risk (<4 points) and high-risk (4 - 7 points) groups.

High-risk patients have a stroke risk of 3.5 - 8 % in the next 48 hours and 6–12 % in the next week. Risk stratification enables decisions on the management of a TIA patient to be based on an individual’s stroke risk.

The ABCD² score has also been shown to improve the accuracy of TIA diagnosis, with higher ABCD² scores more likely in those with a true TIA. Accuracy of diagnosis is important given that people presenting with non-specific neurological symptoms are frequently misdiagnosed as having TIA.

Up to 80% of strokes that follow TIA may be prevented. This is likely due to the institution of anti-platelet therapy, anti-coagulation for those in atrial fibrillation, cholesterol and blood pressure lowering therapy, carotid re-vascularisation for surgical candidates with moderate to severe ICA stenosis, and education about the importance of urgent hospital presentation if there are further symptoms so that thrombolytic therapy can be considered.

Provision of a service that assesses TIA patients within 24 hours can potentially lead to a 5 - 8% absolute risk reduction of stroke with 12 to 21 TIA patients needing to be seen within 24 hours to prevent one stroke. It is therefore of concern that two DHBs stated that most patients were assessed in outpatient clinics with a usual waiting time of 1 week or more. This failure to rapidly assess patients with TIA represents a missed opportunity for stroke prevention.
This survey identifies significant delays in obtaining investigations. All TIA patients with non-disabling carotid territory symptoms and who are fit for surgery should have carotid imaging performed. This is because the prompt identification and surgical management of moderate to severe ICA stenosis in selected TIA patients can significantly reduce the risk of subsequent stroke. In those patients with symptomatic 70–99% ICA stenosis, the number needed to treat (NNT) with carotid endarterectomy is six to prevent one ipsilateral stroke by 2 years.13

The benefit is less in patients with 50–69% ICA stenosis and the place of surgery needs to be considered on a case by case basis in conjunction with a vascular surgeon. The benefit of carotid endarterectomy diminishes as the time from TIA increases with the absolute risk reduction halved if surgery is delayed beyond 2 weeks, and halved again if the delay is more than four weeks. However, access to carotid ultrasound scans is limited with a wait of more than 1 week in half of the DHBs. It is also of concern that the usual wait for carotid endarterectomy is greater than 1 week in 16 (76%) DHBs and more than 1 month in 4 (19%) DHBs.

This study has a number of limitations. Questionnaires offer a convenient means of surveying clinical practice in a large number of hospitals. This survey is one of a number on the provision of stroke services carried out over a number of years and so we have been able to identify individuals with interest in stroke and TIA in most of the DHBs.14,15 However, it is possible that these are not the most appropriate people to complete the survey within an institution. Furthermore, responses may reflect the opinions of the respondents and not actual practice.

We did not attempt to verify responses but made it clear that no hospital would be identified. It is reasonable to assume that the survey gives an acceptable picture of TIA services within New Zealand.

So what is the way forward? Public education campaigns to increase awareness of the symptoms and signs of TIA and stroke are required. In a 2007 telephone survey, 35% of 1000 respondents could not identify any stroke symptoms and a further 25% could only name only a single symptom.

The Stroke Foundation of NZ, along with many international stroke associations promote the FAST message (Face, Arm, Speech and Time), which identifies more than 80% of those who present with stroke and TIA.6 Electronic decision support software tools for general practitioners may improve the accuracy of TIA diagnosis and indicate appropriate, investigation, treatment and triage for individual patients. A trial of such a system is planned in the MidCentral District Health Board from late 2009.17

The New Zealand Guidelines for the Assessment and Management of People with Recent TIA recommend that DHBs should plan TIA services for 3 per 1000 people per year.6 This figure is based on data from the population-based OXVASC study and includes a projected outpatient referral rate for minor stroke and TIA of 1.79 per 1000 and “non-cerebrovascular diagnoses” in the remaining 39% of patients.12 A “non-ischaemic” diagnosis was made in 22% of patients presenting to a large acute TIA service in Paris.3 Many of the non-ischaemic patients seen in a TIA clinic have conditions such as epilepsy or migraine and still need to be seen by a specialist.

TIA services should include an appropriately resourced, open-access, daily specialist outpatient clinic, an inpatient short stay unit or a combination of these services. In
smaller DHBs with insufficient population to warrant specialised TIA services, this should be provided by general medical services with access to neurology and vascular surgical support. Each DHB should have locally agreed protocols for the assessment and management of TIA, regardless of where patients are initially seen.

High-risk TIA patients should be seen within 24 hours, including weekends and public holidays, and appropriate investigations performed and secondary prevention measures started. Carotid endarterectomy should be performed within 2 weeks when indicated.6

Meeting these recommendations will require a major commitment from clinicians, DHB management teams and the Ministry of Health, and both fiscal and personnel resource constraints will need to be addressed. Substantial underestimation of the need for outpatient services for TIA and minor stroke exist.12 However, organised, appropriately resourced TIA services have the potential to reduce the number of people with stroke and, with direct DHB health costs of approximately $50,000 per new stroke patient,16 only a small number of strokes need be prevented to justify any increase in spending.

Competing interests: None known.

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References:


Hospital stay and early complication rates following joint replacement: is there any ethnic difference in New Zealand?

Pai Vasu, Vishal Pai, Sophie Wrighton

Abstract

It is clear that there is no benefit in considering the ethnic origin of a patient when preparing for surgery. Instead, each patient should be considered in turn, taking their comorbidities, lifestyle, and ASA score into account. Thorough preoperative assessment is vital to enable recognition and treatment of any pre-existing medical conditions thus ensuring optimal fitness of the patient prior to surgery. It is also of financial and medical benefit to minimise waiting time prior to surgery.

Osteoarthritis is a degenerative condition of the joints. The joints most commonly involved are the hip; knee; and distal interphalangeal, proximal interphalangeal, and carpometacarpal joints in the hand. Its prevalence and severity increase with age.

Total joint replacement (TJR) has been widely used for the treatment of advanced osteoarthritis which has not responded well to nonoperative methods.\(^1\) The most commonly seen of these are total hip replacement (THR) and total knee replacement (TKR). The operations are effective (reducing pain and increasing mobility) but are not without complications.\(^2\) As well as general surgical complications (bleeding, thromboembolic events, infection), there is a risk of periprosthetic fracture, dislocation (in THR), nerve damage, and aseptic loosening.\(^3\)

Factors effecting complication rates have been investigated at length and include surgical technique, implant selection, and absence of follow-up.\(^4\) One other factor that could affect outcome, but not yet investigated, is ethnic difference.

Gisborne has a high Māori population (47%) as compared to rest of New Zealand and is therefore an ideal place to compare Māori to Caucasians (European New Zealanders). There are definite differences with respect to medical comorbidities between the two populations, with smoking, alcohol consumption, obesity, diabetes, gout, and cardiac problems being particularly prevalent in Māori patients.\(^5\)

A prospective study was carried out at Gisborne Hospital by a single surgeon [VSP] to ascertain whether there is any difference between these two populations. This study is to document any difference exist between Māori and Caucasians with respect to postoperative hospital stay and early complication rates.

Materials and Methods

Of the 100 consecutive patients, 10 were not included in the study (4 did not undergo operation due to high medical risk, 3 were not adequately followed up, and 3 failed to answer the questionnaire). The remaining 90 received THR (n=54) or TKR (n=36).

All patients were grouped under ASA classification\(^6\) to help recognise those requiring postoperative high dependency unit admission.\(^7,8\) Fifty patients required a preadmission anaesthetic review to assess pre-existing medical comorbidities, while the remaining 40 were considered medically fit for surgery.
Age range was 43 to 87 years (mean: 64.9 years for Māori and 67.8 years for Caucasians). Fifty percent were women (n=45). Fifty-two participants (58%) were Caucasian and 38 (42%) were Māori. The two populations were comparable with respect to age, sex, and clinical indication for THR and TKR (Table 1), and showed little difference in ASA scores (Table 2). However, Māori patients were more likely to be obese (37% had BMI>30), more likely to be diabetic (15%), and more likely to be smokers (32%).

Table 1. Demographics of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Māori (n=38)</th>
<th>Caucasian (n=52)</th>
<th>All patients (N=90)</th>
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</thead>
<tbody>
<tr>
<td>Age range (years)</td>
<td>43–82</td>
<td>45–87</td>
<td>43–87</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>64.9</td>
<td>67.8</td>
<td>66.56</td>
</tr>
<tr>
<td>Gender ratio (M:F)</td>
<td>19:19</td>
<td>26:26</td>
<td>45:45</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>32.4</td>
<td>13.4</td>
<td>21.1</td>
</tr>
<tr>
<td>Diabetics (%)</td>
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<td>10</td>
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<tr>
<td>BMI &gt;30 (%)</td>
<td>36.8</td>
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<td>24.4</td>
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Table 2. ASA* scores

<table>
<thead>
<tr>
<th>ASA score</th>
<th>Māori</th>
<th>Caucasian</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>II</td>
<td>21</td>
<td>25</td>
<td>46</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*American Society of Anesthesiologists

The surgeon observed that Māori patients were less likely than Caucasian patients to have family or friends who had received joint replacement or to have a good understanding of joint replacement as a form of treatment.

Following the procedure, all early complications (3 months postoperative) were obtained from clinical notes by an independent assessor. In addition, length of postoperative hospital stay was noted.

Results

Perioperative and postoperative complication rates showed no significant difference between the two populations, relative to the population sizes (Table 3). Similarly, the postoperative hospital stay was comparable in both populations, with Māori patients staying slightly longer on average (Table 4). The trend seen with hospital stay and ASA scores showed a positive correlation as expected, with higher ASA score predicting longer recovery periods (Table 4).
Table 3. Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Māori</th>
<th>Caucasian</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Deep</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound ooze</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Haematoma</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>1 DVT</td>
<td>1 DVT and PE</td>
<td>2</td>
</tr>
<tr>
<td>Nerve damage</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dislocation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Revision joint</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intra-operative fracture</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Aseptic loosening</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

DVT=deep vein thrombosis; PE=pulmonary embolism.

Table 4. Postoperative hospital stay

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (days)</th>
<th>Range (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Māori</td>
<td>7.42</td>
<td>4–15</td>
</tr>
<tr>
<td>Caucasian</td>
<td>7.22</td>
<td>4–14</td>
</tr>
<tr>
<td>ASA I</td>
<td>6.0</td>
<td>4–9</td>
</tr>
<tr>
<td>ASA II</td>
<td>7.8</td>
<td>5–15</td>
</tr>
<tr>
<td>ASA III</td>
<td>9.3</td>
<td>6–14</td>
</tr>
</tbody>
</table>

The mean time from orthopaedic clinic to the anaesthetic clinic was 1.38 months. Four patients had a 6–7 month delay due to sophisticated cardiac investigation (not included in mean wait time). The mean time from the orthopaedic clinic to the date of surgery was 2.81 months (range: 15 days to 7 months).

Discussion

Despite notable differences in pre-assessment findings of comorbidities and lifestyle among Māori and Caucasians, hospital stay and complication rates were similar in both populations. Research suggests that patients with diabetes mellitus have higher postoperative requirements for rehabilitation, therefore, it might be expected (due to higher prevalence) that hospital stay in Māori patients would be higher. This study did not produce conclusive data on this matter.

It has been noted that complication rates are particularly low in this series. We feel that preoperative assessment has a major role in lowering postoperative medical complications. Clelland\textsuperscript{10} found that 32% of patients evaluated for TJR benefited from findings on the preoperative medical evaluation. This thorough preoperative assessment may also explain the equivocal outcome with respect to ethnicity seen in this study.

Fielden et al\textsuperscript{11} found that longer waits for THR incur greater economic costs and deterioration in physical function while waiting. In New Zealand, 30% had been waiting for 6 months or more for care and 6% had been waiting for 24 months or more. Our series, no patient waited more than 4 months and the average wait from
orthopaedic clinic to surgery was 2.81 months (range 15 days to 7 months). This is probably due to the “Government Joint Initiative Scheme”, but we feel that the efficiency of the waiting list co-ordinator as well as hospital staff involved in this work is equally important.

Although our investigation suggested no difference between Māori and Caucasian patients with regards to hospital stay, there was good correlation between length of stay and ASA score. Patients with ASA I stayed an average of 6.0 days compared to 9.3 days for patients with ASA III. These findings were in line with those previously documented.6,7

Competing interests: None known.

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References:
Dietary supplement use in the prevention of age-related macular degeneration progression

Aparna Raniga, Mark J Elder

Abstract

**Purpose** The Age-Related Eye Disease Study Group (AREDS) has found high-dose vitamin supplementation may have a role in preventing the progression of Category 3 and 4 age-related maculopathy. The aim of this study is to compare dietary antioxidant, zinc, and copper intakes of Australia, New Zealand, United Kingdom, and the United States to determine the difference between the actual and suggested AREDS intakes for these nutrients. A further aim is to investigate the constituents of commonly available single and multivitamin preparations in New Zealand and carry out a cost analysis.

**Methods** The total median intake of vitamins A, C, and E; zinc; and copper is analysed from the most recent nutrition data published by the four countries. Forty multivitamin brands and 32 individual nutrient brands were analysed. An average price per tablet for each brand has been calculated in New Zealand dollars.

**Results** The median intakes of antioxidants, zinc, and copper for these countries were comparable, but lower than the AREDS suggested intakes. Sixteen of the 40 multivitamin preparations contained all recommended nutrients. Of these, only two fulfilled the AREDS-recommended levels. The cost of different preparations is similar.

**Conclusion** Dietary supplementation is required to achieve the AREDS nutrient intake recommendations. This may be achieved by using any combination of multivitamin and individual supplement preparations available. Comprehensive tables have been constructed to guide ophthalmologists in the process of suggesting supplementation to prevent the progression of Category 3 and 4 age-related maculopathy.

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in the developed world among people aged 65 years or older. Oxidative damage has been implicated in the pathogenesis of AMD, secondary to the retina’s high consumption of oxygen, its high proportion of polyunsaturated fatty acids, and its exposure to visible light.

Further evidence suggests that a complex interaction of cellular and vascular factors also plays a part. Currently, there is no proven treatment that slows or prevents the progression of advanced dry AMD but laser photocoagulation and photodynamic therapy may slow the rate of visual acuity loss. Of late, anti-vascular endothelial growth factors such as bevacizumab and ranibizumab have have shown unprecedented efficacy in treating neovascular AMD with many patients experiencing improvement in vision. However, the literature describes some potentially serious side effects such as endophthalmitis, retinal pigment epithelial tears, and submacular...
haemorrhage so ongoing trials will help guide their use in age-related macular degeneration.\textsuperscript{6,7}

Over the last decade, numerous cross-sectional and cohort studies have investigated the role of antioxidant supplementation in preventing age-related maculopathy.\textsuperscript{8} The largest randomised controlled trial, undertaken by the Age-Related Eye Disease Study (AREDS) Group, compared antioxidant and zinc supplementation to placebo.\textsuperscript{4} The trial arm included patients with extensive intermediate size drusen, at least one large druse, non-central geographic atrophy in one or both eyes (Category 3), advanced AMD, or vision loss due to AMD in one eye (Category 4).

Antioxidant doses used were 500 mg vitamin C, 400 IU vitamin E, 15 mg beta carotene, with 80 mg zinc as zinc oxide and 2 mg copper as cupric oxide.\textsuperscript{1} The AREDS Group demonstrated a statistically significant odds reduction for the risk of progression to advanced AMD and reduction in the rate of at least moderated visual acuity loss with the use of tablets containing antioxidants plus zinc (OR 0.72; 99\%CI 0.52–0.98).\textsuperscript{4}

A Cochrane review found that people taking supplements were less likely to lose 15 or more letters of visual acuity (adjusted OR 0.77; 99\%CI 0.58–1.03).\textsuperscript{11} Since the publishing of the AREDS study, dietary supplements of all varieties have been increasingly marketed across the world, including single-ingredient products and various combinations of vitamins, minerals, botanicals and other constituents.

We evaluated commonly encountered dietary supplements and eye nutrient products in order to compare their ingredients with the AREDS Group recommendations for age-related macular degeneration. Furthermore, we carried out a cost-based survey of products marketed in New Zealand (NZ) in order to provide ophthalmologists and other medical practitioners a resource when advising dietary supplementation in Category 3 and Category 4 AMD.

Currently, an unknown proportion of New Zealanders have been self-prescribing such over the counter formulations. In Australia, Ng and Goggin reported that while 53\% of participants in their study were aware of the availability of Macu-Vision as one of the available multivitamin supplements, only 38\% were taking the supplement.\textsuperscript{12}

A further aim of this study is to investigate the typical dietary intake of the abovementioned antioxidants, zinc, and copper in the NZ population and compare it to intakes in Australia, United Kingdom (UK), and United States (US).

**Methods**

We collated dietary intake data from the most recently published nutrition surveys in New Zealand (NZ), Australia, UK, and US.

In NZ, the National Nutrition Survey was most recently carried out in 1997.\textsuperscript{13} A subsequent survey was planned for 2007, with results to be reported in 2009. The 1997 Survey was based on a nationally representative sample of 4636 New Zealanders in selected households aged 15 years and above. Survey data collected included a 24-hour diet recall; a qualitative food frequency questionnaire, which estimated the frequency of intake of foods over the preceding 12 months and included questions on food preparation habits and dietary supplements.

Based on survey data collected, daily median intakes of vitamins (A, B, C, and E) and minerals (zinc, copper, calcium, phosphorus, iron, magnesium, potassium, selenium, and manganese) were reported. Dietary supplement consumption with respect to age and gender was also described.
The corresponding Australian National Nutrition Survey was carried out in 1995. The survey was conducted across all States and Territories, for people aged 2 years and above. A 24-hour recall daily food consumption method was used to assess food and beverage intake, usual frequency of intake and food related habits and attitudes. Daily mean and median nutrient intakes of vitamins A and C and of zinc are reported, but no data was collected for vitamin E or copper. Data on dietary supplement intakes were not reported.

The latest British National Diet and Nutrition Survey results were published in 2004. In the survey of adult food consumption, data were collected from 1724 respondents using a 7-day weighted-intake dietary record. This was used to assess food consumption, energy, and macronutrient intakes; micronutrient intakes; and nutritional states. Daily median intakes of beta-carotene, vitamins C and E, zinc, and copper were reported according to age, sex, and geographical areas. Dietary supplements use and their impact on nutrient intakes were reported as part of the study.

The National Health and Nutrition Examination Survey in the US was most recently undertaken in 1999–2000. 8604 persons, 12 years or older, were surveyed regarding their health, lifestyle, diet, and dietary supplement use. Vitamin and mineral intakes were estimated from one 24-hour dietary recall interview. Daily mean and median intakes of vitamins A, C, and E; zinc; and copper were reported, specific to age and sex. Additionally dietary supplement use was examined in terms of frequency and quantity of use.

Based on the survey results of each of the four countries, median intakes of each nutrient (beta-carotene, vitamins C and E, zinc, and copper) for participants 45 years of age and above are tabulated according to age and gender. A comparison of the intakes of each country to the AREDS suggested intake is made. These results are presented in Table 1.

We carried out a search of commonly used dietary supplements and those specifically marketed as ‘eye nutrients’ at major community pharmacies, health food shops, and supermarkets in NZ and through the Internet. For each supplement, information regarding the trade name, recommended dosage, and the quantity of antioxidants (beta carotene, vitamin C, vitamin E), zinc, and copper in each supplement is tabulated.

In the instances that the dosage of beta-carotene was in international units (IU), a conversion scale of 1 IU of provitamin A to be equivalent to 0.0006 mg of beta-carotene was used. Additionally, a conversion scale of 1 mg of vitamin E being equivalent to 1 IU vitamin E was used. The mean price per tablet for each supplement was calculated based on the price at different sources and has been expressed in NZ dollars. These results are presented in Table 2.

Additionally, we carried out a search for individual supplements containing beta-carotene, vitamin E, vitamin C, zinc, and copper as for multivitamin supplements. Information on the trade name; recommended dosage; quantity of antioxidant, zinc, or copper; and the price per tablet in NZ dollars is shown in Table 3.

A. Available over the Internet; B. Available through a prescription; C. Available in health food shops; D. Available in supermarkets and health food shops.

Results

The median intake of vitamin A (beta-carotene) ranged from 0.939 mg (NZ Intakes, 1999) to 0.627 mg (US Intakes, 2004). Vitamin C median intakes varied from 102 mg (NZ Intakes, 1999) to 68 mg (US Intakes, 2004). Vitamin E median intakes ranged from 9.7 mg (NZ Intakes 1999) to 7 mg (US Intakes, 2004), while those of zinc were 11.9 mg (NZ Intakes, 1999) to 9.6 mg (US Intakes, 2004) and median intakes of copper ranged from 1.4 mg (NZ Intakes 1999) to 1 mg (US Intakes, 2004).

(See all tables at http://www.nzma.org.nz/__data/assets/pdf_file/0003/82119/tables.pdf)

Table 1 presents the intakes of antioxidants (beta-carotene, vitamins C and E), zinc, and copper for NZ, Australia, UK, and US. Total median intake for each nutrient has been presented in addition to the intake distribution by gender and age, for each
country. The nutrient intake values presented for all four countries are the average daily intake from all sources; that is, food sources and dietary supplements.

In the British survey, total median intakes for all nutrients were not reported and no data was collected for intakes in participants over the age of 65. The Australian National Nutrition Survey did not report on intakes of vitamin E and copper.

In general, the total median intake of all five nutrients is comparable across the four countries, with the total median intake being estimated in the case of British intakes. The results of the nutrition surveys are remarkably similar, despite the existence of a time lag between the four nutrition surveys. All the median intake values are significantly lower than the recommended AREDS intake to reduce the risk of progression from Grade 3 and 4 to advanced AMD.

Males tended to have slightly higher intakes than females, with males below the age of 65 having the highest intakes. Generally, females below the age of 65 had higher intakes of all five nutrients.

A list of commonly encountered dietary supplements and eye nutrient products has been compiled as Table 2. Forty different multivitamin products have been identified. They are available with a prescription, at pharmacies, health food shops, and supermarkets or through the Internet.

The quantity of antioxidants, zinc, and copper varies widely between the products. Of the 40 dietary supplements, 18 contain all the constituents in the AREDS suggested formula. Two match the suggested intake of antioxidants (beta-carotene 15 mg, vitamin C 500 mg, vitamin E 400 IU), zinc 80 mg, and copper 2 mg. These are Viteyes AREDS formula capsules and Ocuvite PreserVision tablets.

The remaining 16 supplements containing varying amounts of antioxidants, zinc, and copper are Ocuvite Adult, Ocuvite Extra; Icaps AREDS formula; Centrum, Centrum Silver, Centrum Select 50+, Centrum Performance; Kordel’s MacuGuard, Kordel’s Good Health Women’s Multi, Kordel’s Senior Time; NutraLife Macu Guard; Good Health Premium Vision Care; MicroGenics Bilberry 10,000 with Lutein; Solgar Advanced Antioxidant Formula; and Healtheries Women’s Multi.

All these products generally contain smaller quantities of beta-carotene when compared to the AREDS-suggested intake. The average cost per tablet of dietary supplements containing antioxidants, zinc, and copper are generally similar.

Thirty-two single ingredient supplements available in NZ have been identified and presented in Table 3. These may be used in conjunction with multivitamin supplements in order to achieve the AREDS-recommended intakes of antioxidants, zinc, and copper.

**Discussion**

This study details the dietary intakes of antioxidants, zinc, and copper in NZ, Australia, UK, and US. The nutrient intake values presented for all four countries are the average daily intake from all sources, that is, food sources and dietary supplements. The median intakes of antioxidants, zinc, and copper for these countries were comparable, but consistently lower than the AREDS suggested intake. The median intake values reported are not a true representation of intakes with food alone.
and probably overestimate the intake of some (if not all) antioxidants, zinc, and copper.

The British National Diet and Nutrition Survey reported the intakes of antioxidants, zinc, and copper in persons up to the age of 64. This limits the ability of comparison of the UK intakes to those in NZ, Australia, and US in the population above the age of 65.

These studies were undertaken over different periods, with the NZ and Australian intake data almost a decade old. However, all four surveys were conducted within 5 years of each other and it is unlikely for dietary patterns to change markedly within a 5-year timeframe. Hence, it is still possible to use intake data for comparison purposes.

The dietary intakes of antioxidants, zinc, and copper in all four countries are lower than the AREDS-recommended intake by varying magnitudes. Further dietary supplementation is required in order to achieve the AREDS-recommended intakes. This may be achieved through increasing intakes without supplements, that is, by increasing consumption of foods rich in vitamins A, C, E; zinc; and copper. However, it is impossible to accurately estimate the quantity of specific antioxidants, zinc, and copper contained in food.

AREDS-recommended intakes can also be achieved by using either the Viteyes AREDS formula, or the PreserVision capsules once daily. Alternatively, one of the 16 other multivitamins, supplemented with an appropriate individual vitamin supplement(s) can also be a means to achieve an AREDS-recommended intake.

The average cost per tablet for multivitamin and individual vitamin supplements was calculated in NZ dollars and hence is mainly applicable to the NZ population.

The AREDS group acknowledged the potential side effects of antioxidant supplementation at the recommended doses. Vitamin C may cause an increased risk of kidney stones and vitamin E may lead to fatigue, muscle weakness, decreased thyroid gland function, increased hemorrhagic stroke risk. Beta carotene supplementation may cause yellowing of skin and more significantly, in smokers and asbestos workers, increased incidence of cancer and mortality.18,19

Zinc supplementation has been associated with increased risk of anemia, decreased high density lipoprotein cholesterol, upset stomach and increased genitourinary symptoms.20

Bjelakovic et al reported that in low-bias risk trials, after exclusion of selenium trials, beta carotene (RR 1.07; 95%CI 1.02–1.11), vitamin A (RR 1.16; 95%CI 1.10–1.24), and vitamin E (RR 1.04; 95%CI 1.01–1.07), singly or combined, significantly increased mortality.20

Data from AREDS and other studies suggest that lutein/zeaxanthin and omega-3 long chain polyunsaturated fatty acids might also have benefit in AMD and cataract. Leveraging these findings, the National Eye Institute began AREDS 2, a multicenter study that will include up to 100 clinical sites. AREDS 2 will be greatly expanded in 2008 to evaluate these nutrients in the prevention of advanced AMD and cataract. Additional arms of the study will evaluate different formulations than the one used in the original AREDS.21
Conclusion

Analysis of the most recently published dietary intakes of NZ (when compared with those of Australia, UK, and US) revealed that the median intakes of antioxidants, zinc, and copper were comparable across the four countries, but substantially lower than the AREDS-recommended intakes to reduce the risk of progression to advanced AMD.

The AREDS-recommended intake may be achieved by taking dietary supplements and appropriate intakes can be achieved by using either the Viteyes AREDS formula or the PreserVision capsules once daily. Alternatively, one of the 16 other multivitamins, supplemented with an appropriate individual vitamin supplement(s) can also be a means to achieve an AREDS-recommended intake.

The tables illustrating the constituents of each individual and multivitamin preparation, and the price per tablet in NZ dollars will be of use to ophthalmologists, opticians and other health care professionals when discussing dietary supplements to prevent the progression of moderate to advanced age-related macular degeneration.

Competing interests: None known.

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References

An evidence-based approach to minimise contrast-induced nephropathy

Tarek Darwish

Abstract

Contrast-induced nephropathy is a significant cause of iatrogenic renal injury and its incidence is growing due to the increasing number of diagnostic and interventional procedures being performed. It is the third most common cause of hospital-acquired acute renal failure, adding to patient morbidity and mortality, and extending hospital stay.

Pre-existing renal impairment and diabetes mellitus (DM) are the most common predisposing factors; this combination poses the great risk of iodine contrast-induced nephropathy (ICIN). Dehydration is well recognised as an important risk factor for ICIN, but has never been directly assessed in clinical trials.

Table 1 summarises the risk factors for ICIN.

<table>
<thead>
<tr>
<th>Patient related</th>
<th>Contrast media related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing renal failure</td>
<td>High osmolar contrast</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>High contrast volume</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Repeated doses of contrast</td>
</tr>
<tr>
<td>Recent exposure to other nephrotoxic agents</td>
<td>Ionic contrast*</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
</tbody>
</table>

The risk of intravenous iodine contrast exposure may have been overstated. Two trials have shown no statistically significant difference in renal function between subjects receiving contrast media and control group. Similarly, a recent trial has shown that serum creatinine levels can increase in the absence of iodine contrast exposure.

Toxicity usually starts 24 hours after iodine contrast administration; furthermore, creatinine level peaks in 3–5 days and returns to baseline within 10–14 days. Note that serum creatinine should be measured approximately 48 hours after contrast exposure to determine whether ICIN has occurred and to be aware that symptoms of ICIN are variable from asymptomatic patients to transient, non-oliguric renal failure.
Although numerous randomised controlled studies (RCT) have been conducted, no single therapeutic agent has been proved to be superior to another in efficacy for ICIN prevention. However, intravenous (IV) hydration with normal saline (NS) solution is the preferred benign intervention; it should be started 2–4 hours before the procedure and continued 4–6 hours afterwards.\(^1\),\(^2\),\(^8\)

In an outpatient setting, oral saline hydration is as efficient as IV saline for ICIN prevention in patients with renal dysfunction.\(^8\)

Though sodium bicarbonate given with NS 1 hour prior to the procedure is an inexpensive and simple method for ICIN prevention, numerous multicentre RCT studies are warranted to determine its effectiveness.\(^3\),\(^9\)

Given that several reports do not demonstrate a protective role of N-acetylcysteine, 600 mg or 1200 mg orally twice daily on the day preceding and the day of the procedure, it is a debatable prophylactic modality; however, its low cost and fewer side effects broaden its implementation.\(^3\),\(^10\),\(^11\)

Due to the lack of efficacy and convincing evidence avoid using theophylline and fenoldopam as a standard prevention.\(^1\),\(^3\)

Worsening renal failure and developing nephrogenic systemic fibrosis (NSF) in patients with renal dysfunction (e.g. serum creatinine clearance under 30 mL/min) have been documented after gadolinium (Gd) administration. However, in case of exposure and for early recognition, regular skin exam and creatinine level measurement should be pursued.\(^12\),\(^13\)

To reduce Gd-induced nephropathy, risk factors (end stage renal disease, acute renal failure, non-ionlc Gd, linear Gd, and high contrast volume) should be recognised prior to Gd-containing magnetic resonance imaging (MRI) contrast administration.\(^12\),\(^13\)

In conclusion, iodine contrast-induced nephropathy is a serious clinical problem; however, its role may have been overestimated. Intravenous volume expansion accounts the commonest prophylactic intervention; other modalities may play an additional role.

Importantly, Gd-induced nephropathy is an emerging entity that requires further multicentre collaborative studies to determine its mechanism, prevention, and treatment.

**Competing interests:** None known.

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**References:**

Frailty: dominos or deliberation?
Claire P Heppenstall, Tim J Wilkinson, H Carl Hanger, Sally Keeling

Abstract
Frailty is a common, but under-described, condition in older people, that is now better understood thus aiding better identification and treatment. It is characterised by multisystem deterioration and loss of physiological reserve to cope with insults. The traditional physical phenotype of frailty comprises 5 key findings: weakness, sarcopenia, weight loss, physical inactivity, and slowness (which are also modulated by psychosocial factors). Several inflammatory, endocrine and nutritional markers have been proposed as contributory, although cause-and-effect is not clear. Predisposing factors are early childhood development and lifestyle, followed by physical inactivity, chronic disease, and anorexia/ malnutrition in later adulthood. These may form a cycle of deterioration. Frailty predisposes to marked decline in physical and mental function resulting from even apparently small insults. This commonly manifests as a “domino” effect, with a small initial insult leading to a cascade of adverse events.

Several interventions have been shown to be helpful for frail older adults including exercise programs, nutritional support, maximising function prior to a planned interventions such as surgery, and early intervention when an acute insult threatens independence. Specialist geriatric assessment and management identifies and treats unstable medical conditions, reviews polypharmacy, facilitates early mobilisation, offers nutritional support, and assesses social circumstances. Frail older people in whom function has been compromised may be labelled as “unable to cope” but in fact many benefit from early comprehensive geriatric assessment to enable them to regain lost function.

“Unable to cope”, “off-legs”, “decreased mobility”, “falls ?cause” “failed discharge” are commonly documented labels in elderly patients. All may carry a sense of despair or futility on the part of the medical team to make a diagnosis or treat effectively and such patients risk ending up in residential care. However among geriatricians it is recognised that there is a common theme underlying such diagnoses, that of frailty. In this article we discuss some of the issues around frailty in the elderly and the potential for successful intervention. The search strategy for this review is shown in Box 1. The conclusions drawn and stated here from this literature review are the authors own opinions.

Box 1. Search strategy for this review

- Medline search of “frail elderly”; “aged 80+”; “activities of daily living”
- 1966 to present with particular focus on 1996 onwards
- Manual search of reference lists of key articles
What is frailty?

Interest in frailty as an entity began to develop in the 1980s and 90s, with increased recognition of a unifying diagnosis among the apparently different and non-specific presentations of illness in older adults. Initially it was defined in terms of chronic diseases, the “geriatric giants”, or problems with activities of daily living (ADLs). However with increasing research in the area it became clear that frailty is a spectrum which is separate from, and may predate the overt development of illness or disability. This spectrum is defined as the loss of reserves in multiple systems, such that even an apparently minor insult can tip the balance into disease or disability.

There are currently two ways of thinking about frailty in older people. The first is a physiologically-based definition which produces a physical phenotype of weight loss, self-reported exhaustion, decreased grip strength, slow walking speed, and decreased physical activity. In the Cardiovascular Health Study this phenotype defined a different group of patients from disability and comorbidity measures, although with considerable overlap.

Figure 1 shows these relationships. It can be seen that a large number of patients had comorbidity (2 or more chronic diseases), others had disability, while some had both frailty and comorbidity, frailty, and disability (or all three); while a smaller number fulfilled the criteria for frailty alone, identifying it as a separate entity. The syndrome of frailty independently predicted falls, decreased mobility, the development of ADL disability, hospitalisation, and death.

Other authors have also found that the combination of weight loss and low activity were associated with poor subjective health, poor performance and mortality; that instrumental ADL disability (that is disability in “non-essential” daily functions such as driving or shopping) is predicted by age, mobility, balance, grip strength, body mass index, physical activity, self-perceived health and fear of falling; that poor performance on an obstacle test, gait speed, hip abduction strength and the Romberg test predicted frailty on a physical performance scale which in turn predicted disability, loss of independence, and mortality; and that slowed timed chair stands, decreased arm-strength, decreased vision or hearing, and a higher anxiety or depression score predicted development of the “geriatric giants” of falls, incontinence, and ADL dependence.
This figure illustrates the overlapping but distinct relationships between comorbidity, disability, and frailty in a cohort of community dwelling older adults. It can be seen that many had two or more comorbidities, but only a smaller number fulfilled the criteria for frailty. In many frailty coexisted with comorbidity and/or disability, but a smaller number met the criteria for frailty alone identifying it as a distinct entity.

The second definition of frailty uses a more holistic approach incorporating not just physical measures but also considering psychosocial factors and vulnerability. In 1994 Rockwood et al\textsuperscript{12} reached a dynamic model of frailty incorporating medical factors but also psychosocial factors such as self-rated health, social resources, economic factors, and cognition.

Others have found that impaired physical activity, malnutrition, depression, and cognitive impairment predict the development of functional impairment.\textsuperscript{13} Whitson et al\textsuperscript{14} describe the relationship of physiological (phenotypical) frailty with psychosocial frailty, illustrated in Figure 2.

Patients may fall to the left of the line (be “Frail”) on the graph due to either physical frailty or a lack of psychosocial reserves or a combination of both. In a New Zealand population, frailty was associated with housing situation (renting versus home ownership); housing standards such as cold, damp or poorly maintained; mobility and transport limitation; and lack of social connections.\textsuperscript{15}
Figure 2 illustrates the relationship between frailty and physical or psychosocial risk factors. Subjects who met the criteria for frailty fall to the left of the line, and it can be seen that either very poor physiological reserve, severely decreased psychosocial support, or a combination of both can lead to a subject falling to the left of the line, and hence meeting the diagnosis of frailty.

**But is frailty not just the same as ageing?**

It is clear that as we age the incidence of frailty increases. The frailty index of Rockwood et al\(^1\) has been shown to change with increasing age with a characteristic accumulation in deficits. However this is not the only factor to be considered and it is clear that some people will reach a frail state in their 60s or 70s, while others remain robust and active into their 80s or beyond. Schuurmans et al\(^1\) have demonstrated that frailty is more predictive of a decline in self-management ability than chronological age.

**What about disability?**

Disability is defined in the International Classification of Functioning, Disability, and Health (ICF) by the World Health Organization (WHO): [http://www.who.int/classifications/icf/en](http://www.who.int/classifications/icf/en). Like frailty, the definition covers both physical health as well as social aspects. It implies a state of limited participation. However this is distinct from frailty in a number of ways.
First, disability may be caused by a single catastrophic event such as stroke or amputation rather than the accumulation of insults seen in frailty. Second, disability depends on the environment— a person may be disabled in one environment but fully capable with appropriate aids or modifications (e.g. modified vehicles). In addition frailty may be seen as a “preclinical” or “at-risk” syndrome which is present but may not manifest itself until an insult upsets the fragile balance caused by the loss of reserves, in contrast to the existing deficit(s) described by the WHO definition.

**And chronic disease?**

In the study of Fried et al. a large number of patients had comorbidity, defined by two or more chronic diseases without meeting the criteria for frailty (Figure 1). Chronic disease predisposes to frailty both directly with accumulated deficits and through other mechanisms such as decreased mobility and sarcopaenia, or the loss of skeletal muscle mass.

Several of the proposed biochemical markers for frailty may also be found in chronic diseases, for example raised inflammatory markers and cardiovascular disease. On the other hand, frailty predisposes to the development or manifestation of chronic disease through mechanisms such as malnutrition and decreased physical activity, again illustrating the domino effect of frailty.

**Predisposing factors for frailty**

The life-course model for frailty highlights predisposing factors which begin with early childhood development and growth patterns which influence muscle formation and the later development of sarcopaenia. Socioeconomic status in childhood and motor and cognitive development also play a role.

Peak adult function is critical as this determines how much physiological reserve is available before age- or disease-related deterioration reaches a critical threshold. Lifelong habitual physical activity levels are a vital component of the frailty syndrome, and patterns of physical activity are often set in childhood or early adulthood.

By middle age, predictors of frailty have been established in many cases, and the trajectory of decline determined. These include smoking, excess alcohol intake, body mass index (either high or low), and chronic diseases especially atherosclerosis and diabetes. Using data from the Framingham heart study in 45–88 year olds, a composite deficit measure of 39 abnormal physical findings was shown to predict death and longevity.

**Biochemical and endocrine markers**

Several cross-sectional studies have looked at biochemical, hormonal, and nutritional markers for frailty. Raised IL-6 and CRP have been shown to be related to prevalent frailty and pre-frailty. Abnormal coagulation studies (factor VIII, fibrinogen and D-dimer) have also been demonstrated to be associated with frailty, although it is unclear whether this is a direct effect or a reaction to increased inflammation. In another study raised IGF-1 and lower levels of vitamin D were associated.
Metabolic changes including impaired glucose tolerance and low cholesterol have been associated, but are now generally better explained by low BMI possibly modified through an effect of inflammation. While mitochondrial enzymes, testosterone, cytokines, low albumin, and vitamin deficits have been highlighted as important in cross-sectional studies it is difficult to establish cause-and-effect relationships, and it is not clear whether these markers predispose to frailty or develop in response to the syndrome.

Other laboratory markers for frailty include VO$_2$ max, which may affect muscle or cardiac perfusion. Phenotypical frailty has been shown to be associated with lower muscle density, lower muscle mass, and higher fat mass than found in age-matched non-frail subjects. However none of these markers are sensitive or specific enough to be used as clinical markers or a diagnostic test for frailty.

**Dominos again**

These physiological and biochemical markers often form a “vicious cycle” of deterioration, for example a patient who has low activity levels will go outside less and therefore develop low vitamin D levels. This in turn has been shown to lead to muscle weakness and unsteady gait, hence further limiting mobility and predisposing to falls.

Most authors highlight the key role of low physical activity levels in development of frailty. This has widespread effects on biochemical, hormonal, and nutritional pathways with down-regulation of growth hormones, digestive enzymes, metabolic hormones, and the cardiovascular system such as VO$_2$ max leading to a cascade of chemoregulatory mechanisms.

Down-regulation of these systems leads to anorexia, sarcopaenia, muscle weakness, and decreased exercise tolerance—the classical physical phenotype of frailty, which in turn leads to a further reduction in exercise levels.

**What is the significance of frailty?**

As already discussed, the development of frailty puts older people at high-risk of decline in physical or mental health after apparently minor insults. This leads to hospital admission, institutionalisation, and excess mortality.

Covinsky et al showed that frail older people had a steady decline in function in their last year of life, which was quite different to that seen in malignancy or even single organ disease such as cardiac failure. Lunney et al showed that frail people in their last year of life were significantly more likely to experience ADL disability and have a steady trajectory of decline than those with malignancy, organ failure, or sudden death.

**Measurement of frailty**

We have discussed frailty as an important syndrome in the elderly, but how should a clinician go about the diagnosis? There have been many approaches over the years. For those favouring the classical physical diagnosis of frailty identification of the 5 key features is important. Typically this includes weight loss of >10% in the preceding year; a measure such as calf-circumference for sarcopaenia; decreased grip
strength; decreased performance on a timed-walk test; patients report of physical activity levels; and self-reported exhaustion. This definition has been shown to predict falls, hospitalisation, disability, and death.

Another group simplified this definition further to weight loss, inability to rise from a chair without using the arms, and reduced energy level and found that this predicted falls, development of disability, fractures, and death as well as the 5-item scale.

However if we wish to consider frailty to include multiple risk factors both physical and psychosocial functioning, measures become more complex. The initial approach of the Canadian group of Rockwood and Mitniski was a deficit count of 70 items which was correlated with the phenotype definition, but had a better predictive value for 5-year survival. Another group developed a 48-item count which predicted negative outcomes better than the phenotypic frailty definition.

More recently the Canadian group describe the development of a frailty index. They argue that to gain the maximum precision at least 30–40 variables are required. Their scale had 40 variables and was reproducible in a validation cohort. It was associated with mortality and showed a deficit accrual associated with age.

In a longitudinal study, subjects who remained alive at the end of the study had a significantly lower FI than those who died, and the FI appeared to show a “threshold” effect with age at death being determined by the accrual of deficits, with death occurring at an approximate FI of 0.3 regardless of chronological age.

The disadvantage of this approach is that the 40-, 48-, or 70-item frailty indices are time-consuming and unwieldy to use in clinical practice. Therefore a number of groups have developed more simplified scales.

The Canadian group simplified their measure into a 7-item global clinical assessment scale based on physical activity levels, co-morbidities and ADLs. They found this scale predicted death and institutionalisation. The Vulnerable Elders survey used a scoring system based on age, self-rated health, physical function, and functional disability. They found that the most vulnerable third on this scale had an increased risk of death or functional decline, and that the addition of comorbidities to this scale did not significantly improve its predictive value. However both these scales lose the psychosocial aspects which are felt to be important in frailty.

Another simplified score, the Edmonton Frail Scale is a 11 item scale covering the key physical and psychosocial features of frailty which has been shown to be correlated with a geriatricians’ comprehensive assessment, and the Barthel Index, which is a measure of ADLs. It is a practical scale to use and is shown in Table 1.

Another scale is that of Ravaglia et al which has 9 items and predicted fractures, hospitalisation, disability, and mortality. Owens et al propose a 7-item scale which they found predicts institutionalisation, mortality and prolonged or expensive hospital stays. The same Canadian group propose an 11-item scale with items identified from a standardised comprehensive geriatric assessment as having the highest hazard ratio for adverse outcomes. They then grouped patients into severe, moderate, and mild frailty and found that these groupings predicted institutionalisation and mortality.
These scales are simpler to use in clinical practice and may help non-geriatricians to identify at risk groups in whom a more comprehensive evaluation should be considered.

### Table 1. The Edmonton Frail Scale

<table>
<thead>
<tr>
<th>Domain</th>
<th>Question</th>
<th>0 points</th>
<th>1 point</th>
<th>2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognition</td>
<td>Clock drawing</td>
<td>No errors</td>
<td>Minor errors</td>
<td>Major errors</td>
</tr>
<tr>
<td>2 General Health</td>
<td>How many times have you been in hospital in the past year?</td>
<td>0</td>
<td>1–2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>3 Describe your health</td>
<td>Excellent Good Fair/ poor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Functional dependence</td>
<td>How many of these IADLs do you require help with?</td>
<td>1–2</td>
<td>2–4</td>
<td>5–8</td>
</tr>
<tr>
<td>5 Social support</td>
<td>When you need help can you count on someone to meet your needs?</td>
<td>Always</td>
<td>Sometimes</td>
<td>Never</td>
</tr>
<tr>
<td>6 Medication</td>
<td>Do you take &gt;5 meds?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>7 Mood</td>
<td>Do you ever forget to take your meds?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>8 Continence</td>
<td>Do you have a problem with losing control of your urine?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>10 Functional performance</td>
<td>3m-Timed up-and-go</td>
<td>0–10s</td>
<td>11–20s</td>
<td>&gt;20s</td>
</tr>
<tr>
<td>11 Nutrition</td>
<td>Have you lost any weight recently?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

### Interventions in frailty

The diagnosis of frailty should move clinicians’ thinking away from specific disease models to a more holistic and integrated approach. Several interventions have been shown to be effective for frail older people including exercise regimes to increase strength and promote muscle hypertrophy; nutritional support (especially during hospitalisation); review of medications and polypharmacy; and early comprehensive assessment which may identify undiagnosed or unstable medical conditions, maximisation of function prior to a planned intervention (such as surgery), assessment of social circumstances, and multidisciplinary team intervention especially early mobilisation.

In some circumstances it may also be appropriate to recognise patients on their final trajectory and move towards a more palliative approach.

### Conclusion

Frailty is becoming a better defined syndrome with a background of physiological changes—with physical, mental, cognitive, and socioeconomic factors contributing. The authors propose a model for frailty which incorporates predisposing factors such as early childhood development and peak adult performance plus biochemical and hormonal changes in the development of the physical phenotype of frailty. This is modified by psychosocial factors, and has the potential to form a cycle of deterioration, or the “domino” effect. This model is shown in Figure 3.
Figure 3. Potential mechanisms of frailty
For many doctors encountering frailty induces feelings of despair and futility. We argue, however that making the diagnosis of frailty is a positive step, and a number of simple scales have been developed, of which the authors use the 11-item Edmonton Frail Scale (Table 1). There remain insufficient evidence to draw conclusions on the exact group who should be screened for frailty, but certainly the diagnosis should be considered in all elders presenting with apparently minor or non-specific complaints.

Early identification of frailty—especially in elders who have sustained an acute insult such as physical illness or the loss of a key support person—should prompt comprehensive assessment and intensive multidisciplinary team management. This approach has the potential to prevent the dominos from falling, and to improve outcomes in our patient group.

In summary, frail elderly patients in whom function has been compromised benefit from early comprehensive geriatric assessment to restore lost function and maintain independence.

**Competing interests:** None known.

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Duodenal Kaposi’s sarcoma
Amer A Alkhatib, Douglas G Adler

Case presentation
A 50-year-old man with HIV/AIDS presented with 1 day of haematemesis and melaena. He denied abdominal pain or fever. There was no recent use of non-steroidal anti-inflammatory drugs (NSAIDs). The patient was not taking any anti-retroviral medications. His most recent serum CD4 count was 13 cells per cubic millimetre. The patient underwent oesophagogastroduodenoscopy that demonstrated purple frond-like papillary mounds in the 2nd portion of the duodenum (Figures 1 and 2).

Biopsies of these lesions revealed spindle cells arranged in fascicles with slit-like dense and irregular vascular spaces, creating a sieve-like appearance (Figure 3). Staining for Human Herpes Virus 8 was positive (Figure 4).

The patient was diagnosed with duodenal Kaposi’s sarcoma. He was restarted on HAART therapy and has had no further episodes of bleeding.

Discussion
Kaposi sarcoma (KS) is a low grade vascular tumour associated with human herpes simplex virus 8 (HHV-8) infection.\(^1\) It is classified into four clinical variants:

A. Classic,
B. Endemic or African,
C. Organ transplant recipients, and
D. AIDS-related or epidemic.\(^2\)

Classic type, also known also as Mediterranean type, is rare and primarily affects older men.\(^2\) The Endemic (African) type is found in equatorial Africa and typically not associated with immunodeficiency state.\(^2\) KS in transplanted patient is not uncommon and it has been reported in 0.5—3.3% of renal transplant patients and in 2.16% of liver transplant patients.\(^3,4,5\)

Prior to the highly active antiretroviral therapy (HAART) era, the prevalence of KS in patients with HIV was 20,000 times higher than the general population.\(^6\) The adjusted incidence rate for KS declined from 15.2 in 1992 through 1996 to 4.9 in 1997 through 1999 (expressed as number of cancers per 1000 person-years) with the introduction of HAART.\(^6\) KS can affect any part of GI tract and has been most commonly reported in stomach followed by the hard palate and colon.\(^7\)

Clinical gastrointestinal tract involvement is seen in 40% of cases of patients with AIDS related KS.\(^9,10\) On autopsy, KS is detected in 80% of patients with AIDS.\(^11,12\) In 30% of patients with AIDS, KS is the presenting manifestation. Common presentations include symptoms of gastrointestinal bleeding, abdominal pain, weight loss, diarrhoea, nausea, vomiting, dysphagia, and small intestinal obstruction.\(^9,10\)
Endoscopically, KS frequently manifests as hemorrhagic nodules that can be either isolated or confluent.\textsuperscript{11}

Poor prognostic factors for patients with AIDS and KS are associated oedema or ulceration, extensive oral KS, gastrointestinal KS, KS in other non-nodal viscera, CD4 cell count <200/µL, history of opportunistic infections and/or thrush, presence of \textquotedblright B\textquotedblright symptoms (defined as unexplained fever, <10 percent involuntary, weight loss, night sweats or diarrhoea persisting more than 2 weeks), Karnofsky performance status <70 and other HIV-related illness (e.g. neurologic disease, lymphoma).\textsuperscript{12}

HAART is recommended as first-line therapy for AIDS-related KS \textsuperscript{13}. The response of Kaposi's sarcoma to highly active antiretroviral therapy is unpredictable. For that reason, specific local or systemic therapy such as radiation therapy, systemic chemotherapy, and biological agents (i.e. interferon alpha) should be considered in this setting if HAART alone proves to be inadequate.\textsuperscript{2}

\textbf{Figures 1 (left) and 2 (right). Endoscopic images of Kaposi’s sarcoma in the 2nd portion of the duodenum. Note the raised, nodular, frond-like appearance of the lesion}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Endoscopic images of Kaposi’s sarcoma in the 2nd portion of the duodenum. Note the raised, nodular, frond-like appearance of the lesion.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Microscopic image, H&E, \times20. Spindle cells arranged in fascicles with slit-like vascular spaces, creating a sieve-like appearance.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Microscopic image of same lesion demonstrating positive stain for Human Herpes Virus 8, \times20.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Microscopic image of same lesion demonstrating positive stain for Human Herpes Virus 8, \times20.}
\end{figure}
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List of Members of the British Medical Association (New Zealand Branch) in 1909

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Proceedings the 198th Scientific Meeting of the Otago Medical School Research Society: Thursday 2 July 2009

Mechanism of hyperprolactinaemia-induced infertility. R Brown1,2, I Kokay1, A Herbison2, D Grattan1. Centre for Neuroendocrinology and 1Department of Anatomy and Structural Biology, 2Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.

Elevated levels of the anterior pituitary hormone, prolactin, cause infertility through inhibiting gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus. To do this, prolactin could act directly on GnRH neurons or indirectly on intermediary neuronal populations. To test the hypothesis that GnRH neurons respond directly to prolactin, we mapped the distribution of prolactin receptor mRNA in the mouse forebrain by in situ hybridisation. In addition, we used immunohistochemistry for prolactin-induced phosphorylation of signal transducer and activator of transcription 5 (pSTAT5) as a functional marker of activation.

In situ hybridisation was conducted on female mouse brains, using an S35-labelled riboprobe designed to detect both long and short isoforms of the prolactin receptor. For pSTAT5 immunohistochemistry, female mice were injected with vehicle or prolactin, 45 min prior to perfusion. Sets of coronal sections were immunostained for pSTAT5 or double-labelled for pSTAT5 and GnRH. Prolactin receptor mRNA was expressed throughout the forebrain, with high expression in the anteroventral periventricular nucleus (AVPV). This hypothalamic region is of particular interest as it contains neuronal populations that are known to project to GnRH neurons to influence GnRH secretion. Prolactin also induced expression of pSTAT5 in the AVPV (from 53±24 positively labelled cells in vehicle-treated animals to 809±118, both n=5, P<0.001; one-way ANOVA). Prolactin induced pSTAT5 expression in a subpopulation of GnRH neurons (from 1.0±0.8% under basal conditions, to 11.0±2.5% after prolactin treatment; P<0.01, both n=6).

In conclusion, a small subpopulation of GnRH neurons respond directly to prolactin. The high levels of prolactin receptor mRNA expression, and prolactin-induced activation of pSTAT5 in the AVPV, suggests that this region may be important in mediating inhibitory actions of prolactin on GnRH secretion through an indirect pathway.

The processing and presentation of virus-like particles by dendritic cells to generate anti-tumour immune responses. S Win, S Young, V Ward, M Baird. Department of Microbiology and Immunology, Otago School of Medical Sciences, University of Otago, Dunedin.

Vaccines and immunotherapies against cancer are designed to harness the potential of the immune system to destroy tumours. We have developed a vaccine based on inert virus shells, termed virus-like particles (VLP), which are effective delivery vehicles for immunising proteins or peptides conjugated to their surfaces. Vaccination can be
achieved by employing dendritic cells (DC) to initiate cytotoxic T cell responses through presentation of antigens on Major Histocompatibility Complex class I (MHC I), termed cross-presentation. Here we aim to ascertain whether VLP can be cross-presented by DC and furthermore, elucidate the mechanisms underlying how DC internalise VLP in vitro, and process them into antigenic peptides to initiate cytotoxic T cell responses.

DC derived from the peripheral blood of unrelated human donors (n=7) were assessed for their ability to internalise fluorescent VLP by flow cytometry following the inhibition of uptake mechanisms. Results demonstrated that VLP are taken into DC by both macropinocytosis and phagocytosis but not by receptor-mediated endocytosis.

To determine how VLP are processed by DC and cross-presented on MHC I, DC were treated with inhibitors of antigen processing pathways and assessed for their ability to activate cytotoxic T cells. T cell proliferation and cytokine production confirmed that DC use an alternate, receptor recycling pathway of cross-presentation to load VLP-derived peptides onto MHC I. This pathway was shown to operate independently of the proteasome and TAP transporter.

Access of VLP to cross-presentation pathways inside DC induces antigen-specific cytotoxic T cell responses to VLP-derived antigens through a receptor recycling pathway. The functional T cell responses generated by VLP pulsed-DC indicates that the ability of VLP to be presented on MHC I has the potential to generate superior cytotoxic immune responses effective against tumours.

**Decreased absolute number of dopamine neurons in rats exposed to repeated hypoxia during development. A novel rat model of extreme prematurity. S Kohe, E Gowing, D Oorschot. Department of Anatomy and Structural Biology, Otago School of Medical Sciences, University of Otago, Dunedin.**

Children born extremely prematurely (i.e. from 22-28 weeks of gestation) often experience repeated bouts of sublethal hypoxia. This can result in brain injury and behavioral disorders such as attention deficit hyperactivity disorder (ADHD). We have observed ADHD-like hyperactivity in our novel rat model of extreme prematurity that exposes immature rats to repeated hypoxia. ADHD is thought to be due to hypofunctioning midbrain dopaminergic neurons. We therefore investigated whether there were deficits in the absolute number and volume of midbrain dopaminergic neurons in repeated hypoxic rats.

Rats exposed to repeated hypoxia (n=9) or normoxia (n=6) from postnatal day (PN) 1-3 were perfused with 4% paraformaldehyde at PN 14. Midbrain dopaminergic neurons in the right hemisphere were identified using tyrosine hydroxylase (TH) immunohistochemistry. Their absolute number and average volume were measured in coded sections using stereological methods.

A statistically significant decrease in the absolute number of TH-positive neurons was found in the midbrain ventral tegmental area (VTA) of repeated hypoxic rats (8894±400, mean±SEM) compared to normoxic rats (11683±441, P<0.001, Student’s \( t \)-test). No significant difference was found in absolute number in either the substantia nigra pars compacta (repeated hypoxic, 4424±219; normoxic, 3925±436) or the
rétrorubral field (repeated hypoxic, 2569±167; normoxic, 2578±303). There was no significant difference in the average volume of dopaminergic neurons in these three midbrain regions (e.g. VTA, repeated hypoxic 1558±171 µm$^3$; normoxic, 1696±102 µm$^3$).

These results match what we have found in repeated hypoxic rats at 18 months-of-age. The short- and long-term deficit in dopaminergic neurons of the VTA of repeated hypoxic rats is likely to contribute to the ADHD-like hyperactivity. Further characterization of this rat model may provide a new tool to develop treatments.

**Epigenetic defects are uncommon after *in vitro* fertilisation.** V Oliver$^1$, W Cutfield$^2$, H Miles$^2$, P Hofman$^2$, I Morison$^3$. $^1$Cancer Genetics Laboratory, Department of Biochemistry, Otago School of Medical Sciences, University of Otago, Dunedin. $^2$Liggins Institute and the National Research Centre for Growth and Development, University of Auckland. $^3$Pathology Department, School of Medicine, University of Otago, Dunedin.

*In vitro* fertilisation (IVF) potentially provides a profoundly abnormal environment for an embryo. Recent studies have suggested that IVF causes a small but increased risk of the imprinting aberrations Angelman syndrome and Beckwith-Wiedemann syndrome. Our previously published IVF cohort is on average taller, has higher levels of growth hormones and a better lipid profile than age-matched controls.

As mosaicism for the imprinting defect has been observed in Angelman syndrome and Beckwith-Wiedemann syndrome, we hypothesised that low-level, mosaic imprinting defects may be present in phenotypically normal IVF individuals.

DNA samples from peripheral blood were obtained from 69 IVF-conceived pre-pubertal children and 71 matched controls. DNA methylation of CpG sites within *H19*, *SNRPN*, *KCNQ1OT1* and *IGF2* were accurately quantified using methylation-sensitive restriction digest followed by real-time quantitative PCR (MSQ-PCR). Global DNA methylation was also examined by using MSQ-PCR on Satellite 2 repeats. No differences in the percentage of methylation between the IVF-conceived and control children were observed at *H19* (P=0.75; unpaired t-test), *KCNQ1OT1* (P=0.98), *SNRPN* (P=0.33), *IGF2* (P=0.44) or Satellite 2 (P=0.79).

Detailed analysis of methylation at imprinted genes was performed using bisulphite sequencing and supports the MSQ-PCR results, indicating no difference in methylation between IVF-conceived and control children.

Genome-wide methylation analysis was examined using promoter arrays and methylated DNA immunoprecipitated using an anti-5-methylcytosine antibody (MeDIP). Several differentially methylated genes between the IVF-conceived and control children were identified. Detailed examination of candidate genes using the Sequenom MassARRAY system showed no significant difference between the IVF-conceived and control children.

We conclude that low-level imprinting errors are not a common occurrence in children conceived using IVF. Our data provides reassurance that IVF-associated epigenetic errors are sporadic and rare.
Modification of therapeutic peptides in poly(ethylcyanoacrylate) nanoparticle delivery systems prepared by *in situ* polymerisation. A Kafka, T Rades, A McDowell. School of Pharmacy, University of Otago, Dunedin.

Poly(alkylcyanoacrylate) (PACA) nanoparticulate delivery systems have many applications, particularly oral delivery of peptide drugs. They protect peptides against proteolytic degradation, facilitate their uptake and can effectively target tissues in the body. Peptides may be entrapped to a high extent via encapsulation or adsorption (up to 98%). However, release of the bioactive peptide D-Lys\textsuperscript{6}-GnRH (gonadotropin-releasing hormone) from PACA nanoparticles was less than 10%, affecting its bioavailability. We have found that low release was due to co-polymerisation where D-Lys\textsuperscript{6}-GnRH covalently interfered with nanoparticle formation leading to chemical modification of the bioactive, potentially affecting the safety of patients.

To investigate the potential of a range of therapeutic peptides to covalently interfere with alkylcyanoacrylate monomers, D-Lys\textsuperscript{6}-GnRH, insulin, insulin-like growth factor 1 (IGF-1), [Asn\textsuperscript{1}-Val\textsuperscript{5}]-angiotensin II and human adrenocorticotropic hormone (ACTH) were polymerised *in situ* with ethylcyanoacrylate (ECA) and butylcyanoacrylate (BCA). D-Lys\textsuperscript{6}-GnRH was added *ex situ* to preformed nanoparticles.

Tandem mass spectrometry revealed a chemical modification of the histidine residue in peptides D-Lys\textsuperscript{6}-GnRH and [Asn\textsuperscript{1}-Val\textsuperscript{5}]-angiotensin II corresponding to the addition of oligomeric ECA/BCA after *in situ* polymerisation. ACTH with no histidine residues stayed unmodified. However, the much larger insulin contains 3 histidine residues and was also found unmodified possibly due to its conformational complexity and steric hindrance of the reactive sites. IGF-1 was modified at the glutamic acid residue. The histidine residue in D-Lys\textsuperscript{6}-GnRH was also modified upon *ex situ* addition of to preformed PACA.

In conclusion, therapeutic peptides with carboxylic acid end groups and nucleophilic side chains, such as histidines, may interact with PACA nanoparticles both *in situ* and *ex situ*. The sequence of therapeutic peptide needs to be carefully considered when formulating with PACA nanoparticulate delivery systems.

**Identifying and valuing health resource use in economic evaluation studies: Can participants be trusted sources?** D Pinto\textsuperscript{1}, C Robertson\textsuperscript{2}, J Garcia\textsuperscript{3}, P Hansen\textsuperscript{4}, H Abbott\textsuperscript{1}. \textsuperscript{1}Centre for Physiotherapy Research, School of Physiotherapy, \textsuperscript{2}Department of Medical & Surgical Sciences, \textsuperscript{3}Department of Preventive and Social Medicine, Dunedin School of Medicine, \textsuperscript{4}Department of Economics, University of Otago, Dunedin.

Economic evaluations of interventions require that health service use be identified, measured, and valued appropriately. The present study compares two methods of identifying and valuing general practitioner (GP) use for the cost-utility analysis of the Management of OsteoArthritis (MOA) trial.

Osteoarthritis-related GP service use by trial participants in a 3-month period was obtained from GP office databases and a review of patient notes at 18 GP offices in
Dunedin, NZ. Using a questionnaire, participants were asked to recall the number of osteoarthritis-related GP visits in the same 3-month period and to report their co-payment per visit. Reliability between the two methods was assessed using the Spearman rank correlation coefficient and intra-class correlation coefficient (ICC). Bland-Altman comparisons were used to determine degree of agreement between methods.

Fifty participants (58% women, age range: 55 to 85) were included in the study. GP service use averaged 1.2 visits (SD 1.2) from GP databases and 1.4 (SD 1.1) from participant self-reporting. The two methods showed fair reliability (Spearman’s rho 0.39, P<0.01, ICC=0.32) and moderate reliability of the mean (ICC=0.48). Bland-Altman comparison showed a mean difference of -0.18, 95% confidence interval (CI; -0.56 to 0.20). Reported co-payments showed moderate reliability (Spearman’s rho 0.48, P<0.001, ICC=0.45), substantial reliability of the mean ICC=0.62, yet a significant difference was found between the two methods (P<0.05). Bland-Altman comparison showed a mean difference of $10.70 (CI $2.05 to $19.31) at 2008 prices.

There was no difference in reported osteoarthritis-related GP service use between self-reporting and GP database results, but participants over-reported co-payments. A questionnaire can identify GP use but valuations should be applied by the researcher to avoid over-estimating primary health care costs by as much as 30%.

Ameliorative effects of non-classical estrogen action on basal forebrain cholinergic neurons. Z Kőszegi, I Abraham. Centre for Neuroendocrinology and Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.

The basal forebrain cholinergic (BFC) system is a widely distributed neurotransmitter system in the brain. Cholinergic neurons in this area are involved in important brain functions, such as learning, memory and behaviour. BFC neurons are particularly vulnerable in degenerative disorders such as Alzheimer’s disease. The gonadal steroid oestrogen is one of the essential contributors controlling the vulnerability of BFC neurons. Traditionally, oestrogen was thought to exert its actions by altering gene transcription via oestrogen receptor-mediated “classical” genomic mechanisms. However, it is now known that oestrogen also exerts rapid, non-classical effects through intracellular second messenger signaling systems. In this study, we examined the potential ameliorative properties of oestrogen and the non-classical oestrogen pathway activator, oestren, on BFC neurons using an in vivo neurodegenerative animal model.

N-methyl-D-aspartate (NMDA) was unilaterally injected into the substantia innominata of ovariectomised female mice to elicit cholinergic cell death and thus cholinergic fibre loss in the cortex. One hour after NMDA injection, the animals received a single injection of 17-β-estradiol (1 µg/30 g body weight), oestren (1 µg/30 g body weight), or vehicle (0.1 ml ethyl-oleate/30 g body weight). The survival rates of BFC fibres were assessed in the cortex using quantitative acetylcholine esterase histochemistry. NMDA injection resulted in 58±14% (mean±SD, n=6) cholinergic fibre loss, compared to the contralateral side, in the cortex of vehicle-treated mice. Administration of 17-β-estradiol or oestren ameliorated NMDA-induced cholinergic
fibre loss (21±16% and 30±8%, both P<0.05, n=6, versus vehicle-treated mice, one-way ANOVA followed by Tukey’s post-hoc test).

Our findings demonstrate that ooestrogen can restore fibre density in the cerebral cortex after loss of subcortical cholinergic input, providing a potential treatment against cholinergic neurodegeneration. The experiments with oestren suggest that the non-classical actions of oestrogen are involved in this ameliorative mechanism.

Identification of genomic alterations in the neuronal migration disorder periventricular heterotopia. M van Kogelenberg¹, Christa Murray¹, Hans van Bokhoven², Stephen Robertson¹. ¹Department of Paediatrics and Child Health, Dunedin School of Medicine, University of Otago, Dunedin, ²Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Variation in gene copy number is a common mutational mechanism underlying genetic disease in humans, making the identification of these genetic variants of much diagnostic significance. With the introduction of genome-wide arrays it became possible to detect microdeletions and microduplications at high resolution. We screened a cohort of patients with periventricular heterotopia (PH), a brain malformation caused by failed radial migration of neurons, using Affymetrix genome wide arrays. PH is commonly associated with mutations in filamin A (FLNA) but a substantial fraction of PH individuals have no identifiable genetic aetiology.

Here we present three patients with PH that were identified with novel genomic alterations. A male individual presented with PH, craniosynostosis, a thinned corpus callosum, facial dysmorphology, and developmental delay. Array analysis identified a 0.3 Mb deletion on Xp22 affecting 3 genes. A female patient with PH and joint hypermobility presented with a de novo 0.19 Mb deletion on 14q13. The deletion affects a single gene involved in the mitogen-activated protein (MAP) kinase pathway. Finally, a deletion was detected on 7q21 of 0.26 Mb in a patient with complex malformation of the cerebellum and corpus callosum. The alteration affects a single gene characterised as a cdc2-like kinase. Genomic qPCR and multiplex ligation probe amplification (MLPA) confirmed the deletions and narrowed down breakpoints.

These results demonstrate that it is possible to identify novel genetic aetiologies underlying PH that brings important clinical utilities to families with these disorders but also has the potential to provide new insights into the biology of radial neuronal migration in humans.

Identification of a genetic marker set for peripheral arterial disease susceptibility. H Tsao, G Jones, L Phillips, A van Rij. Section of Surgery, Department of Medical and Surgical Sciences, Dunedin School of Medicine, University of Otago.

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis. Despite interests in genetic markers and disease prediction, there is a paucity of PAD genetic association studies in the literature. The aim of this study was to identify genetic markers for PAD using a candidate gene selection approach.
Genotyping was carried out on 469 PAD and 535 control subjects and examined 42 functional polymorphisms of genes involved in various aspects of vascular pathology including inflammation, remodelling, calcification, blood pressure regulation, signalling, coagulation and angiogenesis. Additional cohorts of coronary artery disease (CAD) and abdominal aortic aneurysm (AAA) subjects were also genotyped to determine whether the observed genetic associations were specific to PAD.

Seven of 42 polymorphisms examined were significantly associated with PAD in multivariate analysis: OPG-163G allele (Odds ratio, OR=1.54, P=0.033), CHRNA3 rs1051730 T allele (OR=1.80, P=0.002), BHMT R239Q A allele (OR=1.75, P=0.004), TGFB1 Leu10Pro C allele (OR=0.50, P<0.001), TGFBR2 intron 6 A>C CC (OR=0.64, P=0.05), VEGF 405C allele (OR=0.64, P=0.01) and FOXC2 -512C allele (OR=0.53, P=0.001). Two of these polymorphisms were also associated with CAD or AAA. In polygenic risk assessment, involving the top 5 candidate polymorphisms, subjects who carried 2 risk variants were 2.3 times more likely to develop PAD (P<0.001) compared to the reference group (0 – 1 risk variant). The odds ratio increased to 3.5 for those who carried 3 or more risk variants (P<0.001).

This study identified a number of novel genetic markers for PAD. In polygenic modelling, the number of risk variants was shown to be more predictive of PAD than individual polymorphisms. These associations will need to be verified in independent cohorts and in meta-analyses.
Aspirin for the prevention of cardiovascular disease

We are aware of the merits of this proposition. But here is a bit more detail. The US Preventive Services Task Force (USPSTF) has long been interested in this primary prevention measure and has recently published an update based on a meta-analysis of 5 large trials. And their A grade recommendations are that men aged 45–79 years should take low dose aspirin for the potential benefit of reduction in myocardial infarction and women aged 55–79 years should take it for potential reduction in ischaemic strokes.

The gender difference is accounted for by the much less risk that younger women have for cardiovascular illness. The USPSTF point out that their advice applies to adults who have no symptoms or history suggesting peptic ulcers and are not taking non steroidal anti-inflammatory drugs. They also recommend that the dose should be approximately 75 mg per day, as this dose is efficacious and has less haemorrhagic potential than higher dosage.


Raised blood pressure management— which drugs are best?

The choice is wide and includes α-blockers, thiazides, β-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers. Law and Wald, the proponents of the polypill, report on a massive meta-analysis—147 trials of antihypertensive treatment published between 1966 and 2007 involving 464,000 people aged 60–69. And the not unexpected result is that all classes of antihypertensive drugs are similarly effective for a given reduction in blood pressure.

They are all equally effective in protection against coronary heart disease events and strokes. The single exception is that β-blockers provide extra protection in the recent myocardial infarction scenario. They recommend a selection of any 3 drugs as this is likely to minimise adverse effects from any one of them.


How to best check for postural hypotension

There is a lot of it about in the elderly and it is a frequent cause of morbidity and hospital admission. This paper from Ireland reviews the topic and the confusion in diagnostic techniques. They prefer to call it Orthostatic Hypotension (OH) and define it as a drop in systolic BP of ≥20 mmHg or a drop in diastolic BP of ≥10 mmHg within 3 min of orthostatic stress. They believe that taking the sitting BP and then a standing BP after 30 seconds is inadequate.
Their proof is that this technique identified 94 out of a cohort of 730 to have OH. But when the same 730 patients were tested by tilt table 636 were found to have OH. So sit-stand BP testing has a very low diagnostic accuracy.

They recommend that the patient should lay supine for a period of 5 minutes prior to assuming the upright posture and should thereafter have their BP measured every 30 seconds for a period of 3 minutes. A bit tedious and time consuming but much more accurate.


**Exercise training in chronic heart failure?**

Some believe that such patients might benefit from exercise training. Whether they do or not is reviewed in 2 recent studies. 2331 medically stable outpatients with heart failure with left ventricular ejection fraction of 35% or less, were randomised to usual care or usual care plus aerobic exercise consisting of 36 supervised sessions followed by home-based training. And the outcome was a non-significant reduction in study end points (death and hospitalisation for cardiovascular causes). On the other hand, the second part of the study on the same cohorts showed a significant improvement in self-reported health status. So the exercise training appears to be beneficial to the psyche but not the heart.

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**Rivaroxaban or enoxaparin to prevent deep venous thrombosis (DVT) after total knee arthroplasty**

Rivaroxaban directly inhibits factor Xa, thus interfering with thrombosis. It is taken orally and needs no laboratory monitoring which makes it an attractive therapeutic option. In this randomised study, 3148 patients undergoing knee arthroplasty received either oral rivaroxaban 10 mg once daily beginning 6–8 hours after surgery, or subcutaneous enoxaparin 30 mg every 12 hours, starting 12–24 hours after surgery. 6.9% given rivaroxaban developed a DVT compared with 10.1% given enoxaparin (p=0.0118). The authors claim superiority for rivaroxaban without a significant difference in risk of major or clinically relevant bleeding. Maybe.

On looking into the details I note 10 major bleeds in the rivaroxaban arm, including 1 death, 5 re-operations and 4 patients requiring transfusion. Of the 4 non-fatal bleeds with clexane, 2 led to re-operation. One could also speculate that starting clexane much later may favour rivaroxaban results. And maybe the dose of clexane should have been 40 mg 12 hourly?

Survival benefit confirmed for prostate cancers diagnosed by PSA testing

The editorial *PSA testing in asymptomatic men to diagnose prostate cancer remains experimental* by Cox and Sneyd—which appeared in the 5 June 2009 issue of the *NZMJ*—denigrated the importance of the first reports on mortality from the two large screening trials for prostate cancer, the ERSPC trial carried out in Europe, and the PLCO trial carried out in the USA.

We contend that these two massive pieces of scientific endeavour have made a very important contribution to our understanding of the value of prostate cancer screening, and that together they provide direction on when screening has the most benefit on prostate cancer mortality, and how screening is most efficiently performed.

Cox and Sneyd believe that the results of the two trials were conflicting, in that the ERSPC trial involving a core group of 162,243 men aged 55–69 years demonstrated a survival advantage for men who were screened, whereas the PLCO trial involving 76,693 men aged 55–74 years did not. In fact, there are reasons given in the report on the PLCO trial which explain why a screening benefit would not be demonstrated by this trial, even if in fact one does exist.

Prostate cancer detection rates have been considerably higher in the US than any other country in the world for many years. This is because of the longstanding prevalence of prostate cancer testing in the US, compared to other countries. In the 3 years prior to participation in the PLCO trial, 44% of men had one or more PSA test, and 55% had a digital rectal examination. This is highly relevant because a previously normal PSA test reduces the chance of a subsequent result being abnormal. Moreover, repeated testing leads to a down-staging of the cancers that are detected, an effect that lessens with each additional test performed.

These ad hoc screening practices within the US population are the explanation for two differences between the results of the PLCO and ERSPC trials. Firstly, the smaller percentage of men who had cancer diagnosed in the screened arm of the PLCO trial compared to the screened arm of the ERSPC trial (7.4% versus 8.2%), even though PSA testing was performed more frequently in the screened arm of the PLCO trial. Secondly, the absence of a down-staging effect with screening in the PLCO trial, whereas in the ERSPC trial screening led to a 50% reduction in the diagnosis of cancers that were already metastatic.

The effect of previous PSA testing on subsequent prostate cancer mortality was demonstrated in the report on the PLCO trial. This showed that the cumulative death rate from prostate cancer at 10 years was 25% lower in all men in the trial who had undergone two or more PSA tests at baseline, compared with those who had not been tested.

Even more disturbing, however, is the contamination of the PLCO control arm during the observation period. Screening of controls increased with greater follow up, and was 52% by the sixth year after entry. This contamination rate means that men in the
control arm were nearly two-thirds as likely to have a PSA test as men in the intervention arm (rate of testing 85%), and the trial was grossly underpowered to detect the small survival differences that might exist between two arms that underwent such similar PSA testing patterns. The confidence intervals for the rate ratio of prostate cancer mortality in the intervention to control group were therefore wide, with the trial being unable to exclude up to a 25% reduction in mortality as a result of screening. Frequent PSA testing of controls explains why the percentage of cancers in the control group for the PCLO trial was higher than in the control group for the ERSPC trial (6.1% versus 4.8%).

The ERSPC trial, in contrast, recruited from a population in which at the start of the trial PSA testing was not commonly performed. Although some contamination of the control arm did occur during the trial, this was limited, and the trial was powered to allow for a 20% contamination rate.

Clinicians familiar with prostate cancer are surprised by the ERSPC result, not because it showed a survival advantage with screening, but because the advantage was already demonstrable after a median follow-up of just 9 years. The authors of the ERSPC report project that survival differences between the arms will get bigger with longer follow-up, a pattern already displayed in other randomised trials in which prostate cancer survival is the primary end point. This is not surprising as prostate cancer often has a long natural history, and the death rate goes up 3-fold after 15 years of follow-up. Furthermore, the ERSPC authors pointed out that with adjustments for non-compliance and contamination, the true survival advantages resultant from screening would be even greater.

Cox and Sneyd are rightly concerned that PSA testing leads to over-diagnosis and overtreatment. Clinicians who treat prostate cancer are also concerned, but they would not agree that this is a reason for abandoning PSA testing altogether. Instead, they have adopted a strategy to minimise the problem. They recognised that the over-diagnosis rate begins to go up sharply as men pass the age of 70 years, so the policy of *Active Surveillance* has been developed for older men. This policy permits invasive treatment to be withheld, often indefinitely, in those men with indolent cancers, whilst allowing intervention in the smaller group of men who present with aggressive cancers, or who have cancers that behave aggressively during the surveillance period.

The over-diagnosis rate also goes up with increased frequency of PSA testing. It is therefore encouraging that the survival gains in the ERSPC trial were achieved mainly with a PSA test every 4 years, making it probable that the annual testing performed in the PLCO trial is more frequent than necessary.

The title of Cox and Sneyd’s paper is baffling. PSA testing is far from “experimental”, as its use in asymptomatic men to diagnose prostate cancer has been standard medical practice for many years in Western countries, and it is now the main method by which localised prostate cancer is diagnosed. The issue is now how PSA testing can best be used in male populations to achieve maximum benefits, whilst at the same time keeping the risks associated with over-diagnosis and overtreatment to a minimum.

New Zealand and Australia have a lot to learn from these trials. In both countries there are regions, mainly urban, where PSA testing is already prevalent, and many of
the male population aged 50-70 years have already been tested. In these regions, there is little to be gained by organising population-based screening programmes. In contrast, there are regions, mainly outside main centres, where men infrequently undergo PSA testing.\textsuperscript{10}

Certain ethnic groups, and men in lower socioeconomic groups, have also been shown to have a reduced prevalence of PSA testing.\textsuperscript{11,12} These men stand to benefit greatly from a balanced education programme encouraging them to attend for accessible PSA testing, especially if a close family member has already been diagnosed with the disease.\textsuperscript{9}

To advocate for maintenance of the status quo, as Cox and Sneyd have done, is synonymous to turning a blind eye to the health inequalities that are known to exist on both sides of the Tasman.

\textbf{David S Lamb}\textsuperscript{a}, \textbf{Brett Delahunt}\textsuperscript{a}, \textbf{James Denham}\textsuperscript{b}, \textbf{David Slaney}\textsuperscript{c}

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\textbf{Professor Brett Delahunt} is Trial Pathologist for the TROG RADAR Trial, and is reviewing cancer tissue from all 1071 men enrolled. He is the Immediate Past President of the International Society of Urological Pathology.

\textbf{Professor Jim Denham} is Director of the Prostate Cancer Trials Group in the University of Newcastle, NSW. He is Chairman of the TROG 96.01 and RADAR prostate cancer trials, and supervises the Central Database for these trials.

\textbf{Doctor David Slaney} is a Science Leader at the Institute of Environmental Science and Research in Wellington. He has a special interest in cancer epidemiology.

\textbf{Competing interests:} None.

\textbf{References:}


The use of placebos to mollify difficult patients: in their best interests?

Holt and Gilbey’s recent survey into placebo use by New Zealand medical practitioners concluded that placebos do have effects and so “as long as the doctor considers their use to be in the best interests of the patient”, such use is “consistent with medical ethics”. Presumably they mean that placebo use will promote the patient’s welfare.

It was therefore of concern to note that nearly 46% of situations where a placebo was prescribed were “to get [the] patient to stop complaining” and, “after ‘unjustified’ demand for medication”. This compares with a national survey of Danish clinicians who found that the “most frequently reported reason for the use of placebos was to avoid a confrontation with the patient.”

It would seem that in many cases a placebo was given not necessarily in the best interests of the patient, but rather to serve the convenience and interests of the medical practitioner. In other words, in nearly half the cases where a placebo was prescribed, the justification appears motivated by a desire to get the demanding patient off the practitioner’s back.

Undoubtedly some patients are difficult, demanding, manipulative, and malingers. Combined with the uncertainties of medicine and the pressure of time, one may attempt to justify prescribing placebos on the grounds that they are basically harmless interventions that may alleviate a patient’s problem(s). In fact one may go as far as to describe the prescribing of placebos as ‘benevolent deception’: a compassionate white lie that has the best interests of the patient at heart.

Why then might the use of placebos to appease difficult patients be considered ethically dubious practice? I believe the use of placebos in these kinds of situations is intentionally deceptive and cannot be justified as being in a patient’s best interests. Patients are deceived as to the nature of the ‘treatment’ they are prescribed. This is true even where a medical practitioner may skip around the issue by stating ‘I have faith that these pills may help you, because they have helped other patients of mine with the same problems’.

The medical practitioner may truly not know what is wrong with the patient, but prescribing a placebo may effectively quash any further communication with the patient about their problem(s). Prescribing a placebo then becomes an easy and convenient solution to a frustrating problem that may seem irresolvable.

Rather than reassure the patient they will continue to be cared for and discuss with them why there may be very little that can be given to them to ameliorate or cure the problem, the patient may come to expect that there will always be some medication or procedure that can be (and ought to be) prescribed. This attitude simply perpetuates the myth that all medical problems can be successfully treated. Furthermore if patients find out they have received a placebo, they may well lose confidence in their physician and in bona fide medication. This is not implausible when we consider that
many patients misunderstand how placebos work and are generally not well informed about the placebo effect.⁴

Although one may object that the success of a placebo lies in the power of suggestion, it is not true that information must be concealed from a patient in order to secure a (potential) benefit. Placebos have been used successfully in clinical trials where transparency about their properties is disclosed.⁵

Within the ethical and medical literature the acceptability of using placebos in clinical practice is contentious and divided. Some commentators claim that placebo use is ethically permissible even though it entails deception⁶; others claim that the practice of deception sets the stage for abuses and growing mistrust.⁷

Although Holt and Gilbey plausibly claim that when placebos are used in the best interests of patients they are consistent with medical ethics, it is questionable whether many instances of placebo use in New Zealand are in fact in a patient’s best interests. Demanding and difficult patients are not easy to manage, but the use of placebos may not be the answer to their problem(s).

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References:

Estimating the reproduction number of the novel influenza A virus (H1N1) in a Southern Hemisphere setting: preliminary estimate in New Zealand

On 11 June 2009, the World Health Organization raised the influenza pandemic alert level from phase 5 to phase 6, declaring that the newly emerged influenza caused by a novel influenza A virus (H1N1) had reached pandemic levels. Although summer conditions in the Northern Hemisphere might be impeding the spread of this pandemic, in some Southern Hemisphere countries (including New Zealand) there appears to be very active and widespread transmission.

The first imported cases in New Zealand arrived on 25 April in a group of students returning from a visit to Mexico. On 30 April, this novel pandemic influenza became a notifiable and quarantinable disease in New Zealand, and widespread indigenous transmission became evident in June. By 6 July, 1059 confirmed cases had been reported, including 3 deaths (and subsequently additional deaths have occurred).

To assess the transmissibility of this pandemic influenza virus in New Zealand (i.e. the expected magnitude of an epidemic), we investigated the time-evolution of confirmed and probable cases in New Zealand up to the end of June 2009. In particular, we estimated the reproduction number, $R$, which is the average number of secondary cases generated by a single primary case. $R$ is a summary measure of the transmission potential in a given epidemic setting, and has been estimated to range from 1.4–1.6 in Mexico\(^1\) and 2.0–2.6 in Japan\(^2\) for this current pandemic.

**Methods**—We analysed the temporal distribution of novel influenza A virus (H1N1) cases notified to medical officers of health and recorded on the national surveillance system (EpiSurv). Figure 1 shows the observed temporal distribution from 28 May to 28 June 2009, including 585 confirmed cases and 38 probable cases.\(^3\)

The time-evolution is illustrated by the earliest date entered in EpiSurv, which is either date of symptom onset, hospitalisation, death, or reporting, because the date of onset has not been available for all cases (though in fact no deaths occurred in this time period).

A confirmed case was defined as a person with laboratory-confirmed novel influenza A (H1N1) virus infection by means of real-time PCR, viral culture or 4-fold rise in specific neutralising antibodies. A probable case was defined as a person with an influenza-like illness (i.e. [i] history of fever, chills, and sweating or clinically documented fever greater or equal to 38°C, plus [ii] cough or sore throat) who has a strong epidemiological link to a confirmed case or defined cluster.

To estimate $R$ we first removed 63 imported cases from the epidemic curve and assessed the growth of the remaining cases who were healthcare workers, those with known contact/s, or those with unknown contact/s. Second, we investigated the initial growth phase which was counted from 2 June when the first indigenous secondary case was reported.
The exponential growth phase was assumed to have a mean duration of 15 days (from 2–16 June) but windows in the 15±2 days were also used. It should be noted that the latest time points of the exponential growth phase were before 22 June, when constraints on testing began to occur due to high demand. This was also the day when health authorities switched from a containment to a “manage it” phase of pandemic control.

Assuming that the reporting delay (from onset to reporting and from onset to hospitalisation) was independent of calendar time, the growth rate of reported cases in the epidemic curve (Figure 1) mirrors the exponential growth rate of infections.4

Figure 1. Epidemic curve of the novel influenza A virus (H1N1) infection in New Zealand

The horizontal axis represents the earliest date entered in EpiSurv, which is either date of symptom onset, hospitalisation, death, or reporting. Imported cases from early April to early May are not shown.

Third, we estimated the intrinsic growth rate \( r \), which is also referred to as the Malthusian growth rate. We estimated \( r \) based on a pure birth process.5,6 Given our observations of the cumulative number of cases, \( C(0), C(1), C(2), \ldots, C(t) \), we have

\[
Pr \left( C(i) = n + m | C(i-1) = n \right) = \binom{n + m - 1}{n - 1} \exp(-r\mu)(1-\exp(-r))^m
\]

which was used to construct a likelihood function for \( r \),

\[
L(r) \propto \exp \left( -r \sum_{i=0}^{t-1} C(i) \left[1-\exp(-r)\right] \right)^{\Phi(\Phi-\psi)}
\]

Equation (2) was used for estimating \( r \).2,6 The 95% confidence intervals (CIs) were derived from profile likelihood. Fourth, assuming that the generation time follows a gamma distribution with mean \( \mu = 2.8 \) days and coefficient of variation \( k = 0.471 \), the reproduction number was estimated using the following estimator.7
Since the generation time of the ongoing pandemic influenza has yet to be fully clarified, we investigated the sensitivity of $R$ to different $\mu$ ranging from 1.6 to 4.0 days.

**Results**—Figure 2 compares the observed and predicted number of indigenous cases during the first 15 days of the pandemic in New Zealand. The maximum likelihood estimate of $r$ was 0.26 (95% CI: 0.23–0.30) per day, and thus, $R$ was estimated as 1.96 (95% CI: 1.80–2.15).

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**Figure 2. Temporal distribution of the novel influenza A virus (H1N1) infection in New Zealand during the initial growth phase of indigenous cases**

![Figure 2](image)

Dots, observed number of cases; Continuous line, expected number of cases; Dashed lines, uncertainty bounds of expectation based on the confidence limits of the intrinsic growth rate.

Figure 3A illustrates the sensitivity of $R$ to variations in the mean generation time in the range of 1.6 to 4.0 days. The corresponding maximum likelihood estimates of $R$ lie in the 1.49 to 2.55 range. The observed pattern was consistent with our analytical understanding; the longer the mean generation time, the greater the estimate of $R$ we will obtain.

Figure 3B shows the sensitivity of $R$ to variations in the initial growth phase (i.e. taking 14 June to 18 June as the latest time point of reporting to observe exponential growth). The intrinsic growth rate ranged from 0.20 to 0.29 per day, and accordingly, maximum likelihood estimate of $R$ ranged from 1.69 to 2.11.

$$R = \left(1 + \frac{\mu t^2}{\mu^2}\right)^\frac{1}{\mu^2}$$ (3)
Figure 3. Estimates of the reproduction number of the novel influenza A virus (H1N1) infection in New Zealand.

A) Estimated reproduction number by different mean generation times, based on the initial growth phase of the epidemic (i.e. first 15 days). B) Estimated reproduction number by different dates at the end of the initial growth phase. The mean generation time was assumed to be 2.8 days.

Discussion—The present study is the first to report $R$ in a Southern Hemisphere setting for the ongoing pandemic, caused by a novel influenza A virus (H1N1). The estimates for $R$ are generally in between the two existing estimates for Northern Hemisphere settings but were closer to the higher estimate in Japan.\(^1,2,8\) It should be noted that our estimate of $R$ is greater than published estimates for seasonal influenza in temperate countries.\(^9\) Moreover, our estimate is slightly greater than that of Spanish influenza pandemic from 1918–19 in New Zealand.\(^6\)

We are aware of three plausible reasons to obtain a higher estimate of $R$ than that in Mexico:

(i) higher virus fitness to the winter season in the Southern Hemisphere setting;

(ii) possible large clustering of cases in certain settings (e.g. healthcare workers in hospital settings, extended families and large gatherings in Pacific People’s communities); and

(iii) possibly time-variations in the frequency of ascertaining infected individuals during the early phase of the pandemic (i.e. potential increase in the diagnostic coverage of infected individuals as a function of time).

We are actively investigating ways of improving the robustness and generalisability of $R$ estimates for New Zealand. Addressing the impact of heterogeneous mixing on the estimate of $R$ as well as potential under-reporting of symptomatic cases may provide more detailed insights into the transmission dynamics of pandemic influenza in this country.

Clarification of the heterogeneous patterns of transmission (e.g. age-specificity) would also permit optimising the distribution of upcoming pandemic vaccines to different age- and risk-groups. In addition, it would also be useful to explore the transmission potential using epidemic data for other outbreak-settings (to address uncertainties with respect to time, space and other risk-attributes of sub-populations).
Given that $R$ is estimated to be 1.96 in a randomly mixing population, this would suggest that 78.6% of the population will experience infection by the end of the pandemic. Nevertheless, a smaller estimate may be more likely in a realistically-structured heterogeneously mixing population and if public health interventions around hygiene behaviours and social distancing are effective.

Thus, the transmission potential of this virus in this Southern Hemisphere setting should be regarded as relatively high. Therefore, in the context of some serious morbidity and mortality, these findings support the continuing promotion of public health interventions in this and other Southern Hemisphere countries.

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References:

Socks on shoes for icy Dunedin streets is nothing new

I recently read the article in the Dominion Post about the survey regarding socks over footwear on icy slopes in Dunedin.

What is new? I lived in Stuart Street and spent over 30 winters walking down to Dunedin Hospital where I worked as an RN and always wore socks over my shoes during severe icy periods.

Was it necessary for the University to waste time and money on a subject that only requires commonsense?

Olive M Allen
Paraparaumu Beach
Mr Taine saved my arm

On 12 July 2009 it was 33 years (1976) since Mr Taine\(^1\) operated on my arm after I had it almost completely severed by an aeroplane propeller. I was en route to Auckland for an amputation via Napier Hospital where Mr Taine took over.

The surgery was ground-breaking and thanks to Mr Taine I have my arm fully intact. I only have some minor pain in the hand now and again. I wanted to thank him myself and found your obituary on the Internet. What an incredible man!

Please pass my thanks to his son. I know I am extremely lucky.

Yvonne Cunningham
NSW, Australia

Reference:
   http://www.nzmj.com/journal/120-1263/2761
Robert Ross Manning

MB ChB [UNZ], FFARCS[Eng], FANZCA

Ross Manning died suddenly at Dunstan Hospital (Clyde, Central Otago) shortly after suffering a myocardial infarct at his home in Wanaka in his 81st year. He was a pioneer in Anaesthesia and Intensive Care in Auckland, making a major contribution to both when they were emerging specialties.

Ross was born on 22 June 1928 at Brown St in Dunedin, the youngest by 12 years of 5 children. He was educated at Arthur St Primary School, Otago Boys High School, and Otago University, graduating MB, ChB in 1953.

During his undergraduate years Ross spent many of his holidays working as a shearer and rabbiter in Central Otago at Benmore Station and Moa Flat, beginning a lifelong love of Central Otago, where he was eventually to retire.

After graduating Ross worked at Dunedin Hospital as a house surgeon and registrar, where he first developed an interest in Anaesthesia.

After a further year at Oamaru Hospital he left for England to pursue a career in Anaesthesia. His first post was Queen Victoria Hospital in Swindon. Later he was to move to Newcastle General Hospital in Newcastle upon Tyne, and finally to the Radcliffe Infirmary in Oxford under Sir Robert Macintosh. It was there that Ross gained his FFARCS[Eng].

Ross returned to Auckland, New Zealand, in January 1961 at the time of just before the poliomyelitis epidemic. He was appointed to the dual role of Anaesthetic Specialist, and also Assistant Medical Officer to the newly formalised “Respiratory Unit, Auckland Hospital”, under Dr Matthew Spence, who left soon after on 5 months sabbatical leave. Ross’s contribution during this time will be discussed later in the text.

Ross worked at National Women’s and Green Lane Hospital in the Cardiac Unit with anaesthetists Eve Seelye and Marie Simpson. It was here that he began a long association with Sir Brian Barratt-Boyces.

In 1965 Ross made the decision to enter private practice, and joined Drs Nils Theilman and Derry Lawler to form the Epsom Anaesthetic Group, which now has more than 40 members.
Ross continued working part-time in Auckland Hospital’s Princess Mary Hospital, where his special skills in Paediatric Anaesthesia were invaluable at a time when many anaesthetists had little experience in Neonatal Anaesthesia. Over the years he developed a busy and varied private practice, encompassing all types of surgery. In particular, he enjoyed a long association with Sir Brian Barratt-Boyes at the Mercy Hospital. Ross also maintained an extensive practice in Dental Anaesthesia, mainly in South Auckland, until his retirement.

On retirement Ross moved to his beloved Central Otago, first building a home at Roxburgh. There he planted over 2000 shrubs and trees and landscaped the section. He was able to pursue his love of golf (a colleague remarked that he was less interested in his score than the number of balls he found). During this time Ross was occasionally called on to assist the local doctors in resuscitation of accident victims, and on one occasion, to intubate a neonate who required ventilating.

Ross then moved to his final home in Cardrona, which was tragically razed by fire, destroying all the possessions, including a valuable art collection.

Ross Manning was not only a superb anaesthetist, he was a valued colleague and friend. He was disarmingly modest about his achievements, but always ready to share his wisdom and expertise.

Evan Watts (FANZCA) wrote this obituary.

**Ross Manning’s Intensive Care Pioneering**

It is appropriate to hail Ross’s innovative role at Auckland Hospital in Intensive Care Medicine as (sadly) it is little recognised. Early in 1961, arising from his initial mild “exposure” to it in the Respiratory Unit at the Churchhill Hospital (Oxford) and following his return to New Zealand, Ross was seconded for a couple of sessions a week to Matt Spence’s fledgling “Respiratory Unit, Auckland Hospital”, which was then functioning with a modest intake.

Soon afterwards, that year’s polio outbreak started and in a short time one patient had died; but then (“just before the epidemic exploded”) Matt Spence departed for overseas study leave. Ross acted as locum throughout the epidemic’s brunt for the torrid 5 months Matt was away.

Together with Dr Ruthven Lang he reported their further 16 respiratory/bulbar failure patients treated by tracheostomy and IPPV (with newly acquired Bird ventilators), but without any further mortality—a remarkable outcome and achievement [NZMJ 1961;60:450–4].

Ross described it to me as

“...all heavy work. I was taken off all lists, I think, but it was extremely rewarding”. (Ross personally restored the non-functioning Radcliffe ventilator, when even local experts could not). “When Matt came back I partly withdrew from the unit. His arrival back was the start of new initiatives and directions and the full realisation that the Respiratory Unit was here to stay.”

This time period was short, but its importance from Ross’s vital, IPPV “first” was significant for New Zealand Intensive Care.

Ron Trubuhovich (FJFICM, FANZCA, FRCA) wrote these additional comments.
David Henry Hamilton Pullon

MBChB (NZ), Dip Child Health, FRCP (Edin), FRACP, FRCP (Lond), Paediatrician

Died at his home in Hamilton, New Zealand on 7 June 2009, aged 85.

David Henry Hamilton Pullon was born on November 16 1923 in Christchurch. He was the elder son of Dr Edwin and Mrs Jean Pullon. He was educated at Medbury Preparatory School, Christ’s College, and then Otago University, graduating MB ChB (NZ) in 1947.

After 3 years in posts at Christchurch Hospital, he was appointed House Physician at Edgware General Hospital, Middlesex, London. There he gained the Diploma in Child Health in 1952, and MRCP (Edinburgh) in 1953. Whilst a medical Registrar at St Mary’s Hospital Paddington, London, he had to return to NZ, after his father died suddenly in mid-1953.

Back in Christchurch, David completed the MRACP in 1955. He decided to return to Britain, where he became a House Physician at Edgware General Hospital, Middlesex, London. There he gained the Diploma in Child Health in 1952, and MRCP (Edinburgh) in 1953. Whilst a medical Registrar at St Mary’s Hospital Paddington, London, he had to return to NZ, after his father died suddenly in mid-1953.

Shortly afterwards he returned to New Zealand and in 1960 was appointed as the second specialist Paediatrician at the Waikato Hospital, in Hamilton. Over the subsequent 28 years he was very involved with the development of the Paediatric Department, right through until his retirement in late 1988. In 1969/1970 David took a considerable part in establishing and raising funds for the Waikato Mothercraft Unit. He also worked for the Dept of Health, the IHC Society, and in private practice.

David wrote about toxoplasmosis, and then with others about amoebic meningencephalitis, of which he had a number of cases in his area. He was elected FRACP in 1971 and FRCP (Edinburgh) in 1972. Of Inborn Errors of Metabolism he was the first to describe cases of Lesch-Nyhan Syndrome in NZ.

David also had a number of cases of phenylketonuria and homocystinuria. After publishing papers on these, he was invited by Professor Bob Guthrie to be an international guest speaker on homocystinuria at Heidelberg, in Germany in 1978. With the support of Professor Guthrie, David worked with Professor Arthur Veale to establish the NZ national screening programme, using the heel-prick samples collected from all newborns on to the Guthrie card. With his now well known interest in inherited metabolic disorders, David became a member of the Human Genetics

David served on the Waikato Medical Research Committee from 1973–1988. He was a strong supporter of the Waikato Postgraduate Medical Society. He chaired the Waikato Hospital Pharmacy Committee from 1975–1988, and represented the NZMA on the Pharmacology and Therapeutics Advisory Committee reporting to the Minister of Health from 1985–1988. In 1988 he was elected Honorary Life Member of the Paediatric Society of New Zealand, and in 1989 was elected FRCP (London). In his retirement he regularly attended the Waikato Hospital Grand Round, where he was renowned for often having a difficult question prepared.

Outside of medicine, David was a middle distance runner in his youth, breaking several school records whilst at Christ’s College. He skied for the University of Otago, and became an adept trout fisherman. In his retirement he wrote *A Hamilton Pedigree* and *The Hamilton Diaries* about his mother’s family. In 1994 he also wrote *Pullon Kinsfolk*, describing his father’s family. His interest in natural history led to his membership of the Royal Society of NZ.

David married Margaret Weir Hanna of the Upper Murray district of Australia in 1953. He is survived by her, a daughter, two sons, and six grandchildren. His daughter Susan and son Humphrey followed him into medicine.

This obituary was largely self-written.
Pericardial Diseases: Clinical Diagnostic Imaging Atlas with DVD


This is a very good book. Any medical practitioner who wishes to have a sound understanding of pericardial disease, or is involved in imaging the pericardium would be well advised to read this book and retain it for reference.

This book describes the pericardium in health, and its various disease states. The writing is clear, didactic, and has detailed descriptions of the pathophysiology of the various pericardial disease states. It provides a comprehensive review of all pericardial disease states and their clinical features, diagnosis, and treatment.

As the title indicates, it focuses on imaging, including plain radiology, computerised scanning, magnetic resonance imaging, and particularly echocardiology.

The illustrations are copious and of good quality. However some would be improved by better labelling, including the views in the radiology, labelling of structures in echocardiograms, and including scales, units, and labelling of the haemodynamic tracings. The illustrations are completed by a digital library.

The book is unusual in a modern medical book in having a single author, which improves the continuity and coverage of the book compared with the more common multiauthor volumes.

Stuart Hutchinson is to be congratulated on this book. It is a valuable book and can be recommended to those interested in pericardial disease, and cardiac imaging.

Ian Crozier
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