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This Issue in the Journal

The excess cost associated with healthcare-associated bloodstream infections at Auckland City Hospital
Andrew Burns, Lesley Bowers, Nick Pak, Jean Wignall, Sally Roberts

Up to 5 to 10% of patients admitted to hospital acquire an infection which may prolong their hospital stay. These infections cost the health sector money and prevent the bed being used for other purposes. This study has put a monetary value on the cost of an episode of healthcare-associated bloodstream infection. This is the cost to the hospital not to the patient. There will also be a cost to the patient in terms of loss of income for them, or family members, as they support the patient’s delayed return to full health. Initiatives within the health sector that are aimed at reducing healthcare-associated infections need to be supported.

Introduction of continuous regional analgesia via wound catheters in a peripheral hospital
Ei Thu Aung, Pascale Fluri, Semisi Aiono

This study reviewed the effectiveness of continuous regional analgesia (CRA) via wound catheters after abdominal surgery in a district general hospital (Wanganui). Results showed that CRA via wound catheters provides effective and safe analgesia (pain relief) after abdominal surgery for patients in a small district general hospital. This technique was readily accepted by theatre, HDU, ward, and anaesthetics colleagues in the hospital.

Ten-year review of intussusception at Starship Hospital: 1998–2007
Hemal Kodikara, Amiria Lynch, Phillip Morreau, Sally Vogel

Intussusception, a condition in children where part of the bowel telescopes into another part, is being managed successfully at Starship Hospital. Rates of reducing the intussusception by enema and rates of surgery and outcomes of both are comparable to other studies around the world.

Christchurch experience of pulmonary embolism with and without thrombolysis
Wandy Chan, Tiffany Campbell, Sharyn MacDonald, Ian Crozier

We documented our first 6-year experience of thrombolysis (powerful clot busting agent) in patients with pulmonary embolism (blood clot to the lungs) with large clot burden. Our experience was good with a relatively low in-hospital and 6-month event rate. When comparing CT chest markers for clot burden and right heart strain (markers of severity of pulmonary embolism), they had good correlation with echocardiography.
Surgical outcomes following laparoscopic adrenalectomy for treatment of Conn’s syndrome (primary hyperaldosteronism) between 1999 and 2006
Andrew Herd, Richard Harman, Eletha Taylor

In a small number of people, high blood pressure and electrolyte disturbances can be caused by a benign growth in the adrenal gland. This can lead to further health complications and requirement for medications with side effects. Laparoscopic resection of this growth is safe and offers potential cure in a number of cases.

Task Manager: an innovative approach to improving hospital communication after hours
Mary E Seddon, David Hay

In the evenings and overnight the hospital is staffed with fewer doctors and nurses than it is during the day. It is important that these healthcare professionals are able to communicate quickly and clearly so that patients receive the care that they need. At Middlemore Hospital we have introduced a tool (Task Manager), that staff are able to access on any computer. This tool shows all the tasks that need to be done, it colour codes them for urgency and it displays who has accepted the task. This has dramatically reduced the number of pagers that each doctor receives (allowing them to do their work without distraction) and has shown for the first time, what tasks are actually being done, by whom, and when. This should inform how we staff hospitals at night.

Outcome of patients on azathioprine: a need for a better pre-treatment assessment and dosing guideline
Dinar Jabin, Sunil Kumar, Peter J Gow

This is a retrospective study on rheumatologic patients who were on Azathioprine (AZA), a disease modifying anti-rheumatic medication. AZA metabolism depends on few enzymes; TMPT is one of them. British Society of Rheumatology (BSR) recommended TPMT testing prior to initiation of AZA to avoid bone marrow toxicity. This study looked at our practice of AZA dosing and escalation regimen, compared with the BSR guideline. Also identified patients who suffered drug-related side-effects. Finally, we emphasized on guideline based practice of AZA dosing regimen as well as TPMT testing prior to initiation of the drug.
Using economic data to reduce healthcare-acquired infection

Kate Halton, Nicholas Graves

In this issue Burns et al\(^1\) report an estimate of the economic loss to Auckland City Hospital from cases of healthcare-associated bloodstream infection. They show that patients with infection stay longer in hospital and this must impose an opportunity cost because beds are blocked. Other costs fall on patients, their families and non-acute health services. Patients face some risk of dying from the infection.

Teasing out the independent effect of infection on outcomes is difficult. Those at high risk of infection often have independent higher risks of a longer stay and death, and infection can arise at any time during the admission. The method used by Burns et al was applied carefully and the authors should be commended for this; methods are however changing rapidly for this research area and other approaches are available.\(^2\)

The chief message from this study—that those who hold the purse strings for health budgets should pay attention to—is that infections are costly and these costs can be reduced. There is an easy to understand economic paradigm. Additional money and resources might be diverted toward careful and vigilant infection control; in return costs and lives are saved.

Economic evidence is currently not a powerful influence on infection control decision-making. Use of explicit evidence, e.g. “spending X on infection control will give us Y in return and this is better that other uses of resources” is a sensible way to allocate infection control spending.\(^3\) There might be problems acquiring rigorous and relevant cost-effectiveness evidence.\(^4\) The argument can be time-consuming and complicated to make and results hard to interpret.\(^5\) A distrust of the methods and assumptions used in economic evaluations is a deterrent to their use.\(^6,7\) The quality of the infection control literature that exploits the economic paradigm has been poor\(^4,8\) but is improving.

Rather than dwell on quality issues we discuss whether economic data are likely to be used by decision-makers. This is what matters to patients and their families currently disadvantaged by infection. And there is very little research on this topic.

Decision-makers might not have the time or motivation to find, read, understand and then act on cost-effectiveness data. Decision-makers under pressure to respond quickly to a problem may instead focus on simple evidence that is easy to understand and communicate to people e.g. “infections are expensive and so we must do something about it”. But without cost-effectiveness information on how to reduce the problem resources could be wasted.

Solutions include closer collaboration between research and decision-making bodies to improve the relevance of evaluations, better communication of research findings, and the provision of health economics training to decision makers.\(^9\) National guidelines that incorporate a cost-effectiveness perspective may also enhance uptake.
There are institutional barriers to using economic evidence. Authors of cost-effectiveness studies assume resources can be transferred easily from one budget to another. A control program might incur costs in the intensive care unit but the cost savings arise in the general medical ward. An intervention may be cost-effective but without appropriate compensation, funds may not be made available to implement it. Where all cost changes occur in one budget, such as a haemodialysis speciality, the lion’s share of savings arise from released bed days. These represent a fixed cost to the hospital and few cash-savings will arise to fund the prevention programme. Infection prevention might only increase patient throughput—that is, improve production efficiency—rather than generate cash savings.

Political objectives might restrict the uptake of cost-effectiveness studies. Targets imposed externally, such as reducing rates of healthcare associated infection to zero may contradict the economic evidence, yet these targets may impel decision-making. As infection rates fall residual infections become harder and more costly to prevent. There is no good evidence of whether zero is sustainable. Hospitals that attempt eradication may find as they approach zero the marginal investment required for infection control is not appropriately rewarded. These initiatives currently dominate the infection control landscape and they might be a flag around which the infection prevention community rallies, rather than a realistic policy goal.

Cost-effectiveness is one factor for decision-makers. Improving knowledge about its relative importance for decision-makers would be useful. Studies of national reimbursement and policy decisions in the UK and Australia have shown that greater importance was attached to levels of effectiveness and safety of interventions, the availability of alternatives, the seriousness and magnitude of the health issue and the perceived need in the community.

At the healthcare provider level studies have shown that clinicians raise moral objections to rationing care. A study of factors influencing physicians’ decision to discharge patients with methicillin-resistant Staphylococcus aureus showed that severity of illness and the social support available for patients were prioritised over economic considerations such as targets to reduce length of stay.

Infection control decision-making requires consideration of the economics of infection control not just the cost of infection. To support healthcare professionals in this endeavour we must increase our understanding of how they comprehend economic evidence, how they use this information and what barriers they face in integrating this evidence into their decision-making process. This will improve the impact of economic evidence on clinical decision-making. Research should be done about this.

**Competing interests:** None.

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Regional anaesthesia and pain relief after surgery

Michael J Fredrickson, R Ross Kennedy

Pain relief after surgery is important for many reasons beyond the ethical duty to minimise pain and suffering. The physiological insult of surgery is lessened, recovery and general patient wellbeing may be improved with patients returning to normal activities faster, and the incidence of chronic pain is reduced. Despite widespread understanding of these principles there are frequent impediments to implementing high quality pain relief. Current practice emphasises “multimodal analgesia”. Although this is commonly understood to mean using a range of drugs, appropriate use of local anaesthetics is frequently an important part of a multimodal approach to pain relief after surgery.

In this issue of the Journal, Aung and colleagues discuss the use of abdominal wound catheters as an alternative to epidural administration of local anaesthetics.

The peripheral application of local anaesthetics has increased dramatically in recent years through the increased use of interventional regional anaesthesia/analgesic techniques. While this change has been due in part to the perceived complexity and complications of optimal management of epidural blockade mentioned by Aung et al, and to developments in the available analgesic agents, two technological breakthroughs have played a key role. These are ultrasound guidance for nerve localisation and perineural catheters for providing extended peripheral nerve blockade. Both technologies emerged in the late 1990s, and have been progressively incorporated into routine clinical practice over the last decade.

Advances in ultrasound technology have made high quality portable ultrasound machines, capable of nerve localisation for local anaesthetic deposition, commonplace in the operating suite. In addition to allowing visualisation of nerves and plexuses, real-time ultrasound guidance has, for the first time, enabled visualisation of important adjacent structures, the advancing needle and subsequent local anaesthetic spread.

Evidence from randomised controlled trials have shown a reduction in the number of needle passes, small reductions in procedure related pain and a reduction in procedural time when compared to traditional nerve localisation techniques. However, ultrasound has not been shown to unequivocally increase block success rates, as success rates were already high with blocks performed by experienced practitioners using existing techniques. Intuition would suggest that real-time needle guidance should translate into a reduction in iatrogenic needle related complications; to date this has only been demonstrated with respect to inadvertent vascular puncture.

The most feared complication of peripheral nerve blocks, iatrogenic nerve injury, is fortunately very rare so it is unlikely to ever be demonstrated whether real-time ultrasound needle guidance has any impact on this complication. Although the evidence of reduced risk is equivocal, ultrasound has resulted in more patients
receiving perioperative peripheral nerve blockade, which has been good for the perioperative care of surgical patients.

While ultrasound technology has attracted most of the attention over the last 5 years, the development and availability of perineural catheters, allowing continuous peripheral nerve blocks, has had the greatest positive impact on the perioperative experience of orthopaedic patients. The management of pain after shoulder surgery exemplifies this development.

As recent as 2003, it was not uncommon for patients having had rotator cuff surgery to require a 2-night hospital admission for intravenous opioid. Now, with our ability to accurately and safely place catheters at the appropriate position along the brachial plexus, together with the availability of affordable ambulatory local anaesthetic delivery systems, we can provide prolonged brachial plexus blockade in the ambulatory setting (typically 3–5 days), thereby providing extended potent postoperative analgesia largely devoid of opioid related side effects.

The technique has been shown to be well tolerated and associated with high patient satisfaction. Consequently, rotator cuff procedures can now be performed as overnight or even day stay procedures. Similar results have been achieved for a wide range of painful peripheral limb surgery and promising results have been reported for major knee surgery.

Although many still consider continuous epidural analgesia the gold standard for pain relief after abdominal surgery, there are valid concerns about the risks and costs of postoperative epidurals. The development of peripheral catheters and self contained local anaesthetic delivery systems have allowed widespread use of wound catheters in abdominal surgery as a simpler alternative.

The audit of Aung et al suggest that although the improvement in analgesia is not as spectacular as seen in peripheral orthopaedic surgery, abdominal wound catheters can be used simply and safely in a wide variety of hospital settings.

Competing interests: MJF: Research support from I-Flow International.

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References:


Front-of-pack nutrition labelling: where to now?

John White, George Thomson, Louise Signal

Food labelling is an area of continuing concern to health organisations, the food industry, consumers and governments in both New Zealand and Australia. Some big decisions on such labelling affecting both countries are expected over the next year. These are likely to have long-term effects on health outcomes.

The background and issues

In response to the continuing issues the Council of Australian Governments (COAG) has asked the Australia and New Zealand Food Regulation Ministerial Council to undertake a comprehensive Review of Food Labelling Law and Policy. New Zealand is represented on the Ministerial Council by Minister of Food Safety Kate Wilkinson. The Review is being conducted from Canberra by a panel appointed by the Ministerial Council. The panel, which is currently considering submissions, is due to report to the Ministerial Council in late 2010 and to COAG in early 2011.

A major issue for public health is the possible introduction of an interpretive front-of-pack (FOP) nutrition labelling scheme. ‘Interpretive’ labels provide information that enables shoppers to readily identify healthy food choices without having to perform calculations or understand percentages. An example is the ‘traffic light’ system discussed below, in which colours indicate the extent to which a product should form part of a healthy diet.

Diet has a central role in maintaining good health and preventing major chronic diseases. An estimated 11,000 deaths in New Zealand in 1997 (40% of all deaths) have been attributed to the joint effect of poor diet and physical inactivity, with diet playing the larger part. These included around 85% of deaths from ischaemic heart disease, 80% from diabetes and 70% from stroke.

Interpretive nutrition labels can help shoppers to identify healthier food choices. New Zealand research indicates that those most at risk from chronic diseases—Māori, Pacific and low-income shoppers and their families—are likely to particularly benefit from such labels. It can also be expected that introduction of an interpretive scheme would result in food manufacturers looking for ways of improving the nutritional quality of their products. Under a traffic light scheme, for example, manufacturers would be strongly motivated to avoid having products given a red light, indicating a high level of fat, sugar or salt.

New evidence

We have analysed what submissions to the Review say about FOP nutrition labelling. All 449 submissions available on the Review website as at 26 August 2010 were classified by sector (e.g. food industry) and sub-sector (e.g. retail), and coded for direct or implied agreement or disagreement with a number of propositions. Results are reported only for the 26 submissions from food manufacturers (including beverage
manufacturers), the 46 submissions from the health sector (excluding submissions concerned only with alcohol labelling), and the 6 submissions from Australian state governments and territories.

**A clash of views**

Submissions from the health sector and state governments and territories were generally supportive of the traffic light system, while those from food manufacturers generally opposed it. Food manufacturers favoured the ‘Daily Intake Guide’ (DIG) scheme developed by the Australian Food and Grocery Council and supported by the New Zealand Food and Grocery Council, which shows percentage daily intake per serving for a number of nutrients. Traffic light schemes are ‘interpretive’; DIG is not.

Figure 1 shows how submissions from the health sector, food manufacturers and Australian state and territory governments differed in their views about traffic light schemes. The proposition that “a traffic light scheme would be a good approach to FOP nutrition labelling” was directly or implicitly agreed with by 25 of 46 health submissions (54%), and by 4 of 6 submissions from state and territory governments (67%). No submissions from these groups disagreed, with remaining submissions expressing no view. On the other hand 20 of 26 of submissions (77%) from food manufacturers disagreed with the proposition, with none agreeing.

**Figure 1. Percentage of submissions agreeing and disagreeing that a traffic light scheme would be a good approach to FOP nutrition labelling, by selected sub-sector**

Of the 25 health submissions agreeing that a traffic light scheme would be a good approach, 16 called for a mandatory traffic light scheme to be introduced.

Positions were reversed for the proposition that “the Daily Intake Guide scheme is a good approach to FOP nutrition labelling” (Figure 2). No submissions from the health sector agreed with the proposition, with 9 of 9 submissions from the food manufacturers disagreeing, and all 6 submissions from state and territory governments expressing no view.
sector or state and territory governments agreed with this proposition. Half of health sector submissions and one-third of those from state and territory governments disagreed. The proposition was, however, supported by 16 of 26 submissions (62%) from food manufacturers.

**Figure 2. Percentage of submissions agreeing and disagreeing that the Daily Intake Guide scheme is a good approach to FOP nutrition labelling, by selected sub-sector**

![Bar chart showing percentage of submissions agreeing and disagreeing with the Daily Intake Guide scheme.](http://www.nzma.org.nz/journal/123-1324/4395/)

Submissions were received from the New Zealand Government and from two Australian federal departments. None of these expressed a view on the merits of either scheme.

Several submissions proposed solutions that might increase the likelihood of a compromise position being adopted that still produced long term health benefits. Given the inclusion of red lights (indicating less healthy products) is a major barrier to compromise, one submitter has suggested a traffic light scheme in which green and amber lights were mandatory, but with red lights voluntary.\(^{10}\)

The submission from the New South Wales (NSW) government\(^ {11}\) offered a different approach, proposing that:

> The need to maintain consistency and avoid confusion creates a strong case for prescribing the labelling format and requirements that manufacturers must use if they choose to label products on health or nutrition grounds. This ‘voluntary/mandatory’ approach would not affect a manufacturer’s decision on whether to label but would prescribe the format that any labelling must follow (p2).\(^ {11}\)

The NSW submission listed a number of reasons that make the DIG scheme problematic, and argued for a traffic light scheme.
Where to now?

The diametrically opposed positions of food manufacturers and the health sector on FOP nutrition labelling leaves little room for compromise. Powerful business interests generally prevail in most circumstances when they conflict so directly with concerns about public health. Recently the European Parliament rejected the traffic light approach after intensive lobbying by food manufacturers. There is now substantial evidence that adopting interpretive labelling is a significant and necessary step in reducing chronic disease and turning around the obesity epidemic. Over a third of health sector submissions regarded introduction of a mandatory traffic light scheme as the way forward. Other health submissions were less ambitious, sometimes because of concerns about the political feasibility of achieving a mandatory scheme, in the face of opposition from food manufacturers. If the panel conducting the Review chooses not to support a mandatory traffic light scheme it will, if it is to make recommendations that promote long-term health gains, need to look hard at any compromises proposed in some of the submissions that may reduce the impasse between food manufacturers and the health sector.

Competing interests: All three authors have done work for health sector agencies involved in nutrition policy advocacy. John White drafted the submission from FOE (Fight the Obesity Epidemic) to the Review of Food Labelling Law and Policy.

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The excess cost associated with healthcare-associated bloodstream infections at Auckland City Hospital

Andrew Burns, Lesley Bowers, Nick Pak, Jean Wignall, Sally Roberts

Abstract

Aim This study was undertaken to determine the cost of healthcare-associated bloodstream infections (HA-BSI) in adult patients admitted to an Auckland City Hospital.

Method A matched cohort study was performed with a 1:2 or 1:1 match in which all patients admitted between January and June 2005 who had HA-BSI were included. Controls were selected from patients admitted between July 2004 and December 2006. Patients with haemodialysis central line-related HA-BSI were not matched with controls as the admission was related purely to that episode of infection.

Results There were 106 episodes of HA-BSI in 99 patients. Fifty-five patients were able to be matched 1:1 or 1:2 with controls, group 1. Nineteen BSI episodes were in patients undergoing renal replacement therapy by haemodialysis and the patients were admitted as a consequence of this episode of infection, group 2. An episode of HA-BSI increased the length of the hospital admission by 9.7 days and 7.9 days in group 1 and group 2, respectively. The excess cost associated with an episode of HA-BSI was $20,394 in group 1 and $11,139 in group 2.

Conclusion There are substantial costs associated with HA-BSI. A proportion of these infections can be reduced by effective infection control measures.

Healthcare-associated infections are not uncommon; it is estimated that up to 5–10% of hospitalised patients acquire an infection after admission to hospital. The rate for hospital-acquired infections among patients admitted to Auckland District Health Board (ADHB) hospitals in the 1990s was estimated to be 9.5% with a cumulative incidence of 6.33%.

The cost of healthcare-associated infections is difficult to measure but is not insignificant. It has been estimated that the annual cost to New Zealand hospitals is in excess of NZ$50 million and $85 million for medical and surgical admissions, respectively. The excess cost results as a consequence of the additional length of stay required for the diagnosis and treatment of these infections. A proportion of these infections can be prevented by infection control interventions. Accurate costing of healthcare-associated infections within the New Zealand healthcare setting is needed to help identify the most cost effective strategy for reducing these infections.

This study was undertaken to determine the cost of healthcare-associated bloodstream infections (HA-BSI) in adult patients admitted to an Auckland City Hospital. This will allow all healthcare workers to be better informed about the economic impact of these events.
Method

Auckland City Hospital is a 710 bed tertiary referral, university-affiliated hospital serving a population of 367,740 people; 10% of the New Zealand population in 2001. It provides general and subspecialty medical and surgical care including orthopaedic, urological, vascular, otolaryngology, neurosurgical, cardiothoracic surgery and transplantation surgery, haematology/oncology, older person’s health, women’s health and has three adult intensive care units.

Definitions—A bloodstream infection (BSI) must meet the conditions in one of the following criteria:

- Isolation of one or more recognised bacterial or fungal pathogens from one or more blood cultures;
- If the isolate is a potential contaminant then the presence of at least one of the following signs and symptoms within 24 hours of a positive blood culture being collected, fever (>38°C), chills or rigors or hypotension and the potential contaminant was isolated from two or more sets of blood cultures drawn on separate occasions within a 48 hour period or
- The potential contaminant is from a single blood culture drawn from a patient with an intravascular line and appropriate antimicrobial therapy against that isolate is commenced.5

A healthcare-associated event was defined as follows:

- Acquired during hospitalisation and not present or incubating on admission;
- Is a complication of the presence of an indwelling medical device;
- Occurs within 30 days of a surgical procedure, where the bloodstream infection is related to the surgical site infection;
- An invasive instrumentation or incision related to the bloodstream infection was performed within 48 hours before onset of the infection; or
- Is associated with neutropenia contributed to by cytotoxic therapy.

The healthcare-associated events are subcategorised as being non-inpatient associated or inpatient-associated. Inpatient associated events are those that occur more than 48 hours after admission or within 48 hours of discharge.

Bloodstream infection events—Every episode of bloodstream infection occurring in an inpatient is reviewed by the Infectious Diseases and Clinical Microbiology services. Data from the clinical and microbiology records are recorded on a standard form and then entered into an electronic database by the Infection Control Service.

All inpatients with a documented healthcare-associated BSI (HA-BSI) between January and June 2005 were included in the study. Those excluded were: patients admitted under the care of the Haematology Service; patients \( \leq 15 \) years of age; patients having a second HA-BSI during the same admission and patients who remained in hospital for 30 days or more following their episode of HA-BSI. The latter two exclusions were made because it was felt that these patients would be outliers and would be difficult to match.

Matching—A matched cohort study was performed with a 1:2 or 1:1 match in which all patients admitted between January and June 2005 who had HA-BSI were defined as the cases, group 1. Controls were selected from patients admitted between July 2004 and December 2006. Controls were selected in a sequential stepwise manner according to a 16-point scoring system that had been adapted from a previous study.6 The controls were matched for primary and secondary diagnosis (based on International Classification of Diseases [ICD]) and primary procedure ICD (5 points), length of stay in hospital equal to the interval from admission to infection in cases ± 20% (5 points), age ± 5 years (4 points) and gender (2 points).

Patients with haemodialysis central line-related HA-BSI were not matched with controls as the admission was related purely to that episode of infection and the entire admission was regarded as excess cost secondary to the HA-BSI, group 2.

Costing—Data to assess the cost was extracted from the Auckland District Health Board (ADHB) clinical costing system; Power Cost Manager (PCM). PCM is a ‘bottom-up’ costing tool which means that the cost of individual patient care is identified by capturing every item of utilisation on each patient during his or her stay. Expenditure is allocated according to the utilisation. The increased length of stay and excess costs were calculated by averaging the difference between the cases and matched controls.
for group 1, or by averaging the length of stay and costs for all the cases alone for group 2. The hospital costs included the costs associated with diagnostic tests, allied health input, pharmacology, radiology, and bed costs.

**Results**

During 2005 the rate of HA-BSI for Auckland City Hospital was 1.4/1000 in-patient days. For the six month time period, January to June 2005, excluding patients under the care of the Haematology Service and those ≤15 years of age, there were 106 episodes of HA-BSI in 99 patients. Six episodes in 5 patients were excluded because the patient had two or more episodes of BSI during the same admission and could not be matched (3 patients), the patient was not admitted (1) and the patient died 2 days after the episode of BSI (1).

A further 37 episodes were excluded because the patient was discharged more than 30 days after the episode of BSI (18) or the patient was undergoing renal replacement therapy by haemodialysis (19). Of the remaining 63 patients, 55 were matched with controls (either 1 or 2), and 8 could not be matched. Of the 55 matched patients, 29 patients were matched 1:1 and 26 matched 1:2, group 1.

Nineteen BSI episodes occurred in 16 patients undergoing renal replacement therapy by haemodialysis and the patients were admitted as a consequence of this episode of infection. The entire length of the subsequent admission was attributed to the BSI and was considered an excess cost, group 2.

**Match score**—The use of the modified scoring system allowed for evaluation of the appropriateness of the match. The maximum score was 16. With the matching of group 1, the average score for the controls was 13.3 (83% matching appropriateness). Forty-three of the 81 controls were matched for all four variables (53%) and 69 (84%) of the controls were matched with three or more of the variables.

**Demographics and microbiology**—The demographics of the cases and controls are shown on table 1. Patients admitted to all adult services within Auckland City Hospital were included as cases; surgical services 40, medical services 13, maternity services 2, and intensive care 3. The source was identified for 83% of the episodes; the most common source was vascular access devices (38%) followed by procedure-related events (22%).

The most common cause of HA-BSI was *Staphylococcus aureus* (16.3%), coagulase negative staphylococci (14.9%), *Escherichia coli* (12.7%), *Streptococci* spp. (12.6%), and other *Enterobacteriaceae* (22%).
Table 1. Patient demographics, total and excess length of stay, and average and excess cost for cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases Group 2 (19)</th>
<th>Cases* Group 1 (55)</th>
<th>Controls* (81)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.1 ± 14.0</td>
<td>58.1 ± 21.0</td>
<td>57.7 ± 20.3</td>
<td>p=0.5</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Male</td>
<td>10 (53)</td>
<td>35 (64)</td>
<td>39 (48)</td>
<td>p=0.08</td>
</tr>
<tr>
<td>– Female</td>
<td>9 (47)</td>
<td>20 (36)</td>
<td>43 (52)</td>
<td></td>
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<tr>
<td>Match</td>
<td>1:1 29</td>
<td>29</td>
<td></td>
<td></td>
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<tr>
<td>Total LOS (days)</td>
<td>7.9 ± 4.0</td>
<td>24.1 ± 13.2</td>
<td>14.4 ± 12.4</td>
<td></td>
</tr>
<tr>
<td>Excess LOS (days)</td>
<td>7.9</td>
<td>9.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (median, range)</td>
<td>$11,139 ± $13,561</td>
<td>$53,486 ± $45,426</td>
<td>$33,092 ± $37,388</td>
<td></td>
</tr>
<tr>
<td></td>
<td>($7381, $1038-63,160)</td>
<td>($41,067, $3713-192,342)</td>
<td>($19,020, $1705-192,342)</td>
<td></td>
</tr>
<tr>
<td>Excess costs per episode of HA-BSI</td>
<td>$11,139</td>
<td>$20,394</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Excess length of stay and cost—The average length of stay for group 1, group 2 and the control group is shown in Table 1. An episode of HA-BSI increased the length of the hospital admission by 9.7 days and 7.9 days in group 1 and group 2, respectively. The excess cost associated with an episode of HA-BSI was $20,394 for cases in group 1 and $11,139 for cases in group 2.

Discussion

This is the first study to look at the cost of healthcare-associated bloodstream infections (HA-BSI) occurring in patients admitted to a New Zealand hospital. Patients admitted to Auckland City Hospital were divided into two groups; those admitted to general medical or surgical services and who subsequently developed a HA-BSI, group 1, and those patients undergoing renal replacement therapy with haemodialysis who developed a HA-BSI requiring admission for treatment of the infection, group 2.

The average excess costs associated with HA-BSI in these patient groups were $20,394 and $11,139, respectively. A significant proportion of this cost is due to the additional length of stay resulting from these infections, an average of 9.7 and 7.9 days respectively.

The excess cost associated with healthcare–associated infections is widely appreciated. The estimated cost of predicted healthcare-associated infections (HAI) in medical and surgical admissions to ADHB in 2003 was estimated to be $10.2 million and $8.64 million, respectively. At ADHB post-sternotomy mediastinitis has been shown to be associated with an excess cost of $45,677. These estimated costs only cover the cost to the District Health Board and do not include the cost to the patient and their family from loss of income and the impact of the patient’s quality of life.

It is difficult to compare the results of this study with other studies that have looked at the cost of HA-BSI due to the different methodology used to obtain the costing data.
One study looking at the weight-adjusted mean cost estimates for HAI reported the cost for nosocomial bloodstream infections to be US$23,242 per episode.\(^8\) This study extrapolated the cost from published studies and adjusted the cost to 2005 US dollars calculating a mean cost for each specific HAI. The authors included studies that estimated costs by measuring incremental costs associated with diagnosing and treating HAI but acknowledged that the matching method applied in some of these studies may be suboptimal and incomplete. We attempted to minimise overestimation of costs by matching cases and controls using an adaptation of a previously published matching schema.\(^6\) The controls were matched for four of the six variables used in that study: primary and secondary diagnosis (based on International Classification of Diseases (ICD)) and primary procedure ICD, length of stay in hospital equal to the interval from admission to infection in cases ± 20%, age ± 5 years and gender. Neither the ward of admission nor the presence of a central venous catheter was matched for.

The additional cost associated with HA-BSI in this historical cohort (1994–1995) was €15,413, equivalent to NZ$30,434 in 1995.\(^8\) The costing was determined by estimating the ‘hotel’ average daily cost which included the medical and nursing time and by adding the cost of antibiotic treatment. The increased length of stay attributable to the HA-BSI was multiplied by the single-day hospital cost to produce an overall cost associated with that episode. This approach is likely to overestimate the cost of the HA-BSI episode as it assumes that the daily costs remain the same whereas while the daily fixed costs such as capital expenditure, employee salaries, building maintenance and utilities will remain the same, but the variable costs, diagnostic tests, interventions and treatment, will vary.\(^9\)

Patients with HA-BSI associated with a haemodialysis vascular access device were not matched with controls as the entire admission was due to the episode of bacteraemia. These patients, on average, were hospitalised for 7.9 days, at an average cost of $11,139. This cost did not include the ongoing care provided at the outpatient haemodialysis unit (cost of antimicrobial agent and nursing/medical time) following discharge from hospital nor any other costs associated with subsequent complications arising from the HA-BSI that may have resulted in readmission. This may explain why the cost for an episode of HA-BSI in group 2 is almost half that of group 1.

One other study has looked at the costs associated with \textit{Staphylococcus aureus} bacteraemia among patients receiving long-term haemodialysis and showed a mean cost of US$24,034 per episode.\(^10\) However, 31% of patients in that study had complications arising from the episode of bacteraemia and not surprisingly the cost was significantly greater in those with patients with complications (US$ 32,462 vs $17,011).

Other studies reporting the cost per episode of HA-BSI have focused on central-line associated bacteraemia\(^11-14\) or \textit{Staphylococcus aureus} (methicillin susceptible or resistant) bacteraemia.\(^15\) Central line-associated bloodstream infections accounted for just under half of all the HA-BSI in our study where a source for the episode of bacteraemia was identified.

A simple evidence-based intervention designed to improve patient safety has shown that central line-associated bloodstream infections can be reduced by up to 66%.\(^16\) This intervention, termed the central line insertion ‘care bundle’, involves the use of a
checklist to ensure that five simple interventions occur at the time of insertion of every central line. These interventions are hand hygiene, maximal barrier precautions, chlorhexidine skin preparation, avoidance of femoral site if possible and removing all unnecessary lines. Reducing the rate of central line-associated bloodstream infections by the implementation of such interventions will result in cost savings and is a cost-effective intervention.

Healthcare-associated infections are time-dependent exposures; the longer the patient stays in hospital the greater the risk of acquiring an infection. HA-BSI can occur at any time during a hospital stay and other factors, such as comorbidity and primary diagnosis, can also impact on length of stay. We attempted to address this potential bias by matching cases and controls for the length of time in hospital before the HA-BSI episode.

We also excluded patients who were in hospital for greater than 30 days as their stay was already prolonged and it seemed unlikely that the HA-BSI would have had an impact of the total length of stay and hence the cost of hospitalisation. We also excluded patients admitted to the Adult Haematology Service who have central lines in place for prolonged periods of time, are at greater risk of a HA-BSI and may have lengthy stays in hospital notwithstanding the advent of any infection.

This study has confirmed that there are substantial costs, and bed-days lost, associated with HA-BSI. A proportion of these infections can be reduced by effective infection control measures. Whilst acknowledging that only a limited proportion of the excess cost can be saved because a significant proportion of this excess cost is fixed, it is important to accurately estimate the costs of such infections and to estimate the number of bed-days that can be freed up for two reasons. Firstly, the bed-days can be used for other purposes and secondly, this information can be used for assessing the cost-effectiveness of infection control programmes.

As a consequence limited resources can be directed towards programmes that have been shown to contribute to better outcomes for patients. National initiatives such as the Ministry of Health, Quality Improvement Committee’s Infection Prevention and Control Project are an important start. The implementation of initiatives aimed at improving healthcare worker hand hygiene compliance (Hand Hygiene New Zealand) and reducing central line-related BSI (Catheter-related Bloodstream Infection Prevention Guidance) will result in an overall reduction in the rate of healthcare-associated infections. These two initiative are only a start in the process of improving patient safety in our hospitals by strengthening the delivery of effective infection control programmes.

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References:


Introduction of continuous regional analgesia via wound catheters in a peripheral hospital

Ei Thu Aung, Pascale Fluri, Semisi Aiono

Abstract

**Purpose** To review the effectiveness of continuous regional analgesia (CRA) via wound catheters after abdominal surgery in a district general hospital (Wanganui, New Zealand).

**Methods** Retrospective review of postoperative analgesia after CRA via wound catheters was introduced (April 2008 to December 2008). Pain scores, HDU stay, opiate use and complications were recorded.

**Results** Fifty-four patients’ notes have been reviewed after elective and emergency laparotomies. Twenty-seven had WC (± patient controlled analgesia [PCA]), 15 had PCA only, 12 had epidural (± PCA). Resting pain scores were nil or zero in 18/27 (66.7%) wound catheter, 9/15 (60%) PCA and 5/12 (41.7%) epidural patients. Moderate/severe pain on movement was scored in patients 5/27 (18.5%) with wound catheter, 6/15 (40%) with PCA, 5/12 (41.7%) with epidural catheters. A single PCA syringe lasted over 24 hours in 18/27 (66.7%) wound catheter, 6/15 (40%) PCA, and 5/8 (63%) epidural + PCA patients. Eight adverse effects were seen; 4 wound infections (2 wound catheter, 1 PCA, 1 epidural patient) and 4 blockages of epidural catheters in epidural group. No adverse effect was found directly related to the WC.

**Conclusions** Continuous regional analgesia via wound catheters provides effective and safe postoperative analgesia for surgical patients in a small district general hospital. Used as part of a multimodal approach it allows easy step-down from HDU to surgical wards. This technique has been readily accepted over the year by theatre, HDU, ward, and anaesthetics colleagues.

Effective pain relief plays a crucial role in fast recovery from abdominal surgery. There are various modalities of pain relief used after abdominal surgery. The main methods are patient controlled analgesia (PCA) using either morphine or fentanyl, epidural and combination of both PCA and epidural.

There has been an introduction of innovative pain relief using continuous regional analgesia via wound catheters in recent years. It involves placing catheters such as those used in nerve blocks directly into the rectus sheath during laparotomy. The catheters are then infused with local anaesthesia as continuous infusion.

At our hospital in Wanganui, this method was introduced since late 2007. Wound catheters are inserted into the midline fascia into the space between rectus muscle and posterior rectus sheath before closure of deep fascia (Picture1). They are infused with loading dose of 0.75% ropivacaine after placement of wound catheters during the operation, followed by continuous infusion of 0.2% ropivacaine at 5ml/hour after the
operation. The infusion was given via a set of infusion bottles premixed with ropivacaine using elastomeric pump system (Baxter) (Picture 2).

One set of infusion bottles usually lasts for 48 hours. Wound catheters are used in addition to PCA of morphine or fentanyl. A recent review found the benefits from using wound catheters including improved analgesia, reduced opioid use and side effects, increased patient satisfaction, and decreased hospital stay.3,4,7,10

The aim of our study is to review the effectiveness of using rectus sheath wound catheters as pain relief in abdominal surgery in a New Zealand district general hospital.

Methods
A retrospective case series was carried out on patients who underwent midline laparotomy from April, 2008 to December, 2008. The data was collected from theatre lists by selecting patients who underwent laparotomy either electively or as an emergency. It was collected for audit following the guidelines of the health information privacy code. Decision to put rectus sheath catheters is based on consultant’s preference.

Required data was extracted from patients’ medical records. We collected pain scores at rest and on mobilization within 24 hours post operatively. Pain scores were obtained from standard pain score charts used for PCA, Epidural or wound catheters. On our charts, pain scores were divided into 4 categories. They are nil (0), mild (1–2), moderate (3–6), and severe (7–10). We also recorded the time required to finish a syringe of PCA.

In our hospital, a standard morphine PCA contains 50 mg of morphine in a syringe and fentanyl PCA contains 1000 mcg in one syringe. We decided to use time required to finish a syringe of PCA as a parameter instead of amount of analgesic used due to different types and dosages of opiates used in PCA. Complications such as wound infection, PCA or epidural-related side effects were documented.

Results
A total of 86 operations were identified. Out of 86 operations, 54 operations were included in the study. The reasons for exclusions were non laparotomy operations (such as appendicetomy, open cholecystectomy), 2nd laparotomies (only 1st laparotomies were included), and non-documentation of pain scores.

There were 27 in the wound catheter and PCA group, 15 in the PCA only group, 12 in the epidural and/or PCA combined group. 24 emergency operations and 31 elective operations were performed during our retrospective study period. The majority of surgeries had large bowel resections (33/54) and most of laparotomies were for malignancy (Table 1).
There were 4 wound infections with 2 in wound catheter group, 1 in PCA group and 1 in epidural group. In epidural group, 4 out of 12 patients were noted to have blockage or failure of catheters requiring early removal and switching to PCA.

Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Wound catheter+PCA</th>
<th>PCA</th>
<th>Epidural±PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n =</td>
<td>27</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>female</td>
<td>9</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>male</td>
<td>18</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Age range:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–59</td>
<td>7</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>60–79</td>
<td>13</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>≥80</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>acute</td>
<td>11</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>elective</td>
<td>16</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Colon resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>upper GI</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>others</td>
<td>4</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>tumour</td>
<td>20</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>no tumour</td>
<td>7</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Pain scores for different analgesic groups

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Wound catheter+PCA</th>
<th>PCA</th>
<th>Epidural±PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>27</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>At rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nil</td>
<td>18 (66.70%)</td>
<td>9 (60.00%)</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>mild</td>
<td>9 (33.30%)</td>
<td>6 (40.00%)</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>mod</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>severe</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Mobilisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nil</td>
<td>3 (11.10%)</td>
<td>0</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>mild</td>
<td>19 (70.40%)</td>
<td>9 (60.00%)</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>mod</td>
<td>5 (18.50%)</td>
<td>6 (40.00%)</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>severe</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Time for 1st syringe of PCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24 hour</td>
<td>9 (33.30%)</td>
<td>9 (60.00%)</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>&gt;24 hour</td>
<td>18 (66.70%)</td>
<td>6 (40.00%)</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blockage of epidural catheter</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Catheter infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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URL: http://www.nzma.org.nz/journal/123-1324/4380/ ©NZMA
The pain scores for different groups were shown in Table 2. In wound catheter group, 66.7% patients had no pain at rest, 33.3% had mild pain at rest and none in the group had moderate to severe pain at rest.

On mobilisation, 70.4% had mild pain and only 18.5% had moderate pain in wound catheter group. In contrast, 33.3% in epidural group and 40% in PCA group had moderate pain on mobilisation. (Figure 1 and Figure 2)

In epidural and/or PCA group, there were 8 who had PCA in addition to epidural. On calculating the time needed to finish a 1st syringe of PCA, we had only included 8 patients who had PCAs. We found that, a syringe of PCA containing either 50 mg morphine or 1000 mcg of fentanyl lasted more than 24 hours in 66.7% of wound catheter group (Figure 3).

Analysis using 1-way ANOVA showed no difference between 3 groups in all 3 measures. P-values for the 3 measures are as below.

- Pain at rest p=0.6,
- Pain on mobilisation p=0.6, and
- Time needed to finish a PCA syringe p=0.23.

Figure 1. Pain scores at rest
Discussion

Our case series analysis showed that infusion of local anaesthetic agents via wound catheters provided a safe and adequate alternative pain relief method. Our results showed better pain control on mobilisation in comparison to other established postoperative analgesics. It also reduced the amount of opiates used post operatively. Having catheters connected to small bottles of local anaesthesia had a great advantage in improving mobility. Adverse outcomes were not significantly higher in wound catheter group. Although the results were not statistically significant, the outcomes were not worse than PCA or epidural groups.

Pain relief after abdominal surgery is usually provided in a multimodal approach. In our hospital, PCA and regional anaesthesia via epidural infusion have been the accepted methods. However, the delivery of epidural anaesthesia requires close supervision and monitoring by nursing and medical staff. Moreover, there are
common complications of epidural blocks such as severe hypotension, and reduced mobility (less commonly infection, or nerve injury). This had led us to the use of another safe and simpler alternative pain relief using local anaesthesia via wound catheters.

The wound catheters have been used most frequently for patients who have undergone orthopaedic or "sports medicine" surgery to repair knee and shoulder problems. Some studies showed reduced length of hospital stay associated with continuous wound catheters, especially in the cardiothoracic and orthopaedic surgery subgroups. There are not many studies on efficacy of rectus sheath catheters in abdominal surgery. The literature reviews on use of wound catheters in abdominal surgery showed mixed results. A randomised controlled study by Polglase, et al (2007) showed minimal benefit of wound catheters compared with saline infusion in colorectal surgeries.

An audit done in Tasmania by Blackford, et al (2007) showed reduced pain at rest and on mobilisation using wound catheters in the first four postoperative days. A systemic review of randomised controlled trials using wound catheters (RCTs) by Liu, et al (2006) reported that most RCTs (10 out of 12) showed significant analgesic efficacy by either reduced opiate use or reduced pain scores in general surgical operations.

There were a few flaws in our study. It was a retrospective audit with small sample size. The number of patients was not equal in each group. We had included all laparotomies with mixed pathologies and indications with mixed surgical techniques in our study which was one of the confounding factors in our study. A prospective study comparing local anaesthesia via wound catheter with either PCA or epidural for patients undergoing a specific abdominal surgery (e.g. colorectal surgery) should be conducted to evaluate the efficacy.

**Conclusion**—Local anaesthesia via wound catheters is a relatively safe and effective pain relief. It allows easy step down from high dependency unit to general ward, facilitating fast track recovery in abdominal surgery. It is feasible in smaller hospitals.

**Competing interests:** None.

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**References:**

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Ten-year review of intussusception at Starship Hospital: 1998–2007

Hemal Kodikara, Amiria Lynch, Phillip Morreau, Sally Vogel

Abstract

Aims To review the demographics, presenting features, rates of air enema reduction success, prevalence of pathological lead points and surgical intervention rates and outcomes in patients with intussusception at Starship Children’s Hospital (Auckland, New Zealand). To use this data to guide management of children at a national level in New Zealand.

Method Retrospective case series. Patients discharged from Starship Children’s Hospital between 1 January 1998 and 31 December 2007 with a diagnosis of intussusception were obtained from coding data.

Results 189 patients were analysed. 30% presented with the classic triad of pain, rectal bleeding and mass. 150/189 proceeded to air enema reduction which was successful in 118 (78.7%) of cases with 2 perforations. 54/189 (28.6%) proceeded for operative reduction of which 26 patients required surgical resection. Clinical and radiological evidence of bowel obstruction and duration of symptoms were associated with failed enema and surgical resection.

Conclusion Intussusception only occasionally presents with the typical triad of abdominal pain, rectal bleeding and abdominal mass. Air enema reduction is successful at this institution with a low level of complication. Māori and Pacific patients had higher rates of failed enema reduction and need for surgery compared to European patients. Further research is needed from peripheral centres to evaluate outcomes of children treated in district hospitals to identify how and where these children are best managed.

Intussusception is the most common cause of intestinal obstruction among children and occurs when one segment of bowel invaginates into an adjacent distal segment. If left untreated, this can lead to bowel infarction, sepsis and death.

The exact aetiology of the condition remains unclear in the majority of cases with a small proportion of cases occurring secondary to anatomical abnormalities. Knowledge of the condition is important as early diagnosis may lead to successful enema reduction, lower operative reduction and resection rates and reduced morbidity. It is important to obtain local data of the condition to both understand the possible aetiology and clinical picture of the condition in this setting as well as evaluate radiological and surgical outcomes. There has not been a published study of intussusception in the North Island since a 1981 series of 98 cases. This study was initiated to obtain a comprehensive summary of intussusception including demographics, clinical presentation, management and outcome of
intussusception as seen at Starship Hospital, New Zealand’s largest children’s hospital.

Methods

A retrospective case-based study of all patients with intussusception presenting to the Starship Children’s Hospital, Auckland between 1 January 1998 to 31 December 2007 was performed. The Ethical Review Committee of Auckland Hospital granted exemption from requiring ethical approval. Starship Hospital provides secondary paediatric care for the Auckland region as well as much of the northern half of the North Island for paediatric surgical conditions. It also contains the only dedicated paediatric intensive care unit in New Zealand. Many patients are referred to the hospital from regional centres for investigation and management.

The hospital records of all admissions to the Starship Hospital with a primary or secondary diagnosis of intussusception (as coded by the International Classification of Disease codes (ICD 9 and 10- K56.1 and 560) discharged within this period were reviewed.

Data was collected using a standard proforma. Information collected included demographic factors, presenting symptoms and signs, time and onset of symptoms, time to diagnosis, radiological features, and treatment modality (air enema reduction, surgical reduction and resection outcomes and complications). Details of the presenting history were obtained from the clinical notes of the admitting doctor and standardised definitions were used for each symptom and sign noted. Radiology reports by consultant radiologists were reviewed and findings documented. Histological reports were reviewed and pathological lead points were also noted. A univariate analysis was conducted to identify features associated with failed air enema reduction and need for surgery. Microsoft Excel (Microsoft Corporation 2003) software was used for the data storage and statistical analysis.

Results

There were 210 discharges with a diagnosis of intussusception over this period with 197 individual patients. There were 8 patients who accounted for 13 repeat admissions. 6 patients were incorrectly coded and excluded. 2 further patients who had prior operative resection in the Pacific Islands and who were transferred for postoperative management were excluded. This left 189 patients for analysis.

Demographics—The median age was 10 months (range 3 days to 14 years). 122 (66%) of the patients were boys giving a male to female ratio of 2:1. There was no significant seasonal variation in the incidence of cases or change in incidence rate over the period. The median length of stay was 31 hours (range 8 to 408). Ethnicity data is shown below in Figure 1.

168/189 (89%) patients were from the Auckland region leaving 20 patients transferred from peripheral New Zealand hospitals (Whangarei, New Plymouth, Gisborne, Whakatane) and one from Samoa.

Diagnosis—The range and frequency of presenting symptoms and signs is shown in the table below. 86/189 (45.5%) patients presented less than 24 hours from the onset of abdominal pain. The frequency of various clinical signs and symptoms are noted in Table 1 below. Only 57/189 (30%) presented with the classic triad of abdominal pain, vomiting and rectal bleeding.
Figure 1. Ethnicity of children in study (%)

![Ethnicity Pie Chart]

Table 1. Frequency of presenting signs and symptoms (%)

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Percentage of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>94%</td>
</tr>
<tr>
<td>Rectal bleed</td>
<td>38%</td>
</tr>
<tr>
<td>Bilious vomiting</td>
<td>19%</td>
</tr>
<tr>
<td>Non-bilious vomiting</td>
<td>81.5%</td>
</tr>
<tr>
<td>History of pallor</td>
<td>41%</td>
</tr>
<tr>
<td>Preceding viral symptoms</td>
<td>21%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29%</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>41%</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>11%</td>
</tr>
<tr>
<td>Tenderness</td>
<td>58%</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>5.8%</td>
</tr>
<tr>
<td>Shock</td>
<td>14%</td>
</tr>
</tbody>
</table>

The relative frequency of radiological sign demonstrated by plain film and ultrasound examination are shown below in Table 2. A mass on plain radiograph was present in a similar proportion of patients as that found clinically (41%). No patients had evidence of perforation on plain radiograph.
Table 2. Frequency of findings on plain film and ultrasound

<table>
<thead>
<tr>
<th>Finding</th>
<th>Percentage of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain film mass</td>
<td>41%</td>
</tr>
<tr>
<td>Plain film obstruction</td>
<td>28%</td>
</tr>
<tr>
<td>Free air</td>
<td>0%</td>
</tr>
<tr>
<td>Normal plain film</td>
<td>23%</td>
</tr>
<tr>
<td>Ultrasound mass</td>
<td>91%</td>
</tr>
</tbody>
</table>

**Management**—150 children proceed for air enema reduction. Barium enema was not undertaken at Starship Hospital for reduction purposes. 105/150 (70%) patients had a successful air enema on the first attempt. A second attempt occurred on 37 occasions with success in 13 (35.1%). On five occasions a third attempt was undertaken but was not successful in any patients. This gave an overall air enema reduction rate of 78.7% (118/150). Perforation occurred in two cases (1.5%).

54/189 patients proceeded to theatre of whom 22 proceeded directly to theatre without attempt of air enema reduction. Surgical reduction was attempted in 51 patients and was successful in 36 (71%). This was performed laparoscopically in 17 cases and was successful in 12 (71%). 26/54 (48%) patients required surgical resection for nonviable bowel, perforation or excision of pathological lead point. There were few intraoperative or postoperative complications.

Five patients developed postoperative ileus, three required total parenteral nutrition, two required further operation (perforation) and two patients required treatment in the intensive care unit. There was one case of hospital readmission for postoperative abdominal pain. There were no recurrences of intussusception in surgically managed patients or patient deaths.

19 patients were noted to have a pathological lead point. The range and frequency of pathological lead points are shown below in Table 3.

**Predictors of outcome**—The presence of abdominal distention on clinical examination and plain film obstruction were the strongest predictors of enema failure and need for resection at surgery. There was also a significant association between duration of symptoms and enema failure and need for resection. Maori & Pacific patients were more likely to have failed enema 35% vs 13% compared to European (p=0.005) and proceed to surgery 38% vs 23% (p=0.04) despite no difference in duration of symptoms between the groups.
### Table 3. Number and type of pathological leadpoint

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Number (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplication cyst</td>
<td>6</td>
</tr>
<tr>
<td>Meckel’s Diverticulum</td>
<td>5</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>3</td>
</tr>
<tr>
<td>Caecal ulcer</td>
<td>1</td>
</tr>
<tr>
<td>Appendix mass</td>
<td>1</td>
</tr>
<tr>
<td>Persistent vitelline duct</td>
<td>1</td>
</tr>
<tr>
<td>Small bowel polyp</td>
<td>1</td>
</tr>
<tr>
<td>Previous appendectomy</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 4. Factors associated with enema failure and surgical resection

<table>
<thead>
<tr>
<th></th>
<th>Enema failure</th>
<th>Surgical resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Distension</td>
<td>RR 3.2 P&lt;0.007</td>
<td>RR 5.3 P&lt;0.0001</td>
</tr>
<tr>
<td>Plain film obstruction</td>
<td>RR 3.4 P&lt;0.0001</td>
<td>RR 5.5 P&lt;0.0001</td>
</tr>
<tr>
<td>Tenderness</td>
<td>RR 2.4 P=0.02</td>
<td>n/s</td>
</tr>
<tr>
<td>USS free fluid</td>
<td>RR 2.2 P=0.02</td>
<td>n/s</td>
</tr>
<tr>
<td>Duration of vomiting</td>
<td>P=0.05</td>
<td>P=0.005</td>
</tr>
<tr>
<td>Duration of pain</td>
<td>n/s</td>
<td>P=0.009</td>
</tr>
<tr>
<td>Time from symptoms to enema</td>
<td>P=0.04</td>
<td>P=0.01</td>
</tr>
</tbody>
</table>

RR: relative risk; n/s: not statistically significant.
Table 4 above demonstrates the increased risk of enema failure and need for surgical resection associated with each clinical or radiographic finding.

**Auckland vs Rest of New Zealand**—Patients from outside the greater Auckland region were more likely to have failed surgical reduction and to have surgical resection than patients from the Auckland region as shown in Table 5. However the time to treatment between the two groups did not differ significantly. Six patients transferred had prior attempt at barium enema reduction.

**Table 5. Comparison of patients in Auckland versus the Rest of New Zealand**

<table>
<thead>
<tr>
<th></th>
<th>Auckland region</th>
<th>Rest of NZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enema success</td>
<td>105/134</td>
<td>13/16</td>
</tr>
<tr>
<td></td>
<td>78%</td>
<td>81%</td>
</tr>
<tr>
<td>Proceed to surgery</td>
<td>47/168</td>
<td>620</td>
</tr>
<tr>
<td></td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>Successful reduction</td>
<td>33/47</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>76%</td>
<td>33%</td>
</tr>
<tr>
<td>Surgical resection</td>
<td>21/168</td>
<td>520</td>
</tr>
<tr>
<td></td>
<td>12.5%</td>
<td>25%</td>
</tr>
<tr>
<td>Median time from symptoms to enema (hours)</td>
<td>24</td>
<td>28</td>
</tr>
</tbody>
</table>

**Discussion**

This study aimed to characterize and evaluate the patients, presentation and management of intussusception at Starship Hospital. There have only been two prior studies of intussusception in New Zealand. The first was Raudkivi’s series in 1981 which examined 96 patients and found a low (barium) enema reduction rate of 19%, and a subsequently high operative rate of 88% including a resection rate of 28%. The second study was Reid’s series of 81 South Island cases in 2001 which demonstrated a similarly low barium enema reduction rate of 32% with a similar air enema reduction rate to this study of 79%. This study hence is the largest review of intussusception in New Zealand.

The median age and male predominance found in patients in this study is similar to that quoted in the literature. The lack of a seasonal variation suggests that an infectious aetiology may be less likely in intussusception in New Zealand. The proportion of cases with the accepted symptoms and signs of intussusception are
similar to other reports. However certain symptoms and signs were shown to be more helpful in making the diagnosis.

This study has shown that a history of pallor and the presence of an abdominal mass are both common features of intussusception and can be vital in differentiating intussusception from gastroenteritis and other causes of vomiting and abdominal pain. Plain radiography was also shown to be an important diagnostic aid in the hands of experienced radiologists with a very high proportion having an abnormal film, and a lesser but significant proportion having a mass seen on x-ray.

Enema reduction rates were similar to the range quoted in the literature but not as high as that found in some other studies which have shown rates closer to 90%. The possibilities for this are numerous. One reason is that Starship Hospital receives a significant number of referrals from other regional hospitals, and some referrals were following failed enema reduction in district hospitals. Furthermore the delay in being seen and treated in another hospital as well as the delay in transfer could lead to a less likely chance of successful enema reduction. The rate of perforation following air enema reduction at 1.5% was similar to the rate in other published studies.

We have shown that certain factors are associated with failed enema; with both clinical distension and plain film evidence of obstruction predictive of failed enema and need for surgery. A similar relationship exists for duration of symptoms till enema treatment- emphasizing the importance of prompt diagnosis and treatment/transfer.

The reasons for Maori and Pacific patients having higher rates of failed enema reduction than their European counterparts are unclear as times from symptoms to presentation were similar. One possibility is that there is a fundamental difference in pathophysiology of the condition in these ethnicities leading to these differences in outcome. Another possibility is that there was a delay in recognition of symptoms by parents in the Maori and Pacific group effectively leading to a delay in presentation.

Surgical resection rates found in this study were similar to those quoted elsewhere in the literature. However a higher number of children (27%) proceeded to surgery when compared to other studies. This may be partly explained by the high numbers of patients transferred as detailed above. Laparoscopic reduction was successful in the majority (71%) of cases where attempted and at a similar rate to that quoted in the literature.. Low postoperative morbidity and zero mortality were typical of modern day management of intussusception.

The rate of pathological lead point (10%) was also similar to that found in other studies (2–12%) with the two most common being Meckel’s diverticulum and duplication cyst. This study does however demonstrate a higher rate of duplication cyst (6/19) than that quoted in other studies. The exact reason for this is unclear.

This study’s limitations are that this was a retrospective review of case notes and thus the findings were dependant on the clinical competency of the admitting doctor and the legibility and completion of the documentation. If a particular symptom or sign was not reported in the notes (by either emergency or surgical admitting staff) then it was presumed to be absent. This may of course not be true and that the symptom or sign may not have been sought, or alternatively may have been sought but not documented.
A prospective study would be better equipped to review the clinical presentation as it would ensure that each relevant symptom and sign would be sought as well as provide more information on how children were being triaged to air enema reduction or directly to surgery.

The key issue in the management of intussusception in New Zealand is whether any child with intussusception seen in a peripheral hospital is transferred directly to a tertiary centre once stabilised or whether regional outcomes are of a sufficient standard to allow management in these regions.

A study conducted in the United States into intussusception outcomes compared smaller and larger hospitals and showed children managed in large US children’s hospitals had decreased risk of operative care and shorter length of stay\textsuperscript{10}. This was confirmed in a review conducted in the United Kingdom which suggested “all confirmed cases should be resuscitated then referred to tertiary centres for treatment”\textsuperscript{11}.

In New Zealand this may be further true as there may not be sufficient case volume of intussusception in regional hospitals to maintain high standards in enema treatment which is evidenced by a recent study that showed only one case of intussusception was seen in a one year period at a district hospital in New Zealand\textsuperscript{12}.

In this study all patients who were transferred from peripheral hospitals only had barium enema attempts (no air enema reductions) which confirms the lower success rate of this method of reduction and suggests that early transfer to a paediatric surgical centre may be preferable if facilities for air enema reduction are not available. However further research is required into the management and outcomes of all children treated in peripheral hospitals to determine if centralising treatment of intussusception where appropriate would lead to improved outcomes.

The findings of this study provide useful preliminary data given the well known difficulties of obtaining national data on intussusception in New Zealand\textsuperscript{3}. Wherever children are managed, this study has shown that it is vital for clinicians to know that intussusception does not often present in classical fashion, and early diagnosis and management leads to an increased likelihood of successful air enema and reduced need for operative management. This study has also demonstrated that there are differences in outcome for children with intussusception based on ethnicity which is a finding not previously demonstrated in the literature.

Competing interests: None.

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References:

Christchurch experience of pulmonary embolism with and without thrombolysis

Wandy Chan, Tiffany Campbell, Sharyn MacDonald, Ian Crozier

Abstract

Aims Thrombolysis for normotensive patients with large clot burden pulmonary embolism remains debatable. We aim to document our current management of pulmonary embolism, examining determinants of therapy and outcomes.

Method A retrospective chart-based review of all patients admitted with pulmonary embolism under Cardiology service in Christchurch Hospital between 2002–2007. All related CT pulmonary angiograms were also reviewed for quantification of clot burden and evidence of right ventricular strain.

Results 120 patients were admitted during the audit period. Hypotensive patients had a significantly higher troponin level and Qanadli scores. RV/LV ratio >1 in CTPA was 80% sensitive and 57% specific in predicting RV strain on echocardiogram. Forty-six patients were thrombolysed, most with large clot burden and right ventricular strain. No treatment related death or intracranial haemorrhages occurred; however six patients required blood transfusion and six patients had persistent pulmonary hypertension at 6 months. There was a higher in-patient event rate in thrombolysed group, due to increased bleeding, compared to non-thrombolysed patients.

Conclusion Thrombolysis was successfully performed with relatively low in-patient and 6-month event rate. Long term advantage over routine anticoagulation was not demonstrated. The role of thrombolysis in normotensive patients with large clot burden remains uncertain. CTPA markers of RV strain correlated well with echocardiography.

Pulmonary embolism (PE) is a frequent cause for hospital admission and a significant proportion of cases are first diagnosed at autopsy. The in-patient or 30-day mortality is variable with a stepwise increase in mortality observed subject to the degree of haemodynamic instability, with a mortality of up to 65% for patients who require cardiopulmonary resuscitation.

Patients with right ventricular (RV) dysfunction have a higher mortality than those without in whom the mortality of acute PE is close to 0% with anticoagulation. Subsequent mortality is also high, the overall mortality at 3 months was reported between 10.5–15.3%, with the majority of patients dying of recurrent PE or cancer. Multiple studies have demonstrated rapid resolution of vascular obstruction, reduced pulmonary hypertension and improved haemodynamics following treatment with a thrombolytic agent in acute PE. Thrombolysis has been incorporated into international guidelines for PE with haemodynamic instability with undisputable
mortality benefits. However for normotensive patients with large clot burden, the role of thrombolysis remains controversial.

Meta-analyses of published trials show no mortality benefit from thrombolysis in normotensive patients even in the presence of RV dysfunction. Despite the controversy, thrombolysis has been liberally used in patients at Christchurch Hospital in the setting of acute PE with hypotension or evidence of RV strain, as per the managing clinician.

In this report we describe our experience with PE for the 6 years from January 2002 and December 2007. We aim to assess the safety, short and intermediate term outcomes with thrombolysis and to identify imaging and biochemical risk markers that can distinguish a higher risk subgroup who would benefit from thrombolysis.

Method

An audit of patients admitted with PE under Cardiology service between January 2002 and December 2007 was performed. Patients were identified using International Statistical Classification of Diseases and Related Health Problem, Tenth Revision, Australian Modification (ICD-10-AM) code, I26.0 or I26.9 for pulmonary embolism with or without acute cor pulmonale. This included all patients treated with thrombolysis except those in the Intensive Care Unit as per hospital protocol.

A chart-based review was carried out with data collected comprising basic demographics, clinical status, investigations, treatment received and outcomes both as in-patient and at 6 months. For patients who had no further contact with the hospital system, a questionnaire was sent out to their General Practitioner. Hypotension was defined as the lowest systolic blood pressure ≤90 mmHg.

All computed tomography pulmonary angiograms (CTPA) were reviewed by both a radiology fellow and an experienced cardiothoracic radiologist for evidence of RV strain. RV strain was defined as RV/LV ratio on axial 4-chamber view ≥1, straightening or bowing to the left of the interventricular septum (IVS) or reflux of contrast into the inferior vena cava or hepatic veins.

Clot burden was quantified using the Qanadli score. The Qanadli score is the sum of the presence of clot to each segmental artery, 0 for no clot, 1 for partial occlusion and 2 for total occlusion. A clot proximal to the segmental artery is scored as the sum of affected segmental arteries arising distally. The maximum score is 40. A score of ≥16 is regarded as severe as it indicates ≥40% of pulmonary circulation is involved. Superior vena cava, azygous vein and main pulmonary artery sizes were also measured.

Evidence of RV strain on echocardiogram was defined as dilated RV, RV hypokinesis, abnormal interventricular septal motion or estimated right ventricular systolic pressure ≥30 mmHg using Doppler.

Statistical analysis was performed with GraphPad Prism version 5. Continuous variables were expressed as mean ± standard error. Two-tailed unpaired t-test for difference between two groups, Fisher’s exact test for contingency and Pearson’s coefficient for correlation were used. A p-value of less than 0.05 was considered statistically significant.

Results

During the audit period 120 patients, age 22–87 years, mean 63 ± 1.3 years, with PE were admitted under the Cardiology service at Christchurch Hospital. (Table 1) Patients had PE confirmed on CTPA or ventilation-perfusion scan, except one PE diagnosed at post mortem. Apart from this patient, all but one patient who had a concurrent diagnosis of type B aortic dissection, received heparin or low molecular weight heparin and 46 patients received thrombolysis.

Bleeding problems occurred in 17 patients, seven (six in the thrombolysed group) of which required a blood transfusion. There were two deaths during admission, one
from untreated PE diagnosed at post-mortem and one from an unrelated cause. Follow-up data to 6 months was available in 111 patients, 7 patients were lost to follow-up. There were three recurrences during the follow-up period, one resulting in death. Two more patients died during the follow-up period, one from cancer and the other from heart failure following bone marrow transplant.

Table 1. Patient characteristics of all patients and thrombolysed patients

<table>
<thead>
<tr>
<th></th>
<th>Total N=120</th>
<th>Thrombolysed N=46</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) Mean +/-SE</td>
<td>62.9 +/- 1.3</td>
<td>60.2 +/- 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Qanadll Score Mean +/-SE</td>
<td>16.6 +/- 1.0</td>
<td>24.3 +/- 0.9</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>Hypotension</td>
<td>22</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Peak Troponin (µg/L) Mean +/-SE</td>
<td>0.33 +/- 0.14</td>
<td>0.36 +/- 0.10</td>
<td>P = 0.016</td>
</tr>
<tr>
<td>N = 104</td>
<td>N = 34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP (pmol/L) Mean +/-SE</td>
<td>383.8 +/- 57.5</td>
<td>394.8 +/- 88.5</td>
<td>NS</td>
</tr>
<tr>
<td>N = 41</td>
<td>N = 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of RV dysfunction on Echocardiogram</td>
<td>54/79</td>
<td>31/31</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>PE strongly suspicious on presentation</td>
<td>41</td>
<td>26</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Presented with undifferentiated chest pain or dyspnoea</td>
<td>62</td>
<td>14</td>
<td>P = 0.03</td>
</tr>
</tbody>
</table>

Relationship of biomarkers and haemodynamics—Peak troponin levels were significantly higher in the hypotensive patients compared with the normotensive patients, (1.13 ± 0.67 vs 0.13 ± 0.02 µg/L (p=0.0035)). Eight of 22 hypotensive and 33 of 98 normotensive patients had brain natriuretic peptide (BNP) levels measured. There was no significant difference for BNP between normotensive and hypotensive groups with range between 22 to 899pmol/L and 6 to 1241pmol/L respectively.

Imaging markers—

Right ventricular strain—Echocardiogram was predominantly performed in those with or suspected of having large clot burden but was not routinely performed on all patients. Seventy nine patients had an echocardiogram during the admission. Forty out of 62 patients in the normotensive group and 14 out of 17 patients in the hypotensive group had evidence of RV strain (p= NS).
Seventy-eight patients had both CTPA and echocardiography. Of 54 patients with evidence of RV strain on echocardiogram, 44 had an RV/LV ratio ≥1 on CTPA (p=0.027). The sensitivity of CTPA detecting RV strain using RV/LV ratio was 80% (95% CI 67–89.6%), specificity 57% (95% CI 35–77%), positive predictive value 82% (95% CI 69–91%) and negative predictive value 54% (95% CI 43–75%).

Clot burden—Clot burden in the pulmonary circulation, as assessed by Qanadli scores, was significantly higher for those in the hypotensive group, 21.3 ±2.2 vs 15.6 ± 1.1 (p=0.03). Qanadli score had a positive correlation with CTPA RV/LV ratio, r=0.53 (p<0.0001) and a weak positive correlation with pulmonary pressures, r=0.42 (p<0.001). It also had a weak negative correlation with the worst blood pressure during admission r=−0.19 (p=0.045) but no correlation with troponin levels.

Qanadli score was associated with echocardiographic measures of RV strain; of 54 patients with evidence of RV strain on echocardiogram, 45 had a Qanadli score ≥16. Patients with Qanadli score ≥16 were 1.87 times more likely to have RV/LV ratio ≥1, 1.95 times more likely to have straightening of the IVS, 1.73 times more likely to have reflux of contrast into IVC and/or hepatic veins and 2.76 times more likely to have evidence of RV strain on echocardiogram. (Table 2)

When using CTPA RV/LV ratio ≥1 as a marker of RV strain, there was a weak correlation of SVC size to RV strain but no significant correlation with azygous diameter or main pulmonary artery diameter on CT.

The clinical event rate was too low to have any meaningful assessment of risk markers and their association with clinical outcomes.

Table 2. RV, right ventricle. LV, left ventricle. IVS, interventricular septum. IVC, inferior vena cava.

<table>
<thead>
<tr>
<th>Imaging markers of RV strain</th>
<th>Likelihood ratio if Qanadli score ≥16</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/LV ratio ≥1 on CTPA</td>
<td>1.87×</td>
</tr>
<tr>
<td>Straightening of IVS on CTPA</td>
<td>1.95×</td>
</tr>
<tr>
<td>Reflux of contrast into IVC and/or hepatic veins on CTPA</td>
<td>1.73×</td>
</tr>
<tr>
<td>RV strain on echocardiogram</td>
<td>2.76×</td>
</tr>
</tbody>
</table>

Thrombolysis group—

Forty-six patients, age 22–87 years, mean 60.2 ± 2.2 years had thrombolysis with alteplase or tenecteplase using the standard protocols for thrombolysis for acute ST segment elevation myocardial infarction. Thirty four patients were normotensive, 12 hypotensive, whilst one patient had a cardiac arrest. Forty two patients had large clot burden reported on the original CTPA report (clot seen in pulmonary artery or more than three lobar arteries involved). For the rest, one patient received empiric thrombolysis after a community cardiac arrest coming off a long haul flight, with a subsequent CTPA confirming the diagnosis of PE. One patient had a V/Q scan but not a CTPA due to end-stage renal failure from polycystic kidney disease. In the remaining two patients thrombolysis was administered following clinical deterioration, though the initial CTPA did not show a large clot burden.
Thirty-one patients in the thrombolysis group had an echocardiogram prior to thrombolysis, all had evidence of RV strain whilst 85% of all patients and 100% of hypotensive patients had evidence of RV strain on CTPA. There was a high concordance in the assessment of RV strain in the thrombolysed group, with 28 out of 31 patients showing RV strain on both CTPA and echocardiogram.

Most thrombolysed patients had a relatively uneventful hospital stay. (Figure 1) One patient died during admission due to an unrelated cause, not from PE or thrombolysis. No intracranial haemorrhage occurred. Transfusion was required in 6 patients for bleeding following thrombolysis. Of these patients requiring transfusion, three had a history of orthopaedics surgery within the preceding 2 weeks, two of whom were thrombolysed within 72 hours of surgery, one had ongoing wound ooze. Six patients had minor bleeding not requiring transfusion.

Of the surviving 45 patients followed at 6 months, three overseas patients were lost to follow-up. Two PE recurrences occurred during this period, one resulting in death, the other was due to sub-therapeutic anticoagulation. Persistent pulmonary hypertension was present in six patients, two of whom had symptomatic heart failure. (Figure 2).

Figure 1. In-patient outcome for thrombolysed patients

![Pie chart showing in-patient outcome](image)

- No complications, 33
- Bleed required transfusion, 6
- Minor bleed, 6
- Death unrelated to PE, 1

Figure 2. Six-month outcome for thrombolysed patients. HF, heart failure. PHT, pulmonary hypertension

![Pie chart showing six-month outcome](image)

- No complications, 32
- Persistent PHT, 6
- Death unrelated to PE, 1
- Symptomatic HF without PHT, 2
- Recurrence, 2
- Less to follow-up, 3
Large clot burden without thrombolysis group (Table 3)—

Vascular obstruction on CTPA of ≥40% (Qanadli score ≥16) was present in 28 patients who did not receive thrombolysis. In this group, 5 were hypotensive at some stage. None died of PE during their hospital stay, 2 patients had minor bleeds. Six-month follow-up data was available in 26 patients. No recurrences occurred during the follow-up period, whilst two patients had persistent pulmonary hypertension.

Large clot burden group—

A total 68 patients were identified with large PEs (Qanadli score ≥16), of which 40 were thrombolysed. There was no significant difference in mean troponin or BNP levels, but there was a significantly higher in-patient event rate (death one, bleed with or without transfusion 12, heart failure four) in the thrombolysed group, 17/40 thrombolysed vs 4/28 not thrombolysed (p=0.02), with the main difference being bleeding.

No significant difference of events (death, recurrences, pulmonary hypertension) was observed at 6 months, 11/37 thrombolysed vs 2/26 not thrombolysed (p=NS).

Table 3. Patient characteristics in the large clot burden (Qanadli score ≥16) group

<table>
<thead>
<tr>
<th></th>
<th>Non-thrombolysed</th>
<th>Thrombolysed</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean +/-SE</td>
<td>65.6 +/- 2.3</td>
<td>60.9 +/-2.5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>12</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Qanadli Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean +/-SE</td>
<td>22.9 +/- 0.8</td>
<td>25.8 +/- 0.6</td>
<td>P = 0.003</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>5</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Peak Troponin (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean +/-SE</td>
<td>0.67 +/- 0.52</td>
<td>0.40 +/- 0.11</td>
<td>P = 0.05</td>
</tr>
<tr>
<td></td>
<td>N = 27</td>
<td>N = 30</td>
<td></td>
</tr>
<tr>
<td><strong>BNP (pmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean +/-SE</td>
<td>307.4 +/- 115.5</td>
<td>423.1 +/- 102.5</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>N = 8</td>
<td>N = 16</td>
<td></td>
</tr>
<tr>
<td><strong>Evidence of RV dysfunction on Echocardiogram</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/24</td>
<td>27/27</td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>PE strongly suspicious on presentation</strong></td>
<td>10</td>
<td>21</td>
<td>P = 0.02</td>
</tr>
<tr>
<td><strong>Presented with undifferentiated chest pain or dyspnoea</strong></td>
<td>16</td>
<td>13</td>
<td>P = 0.001</td>
</tr>
</tbody>
</table>
Discussion

We document our experience with thrombolysis for PE with evidence of right heart strain, irrespective of the blood pressure status. Overall clinical outcomes were good, but we could not demonstrate an advantage for thrombolysis, and bleeding rates were increased with thrombolysis.

While our major bleeding complication rate was similar to published data from randomised trials at 13%, half of the patients experiencing bleeding in our series had a history of recent surgery so the drop in haemoglobin was at least in part explainable by perioperative blood lost. The lack of an advantage in clinical outcome in the thrombolysed group in our study should be interpreted with caution.

This study was a retrospective review, with treatment being determined by the managing clinician. The thrombolysed group had a greater clot burden, all had RV strain or circulatory compromise. Indeed, the thrombolysed group had similar clinical outcomes to the nonthrombolysed group despite having more severe PE suggested that thrombolysis may have favourably affected outcomes.

Persistent pulmonary hypertension and right heart failure occur in approximately 4% of patients after PE. Some older, small or non-randomised trials showed a reduction of chronic pulmonary hypertension development in thrombolysed patients. While a recent small prospective cohort showed a higher likelihood of a subgroup of haemodynamically stable patients with large PE of developing chronic symptomatic pulmonary hypertension with heparin only compared to thrombolysed patients, more recent randomised controlled trials have focused on short term analysis only and longer term outcomes are lacking.

In our series we did not find any evidence that thrombolysis reduced the incidence of persisting pulmonary hypertension, however our numbers are small.

RV dysfunction is a well recognised marker for worse outcome in PE regardless of blood pressure. However, echocardiography, the gold standard for right heart dysfunction, is not always readily available. A previous study showed raised RV/LV ratio on CTPA to be associated with >four-fold increase in mortality thus a raised RV/LV ratio identifies a higher risk group and closer observation or more aggressive therapy should be considered.

Our study confirmed good predictive value of CTPA for RV strain using the RV/LV ratio or a high Qanadli score of ≥16. Therefore CTPA is a good initial test in suspected PE, as it provides important information on clot burden and right heart strain in addition to its diagnostic utility and is readily available in most hospitals.

The elevation of biomarkers for myocardial strain or injury in acute PE is a reflection of RV involvement, as a result of sudden development of pulmonary hypertension. It is associated with increased mortality even in normotensive patients. More recent meta-analysis suggested combined raised troponin and BNP reflected higher risk.

Unfortunately, our study is heavily limited by its retrospective design with no standardised management plan of all patients and the overall low event rate, we are unable to draw any meaningful conclusions with biomarkers. The question would be better answered by a prospective cohort.
Conclusion

We document our experience with PE over the last 6 years. Our study confirmed clot burden and RV strain on CTPA were good predictors for RV strain on echocardiography. The role of thrombolysis in normotensive patients with large clot burden remains uncertain. However, our experience shows that thrombolysis can be used, albeit with a modest risk of bleeding complication but with otherwise good clinical outcome.

Competing interests: None.

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References:


Surgical outcomes following laparoscopic adrenalectomy for treatment of Conn’s syndrome (primary hyperaldosteronism) between 1999 and 2006

Andrew Herd, Richard Harman, Eletha Taylor

Abstract

Background Primary hyperaldosteronism is a recognised cause of secondary hypertension with its aetiology most commonly due to a secreting aldosterone adenoma of the adrenal gland. Laparoscopic resection of the adrenal tumour has now become the accepted form of intervention. The aim of this study was to assess the effectiveness of such procedures performed by one surgeon over a 7-year period.

Method An observational study was conducted in respect of 33 patients who underwent adrenalectomies for primary hyperaldosteronism between 1999–2006. Information on blood pressure, electrolytes, medications, histology, patient characteristics and patients’ perception of benefit was gathered via clinical notes and a patient questionnaire.

Results 33 patients were reviewed. The mean follow-up was 38.4 months. Blood pressure and number of medications all had statistically significant decreases. Systolic blood pressure decreased from 146 mmHg preoperatively to 130 mmHg at final follow-up (p<0.00005). Diastolic blood pressure decreased from 91.0 mmHg preoperatively to 81.5 mmHg (p<0.00005). There was also a significant decrease in number of blood pressure medications from 2.3 preoperatively to 1.0 on average (p<0.00005). Only one patient required potassium at final review. Overall 36% had clinical cure and 50% had significant improvement in terms of blood pressure and medications requirements.

Conclusion The results suggest unilateral laparoscopic adrenalectomy is an effective tool in treatment for benign primary hyperaldosteronism caused by aldosterone secreting adenomas.

Conn’s syndrome, or primary hyperaldosteronism, is typified by hypertension and hypokalaemia, accompanied by increased aldosterone secretion from, most commonly, an adrenal adenoma (approximately 60%). Other causes include adrenal hyperplasia. The syndrome was first described by Jerome Conn in 1955 in a patient who had an aldosterone-producing adenoma.

Independently of the effects of elevated blood pressure, primary hyperaldosteronism may cause cardiovascular complications, such as cardiac myopathy and as such patients may be at higher risk than other hypertensive patients in respect of potential damage to the heart and kidneys.

Generally, the most widespread and accepted method of screening for primary hyperaldosteronism is an elevated ratio of plasma aldosterone to plasma renin concentration, which should be greater than 30:1 to confirm the diagnosis.
Confirmatory investigations are then required to demonstrate autonomous secreting adenoma.

The first open adrenalectomy for Conn’s syndrome was performed in December 1954. Since that time, laparoscopic adrenalectomy, first performed in 1992, is becoming the preferred surgical technique. Laparoscopic unilateral adrenalectomies for primary hyperaldosteronism have been shown to result in reduced blood loss, shorter hospital stays and fewer post-surgical complications. Recent studies indicate that cure rates for short and long-term follow-up periods have ranged from 34% to 58%.

The purpose of this study was to examine the long-term outcomes for laparoscopic adrenalectomies for patients referred with a diagnosis of primary hyperaldosteronism, with particular focus on whether there had been a reduction in hypertension and medication use

Method

We conducted an observational review of the hospital clinical records and general practitioner case notes of all consecutive patients (n=33) who underwent a laparoscopic unilateral adrenalectomy for diagnosed primary hyperaldosteronism performed by one surgeon (RH) during the period 1999 to 2006. The data collected from the clinical and general practitioner records was supplemented by a patient questionnaire. Of the 33 patients, there were 16 males and 17 females with an average age of 49 years.

Data collection and analysis—Preoperative and postoperative blood pressure, electrolyte/aldosterone/renin concentrations and medications were recorded from a review of hospital clinical notes, general practitioner records and patient questionnaires.

In particular, preoperative blood pressure readings, electrolyte concentrations and medications were obtained from the anaesthetic pre-admission data of each patient. Preoperative aldosterone/renin concentrations were obtained from a review of the investigations conducted upon admission or prior to admission.

Postoperative data was collected from three sources: discharge records, outpatient clinic notes (either surgical or endocrine specialist follow-up) and general practitioner records. As well as blood pressure, electrolyte/aldosterone/renin concentrations and medications, the histopathology of the adrenal gland was also recorded.

Postoperative data was also supplemented by a patient questionnaire which requested details of current medication regime and patient “satisfaction” subsequent to surgery.

The results recorded for each preoperative and post operative observation were then collated and analysed. Results have been presented as mean and percentages and t-tests were used to identify statistically significant differences.

The study was approved by the Health and Disability Ethics Committees, Ministry of Health New Zealand.

Results

Patient characteristics—During 1999 to 2006, 33 patients underwent a unilateral laparoscopic adrenalectomy for primary hyperaldosteronism. The mean operative time was 138 minutes. Long-term follow-up data was available for 28 of the patients and the mean follow-up time was 38.4 months (range 12 – 86.4 months). 5 patients were lost to long-term follow-up.

A summary of preoperative patient characteristics is at Table 1.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>33</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>49</td>
</tr>
<tr>
<td>Range</td>
<td>25–67</td>
</tr>
<tr>
<td>Tumour size (mm)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>16.4</td>
</tr>
<tr>
<td>Range</td>
<td>6.5–35</td>
</tr>
<tr>
<td>Preoperative blood pressure (mm/Hg)</td>
<td></td>
</tr>
<tr>
<td>Mean systolic</td>
<td>147</td>
</tr>
<tr>
<td>Mean diastolic</td>
<td>91</td>
</tr>
<tr>
<td>Preoperative number of blood pressure medications</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.5</td>
</tr>
<tr>
<td>Range</td>
<td>0–5</td>
</tr>
<tr>
<td>Preoperative number of potassium medications</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.4</td>
</tr>
<tr>
<td>Range</td>
<td>1–3</td>
</tr>
<tr>
<td>Aldosterone/renin ratio</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>176.68 (46–542)</td>
</tr>
</tbody>
</table>

**Histology**—Histology revealed that two patients had adrenal hyperplasia, with the remaining 31 confirmed as having adrenocortical adenomas.

**Postoperative complications**—Postoperative complications in the population included: one ileus; one episode of atelectasis; one port site haematoma and one liver and spleen capsular tear. None of these complications required return to theatre. There were no conversions to an open procedure and there was no mortality associated with the operations.

**Blood pressure**—The mean preoperative blood pressure was 147/91 mmHg. Postoperatively, blood pressure information was recorded both at discharge (“immediate postoperative blood pressure”) and then the most recent recorded blood pressure from general practitioner notes (“recent postoperative blood pressure”), at a mean follow-up time of 38.4 months. The mean recent postoperative blood pressure was 130/82 mmHg. Average preoperative blood pressure was significantly higher than the average recent postoperative blood pressure on follow-up (p<0.00005) (see Figure 1).

**Medications**—There was a significant decrease in the requirement for postoperative blood pressure medications. Medication use was recorded preoperatively, immediate postoperatively and at most recent follow-up (mean most recent follow-up time was 38.4 months).

Prior to surgery, patients were taking a mean of 2.5 types of blood pressure medication, compared to an average of 1.1 types of blood pressure medication at most recent follow-up (p<0.00005).
Figure 1. Average blood pressure pre op, immediate, and post op

Potassium—Only one patient required potassium medication postoperatively. Originally they were on 9.6g of slow K which was reduced to 1.2g. This patient was requiring frusemide prescribed by the general practitioner for peripheral oedema.

Clinical cure rate—Patients were categorised into three separate groups based on most recent follow-up blood pressure and medication usage, as follows:

- **Clinical cure**, being systolic ≤140 mm/Hg and diastolic ≤90 mm/Hg and no antihypertensive medications;
- **Improved management**: being systolic ≤140 mm/Hg and diastolic ≤90 mm/Hg and equal or fewer antihypertensives postoperatively OR hypertensive but on fewer antihypertensive medications;
- **No improvement or worse management**: being hypertensive with the same or more antihypertensive medications postoperatively.

Figure 3 shows that 86% of patients at most recent follow-up had at least some improvement in the management of their hypertension. Only 14% had no improvement or worse management. Thirty six percent of patients had a clinic cure requiring no blood pressure management and were normotensive.

The two patients with hyperplasia on histology were included in the improved management group.
Patient satisfaction—The questionnaire sent to patients asked patients to respond to the following question:

(4) Do you think this surgery has been beneficial to you? (Please circle)
No benefit at all 1
A little benefit 2
Somewhat beneficial 3
Very beneficial 4
Extremely beneficial 5

Of the 15 patients who responded to this question, the mean rating was 4.5.

Discussion

Since the first open adrenalectomy in 1954, laparoscopic adrenalectomies are now becoming the accepted form of treatment for benign primary hyperaldosteronism due to secreting adrenal adenomas. Laparoscopic surgery is safer and reduces complications and length of patient stay.9–12

Our study has shown that this surgery, in general, has significant benefit for the patient and is safe. In both the short and longer term, the majority of the population studied had a reduction in blood pressure and the number of medications prescribed post-surgery. The clinical cure rate at a mean follow-up of 38.4 months was 36% of patients. A further 50% had some form of improved management of hypertension, with either reduced blood pressure equal to or below 140/90 mm/Hg and equal or fewer antihypertensives postoperatively, or if still hypertensive, being on fewer antihypertensive medications (see figure 3).

Only one patient required potassium replacement postoperatively. The amount in this case had been reduced and the patient was also noted to be on diuretic treatment.

Recent studies are consistent with the above, showing relatively significant reductions in hypertension in patients undergoing laparoscopic adrenalectomy over the medium
to longer term. A study by Pang et al\textsuperscript{18} has shown a clinical cure rate of 34% (with clinical cure being defined as normal blood pressure with no medications) and with 51% of participants showing some improvement in blood pressure control over a median follow-up period of 59 months. Only 5.6% of patients required potassium replacement.

Meria et al found, from 212 cases, a cure rate (defined as normal blood pressure with no medications) of 58% over a mean 44 month follow-up period.\textsuperscript{14} None of the patients in this study required a postoperative potassium replacement.

Gockel et al’s study showed that 36.8% of patients had completely discontinued the intake of hypertensive medications at a mean of 45 months postoperatively.\textsuperscript{17}

Interestingly, from our questionnaire, patient satisfaction with the surgery ranked extremely highly. Patients who responded to the question had a good perception about the benefit of the surgery to themselves and their quality of life, with an average ranking of 4.5 out of 5 (with 4 being “very beneficial” and 5 being “extremely beneficial”).

Some limitations of this study are the relatively small size of the population and the fact that the only available data for some patients at follow-up was not as recent as others, as well as a small number of patients being lost to follow-up. In addition, there may have been some recall bias in the questionnaire, although we attempted to alleviate this by asking for general practitioner input so as to confirm patient recollection. However, overall, we have been able to achieve a good duration of follow-up over a relatively long time frame and the study has had sufficient numbers to give statistically significant results.

This study has shown that, for the majority of the patients reviewed, the surgery was beneficial. There were minimal complications and no mortality associated with the surgeries analysed for the study. Eighty-six percent of patients had some or much improvement in their blood pressure and medication use and quality of life resulting directly from the surgery.

In conclusion, laparoscopic unilateral adrenalectomy, appears to be a relatively safe and effective method of treatment of benign primary hyperaldosteronism caused by secreting adenomas.

\textbf{Competing interests:} None.

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\textbf{Acknowledgement:} The authors acknowledge the assistance of Dr Geoff Braatvedt.

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\textbf{References:}

Task Manager: an innovative approach to improving hospital communication after hours

Mary E Seddon, David Hay

Abstract

Aim To improve communication between doctors and nurses after hours, by developing a tool to display ward tasks, allowing staff to prioritise their work, without constant interruption from pagers (beepers).

Setting Middlemore Hospital, a large metropolitan 800-bed hospital in Auckland, New Zealand.

Method Introduction of computerised system (Task Manager) to identify, allocate and complete after-hours tasks.

Results In the first 6 months 21,000 tasks have been completed in Task Manager. Paging of junior doctors has decreased by over 30% and there is broad acceptance of the tool by both nursing and medical staff. Task Manager has collected real-time data on the type of after hours tasks (nearly 50% are phlebotomy-related tasks), busy times of the day (1600 hours to 2400 hours) and who is performing most of the tasks.

Conclusion Task Manager is a simple yet powerful tool for prioritising routine tasks after hours. It allows staff to quickly create tasks, and communicate effectively with other members of the team. It has reduced the frequency of junior doctors paging so that they can continue their work with fewer interruptions. Whilst it was introduced to improve effective communication after hours, it has become apparent that there are multiple 'tasks' that are ordered in a multitude of ways in our hospital and many could be served by Task Manager.

The quality of hospital care provided after hours has been a concern for a number of years.1–3 Factors identified include: lower staffing levels, key services not offered after hours or offered only by a skeleton staff on call (e.g. clinical pharmacists), fatigue of shift workers, overall clinical workload, and fragmented communication between staff. Various solutions have been put forward, including the UK Hospital at Night approach. In this paper we report on a tool designed to improve after-hours communication in a large (800 bed) metropolitan hospital.

Communication between staff has been identified as a problem generally4,5 but is particularly acute after hours. There are two specific problems: the quality of the communication, particularly between ward nurses and the junior doctors, and the distraction caused by our main communication tool—the pager (or beeper). Studies of after-hours communication have shown that pagers ringing frequently6 (for an individual doctor this may be as often as once every 7 minutes),7 and often interrupt clinical care,8 with one study showing up to 65% of the time pagers interrupted direct patient contact.9
The concern is that pagers may inhibit junior doctors from performing effectively and safely. They also contribute to after hours stress on junior medical staff (related to the perceived lack of control one has over one’s workload). With the frequent pagers, junior doctors can feel overwhelmed, they cannot see a view of their overall workload, are unable to prioritise their tasks, and are often unable to complete their work.

"The beeper interrupts; pagers come more quickly than they can be answered."

Furthermore there is evidence that pagers are not a good form of communication, with major differences between junior doctors and nurses in their perception of the appropriateness of calls and their urgency. Earlier work at this institution had identified that the paging process was not standardised and there were significant differences between doctors and nurses when it came to their use. Numeric paging, where a nurse adds the prefix 93 to the pager number and then hangs up and waits for the junior doctors to call back, was of little value to the junior doctor, as they did not know who had paged them, or what the problem was. Often on calling back, they were unable to directly communicate with whoever had called them as the nurse had moved away from the phone. There was a widespread belief amongst the doctors that numeric paging could be responded to as a lower priority than text pages.

Nurses, on the other hand assumed that doctors would see numeric pages as more urgent than text pages. Text paging was seen by the nurses as a lower priority message. Examination of the actual text paging data showed that it often consisted of updating patient investigation status (e.g. ‘patient is back from X-ray’), as opposed to worsening patient status. So there was a mismatch between nurses’ and doctors’ expectations of the paging system and considerable time wasted responding to pages without any effective communication taking place. Doctors reported getting so many pages during a shift that they were constantly being interrupted and distracted causing ‘page rage.’

We therefore introduced Task Manager, designed to capture after-hours ward tasks - from 1600 hours to 0800 hours on weekdays and 0800 to 0800 hours for the entire weekend. The aim was to improve communication after hours, by prioritising each task based on urgency, by making it visible to nurses that the junior doctors had seen the message and would be attending to the task, and to give staff an overview of how busy each shift was. It was also hoped that Task Manager would significantly reduce interruptions from pagers and decrease ‘page rage.’

Method

The idea for Task Manager came from a demonstration of a system at Hutt Hospital (Hutt Valley District Health Board). They had already successfully introduced SPADE (Simply Prioritize and Distribute Electronically), and they were willing to share their results. SPADE was developed using Java Server Pages, and it was not designed to integrate with the Hutt Valley Patient Management System. It was unclear whether it could be used for a much larger hospital, who would support the application (which was an unfamiliar application to CMDHB) and how much it might cost if Hutt Valley sold it to a vendor.

We decided to design our own system, extend it, and to link it with our electronic Patient Management System (PMS). Task Manager is accessed via a log on to our PMS. This provides security and is also the place where staff will be checking electronic laboratory and radiology results so Task Manager fitted with the usual workflow.
Development time for the initial version was six developer weeks at a cost of approximately $30,000. This was only possible as the Hutt Hospital system was used as the model for development, so the usual requirements and design phases were not required.

Task Manager displays after hours tasks, colour codes them for urgency, and filters tasks by patient location or speciality (see Figure 1). It also displays the Early Warning Score—known in our institution as the Physiologically Unstable Patient (PUP) score—if appropriate. Once a task is accepted, the accepting person is displayed. When the task is completed, it disappears from the active screen and is captured in the ‘completed in 24 hours’ tab.

**Figure 1. Task Manager as displayed in the Patient Management System**

<table>
<thead>
<tr>
<th>Task List</th>
<th>Completed In 24 hrs</th>
<th>Task Search</th>
<th>Dashboard</th>
<th>Get Report</th>
<th>Print</th>
</tr>
</thead>
<tbody>
<tr>
<td>Create New</td>
<td>All</td>
<td>CCC</td>
<td>Gen Surg</td>
<td>Medical</td>
<td>Ortho</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Task List (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>View 83</td>
</tr>
<tr>
<td>View 75</td>
</tr>
<tr>
<td>View 34</td>
</tr>
<tr>
<td>View 49</td>
</tr>
<tr>
<td>View 51</td>
</tr>
</tbody>
</table>

It was decided that Task Manager would use 'drop-down' boxes to streamline the process for creating and accepting tasks. The tasks came from discussion with the services, and the responders to tasks were also identified. As Middlemore is a large hospital, there were a large number of responders including junior doctors (6 surgical house officers, 7 medical house officers and 9 registrars), nurses, Patient At Risk (PAR) teams and phlebotomists.

A test version was established for training purposes and a small team undertook training of the staff members. Most staff used the computer frequently and required very little training.

Task Manager was introduced into the general and sub-speciality Medical wards (9 wards) in late December 2009 and extended to the Surgical wards (7 wards) in February 2010. For the first week in each area, there was support for the users of Task Manager with a team of roving 'experts' on hand. A handout was produced taking people through the various steps:

- how to create a task
- how to accept a task
- how to complete a task

Posters of these steps were put near each of the ward computer areas.

Task Manager Newsletters were circulated with updates and fixes to problems.
A convenience sample of junior doctors and nursing staff were surveyed using Survey Monkey™. The impact of Task Manager on the number of pages was assessed by accessing the pager records for each after-hours page in November 2009 and again in March 2010.

**Results**

In the first 6 months since Task Manager’s introduction, there have been over 21,000 tasks completed. On average there are just over 100 tasks completed each evening/night shift (1600 to 0800 hours) and 190 completed on the weekend days (0800 to 0800 hours). The most common tasks were blood tests and cannulations, which made up 47.8% of all tasks (see Table 1).

The vast majority of tasks were entered as routine (59.9%), 33.1% were coded semi-urgent and 6.96% were coded as urgent. The average time from creation of a task to completion was 65 minutes, 94 minutes and 111 minutes for urgent, semi-urgent and routine tasks respectively.

A third of all tasks were completed by phlebotomists (on duty from 1500 hours to 2300 hours), approximately one-third by medical house surgeons and the final third by surgical house surgeons. Very few nurses completed tasks (1.1%) and there were no tasks completed by registrars (see Table 2).

**Table 1. Type of tasks completed and frequency of task**

<table>
<thead>
<tr>
<th>Task</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic Discharge Summary Required</td>
<td>2</td>
<td>0.01%</td>
</tr>
<tr>
<td>Family request meeting</td>
<td>12</td>
<td>0.06%</td>
</tr>
<tr>
<td>New Admission / Transferred Patient</td>
<td>13</td>
<td>0.06%</td>
</tr>
<tr>
<td>Patient Deceased</td>
<td>19</td>
<td>0.09%</td>
</tr>
<tr>
<td>Urinary catheter needed</td>
<td>33</td>
<td>0.15%</td>
</tr>
<tr>
<td>Low haemoglobin</td>
<td>35</td>
<td>0.16%</td>
</tr>
<tr>
<td>Consent Patient</td>
<td>40</td>
<td>0.19%</td>
</tr>
<tr>
<td>Admit Patient</td>
<td>50</td>
<td>0.23%</td>
</tr>
<tr>
<td>Patient At Risk Nurse Review</td>
<td>92</td>
<td>0.43%</td>
</tr>
<tr>
<td>Chart Anti-emetic</td>
<td>112</td>
<td>0.52%</td>
</tr>
<tr>
<td>Patient for Discharge</td>
<td>133</td>
<td>0.62%</td>
</tr>
<tr>
<td>Arterial Blood Gas (ABG)</td>
<td>232</td>
<td>1.08%</td>
</tr>
<tr>
<td>Review medications</td>
<td>225</td>
<td>1.05%</td>
</tr>
<tr>
<td>Fluid Review</td>
<td>233</td>
<td>1.09%</td>
</tr>
<tr>
<td>Multiple tasks—see comment</td>
<td>280</td>
<td>1.31%</td>
</tr>
<tr>
<td>Chart/re-chart pain relief</td>
<td>352</td>
<td>1.64%</td>
</tr>
<tr>
<td>Review Labs</td>
<td>400</td>
<td>1.87%</td>
</tr>
<tr>
<td>Review Patient raised PUP score</td>
<td>431</td>
<td>2.01%</td>
</tr>
<tr>
<td>Chart Warfarin</td>
<td>443</td>
<td>2.07%</td>
</tr>
<tr>
<td>Review Radiology</td>
<td>469</td>
<td>2.19%</td>
</tr>
<tr>
<td>Blood Test / Cannula</td>
<td>597</td>
<td>2.79%</td>
</tr>
<tr>
<td>Review ECG</td>
<td>817</td>
<td>3.82%</td>
</tr>
<tr>
<td>Chart/re-chart IV fluids</td>
<td>1313</td>
<td>6.13%</td>
</tr>
<tr>
<td>Other Task—see comment</td>
<td>1530</td>
<td>7.15%</td>
</tr>
<tr>
<td>Chart/re-chart meds</td>
<td>1697</td>
<td>7.93%</td>
</tr>
<tr>
<td>Review patient - see comment</td>
<td>2349</td>
<td>10.97%</td>
</tr>
<tr>
<td>Blood Test</td>
<td>3489</td>
<td>16.29%</td>
</tr>
<tr>
<td>Cannula</td>
<td>6015</td>
<td>28.09%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>21413</td>
<td>100.00%</td>
</tr>
</tbody>
</table>
Table 2. Health Professionals completing tasks

<table>
<thead>
<tr>
<th>Task completed by</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phlebotomist</td>
<td>5430</td>
<td>30.0%</td>
</tr>
<tr>
<td>Medical On Call House Surgeon (OCHS)</td>
<td>4242</td>
<td>23.4%</td>
</tr>
<tr>
<td>Medical B-call House Surgeon (HS)</td>
<td>1258</td>
<td>7.0%</td>
</tr>
<tr>
<td>Med S-call HS</td>
<td>941</td>
<td>5.2%</td>
</tr>
<tr>
<td>Med C-call HS</td>
<td>148</td>
<td>0.8%</td>
</tr>
<tr>
<td>General Surgery On Call House Surgeon (OCHS)</td>
<td>3918</td>
<td>21.7%</td>
</tr>
<tr>
<td>Orthopaedics OCHS</td>
<td>1245</td>
<td>6.9%</td>
</tr>
<tr>
<td>Orthopaedic Admitting HS</td>
<td>54</td>
<td>0.3%</td>
</tr>
<tr>
<td>Plastics OCHS</td>
<td>448</td>
<td>2.5%</td>
</tr>
<tr>
<td>Plastic Hands OCHS</td>
<td>100</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nurses</td>
<td>201</td>
<td>1.1%</td>
</tr>
<tr>
<td>Patient At Risk Nurses</td>
<td>105</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

The busiest time for tasks to be created coincided with the afternoon change of shift, peaking at 1600 hours and then remaining busy until 2400 hours (see Figure 2).

Figure 2. Time of day that tasks were created

Since the introduction of Task Manager there has been a 30% reduction in pager calls to junior doctors (see table 3) and a 40–50% reduction in pager calls to the phlebotomists.
Table 3. Pager numbers by role pre and post introduction of Task Manager

<table>
<thead>
<tr>
<th>Role</th>
<th>Pre Task Manager (1/11/09–30/11/09)</th>
<th>Post task Manager (1/3/10–30/3/10)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical On Call House Surgeon (OCHS)</td>
<td>719</td>
<td>499</td>
<td>- 31%</td>
</tr>
<tr>
<td>Medical B call</td>
<td>141</td>
<td>102</td>
<td>- 28%</td>
</tr>
<tr>
<td>General Surgery OCHS</td>
<td>257</td>
<td>175</td>
<td>- 32%</td>
</tr>
<tr>
<td>Orthopaedics OCHS</td>
<td>142</td>
<td>100</td>
<td>- 30%</td>
</tr>
<tr>
<td>Plastics OCHS</td>
<td>405</td>
<td>267</td>
<td>- 31%</td>
</tr>
<tr>
<td>Medical Phlebotomist</td>
<td>120</td>
<td>60</td>
<td>- 50%</td>
</tr>
<tr>
<td>Surgical Phlebotomist</td>
<td>86</td>
<td>49</td>
<td>- 43%</td>
</tr>
</tbody>
</table>

Forty-nine junior doctors (out of a possible 174) responded to the survey, but it was clear that Task Manager was predominantly used by house officers (96% used it regularly compared to 9% of registrars). On the basis of this, the responses were from 27 house officers only. Most (83%) found it easy to use and 71% found that it was easier to manage their workload with Task Manager (see Table 4).

“Able to prioritise some clerking, also can get on and do tasks without being interrupted for simple requests that are non-urgent”

“Not constantly being interrupted. Task Manager - nurses are required to state what the job/concern is and then you can prioritise; paging - they often just leave an extension number to call back and then when you call the number, you often wait for them to find the person who paged and found what the job is - lot of time wasted.”

All felt that it had led to a reduction in pages, with most house officers rating the reduction as more than 50% and a quarter of respondents thought that pages had decreased by 80%. The overall satisfaction rating was good with 29.6% satisfied compared to 7.4% unsatisfied.

Table 4. Survey responses from house surgeons

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you find TM easy to use?</td>
<td>83.3%</td>
<td>17%</td>
</tr>
<tr>
<td>Has it made it easier to manage after hours workload?</td>
<td>71%</td>
<td>29%</td>
</tr>
<tr>
<td>Has TM increased your after hours workload?</td>
<td>57%</td>
<td>43%</td>
</tr>
<tr>
<td>Has TM reduced how often you are paged after hours</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If it has decreased pager calls, please estimate by how much</th>
<th>Estimated reduction in pager calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>50%</td>
<td>58%</td>
</tr>
<tr>
<td>80%</td>
<td>25%</td>
</tr>
<tr>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall satisfaction with TM</th>
<th>Very unsatisfied</th>
<th>Unsatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.7%</td>
<td>7.4%</td>
<td>59.3%</td>
<td>29.6%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years since graduation</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>&gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.3%</td>
<td>7.4%</td>
<td>44.4%</td>
<td>11.1%</td>
<td>3.7%</td>
<td></td>
</tr>
</tbody>
</table>
213 nurses responded to the survey and of these 89% found it easy to use, 68% thought that it had improved communication with junior doctors and 70% felt that it resulted in tasks being completed in a more timely fashion.

We are now sure that our tasks will be acknowledged and actioned
Don't have to sit near the phone and wait for the doctors or phlebotomists to respond

Discussion

Task Manager was borne out of our desire to improve after-hours care and communication, decrease interruption by pagers, and allow junior doctors to prioritise their workload. It has succeeded in decreasing pager interruption, and has improved the display and prioritisation of after-hours tasks. It has high user acceptability and it has proven to be a very inexpensive, innovative solution. Furthermore, we were surprised by how little formal training was required as Task Manager uses intuitive drop down boxes and simple instructions.

‘After-hours’ actually constitute 75% of the hours in a week, and the care provided in this time has been a concern recently. The overall shortage of junior doctors, and the requirements to conform to working time directives, means that we need to be more innovative in how we organise after-hours care.

Task Manager is one of the tools which can help prioritise and rationalise after-hours work. Other initiatives, such as Hospital At Night, advocate a central coordinator role (usually a senior nurse) to prioritise work and a physical ‘control centre’ that allows a single point of call for all after-hours calls. We have not gone down this route as it was estimated that we would require 11 FTEs to cover this role and Task Manager allows all staff to see where the tasks are in real time.

Another initiative aimed at decreasing interruptions from pagers, was to have whiteboards on each ward for nurses to write up tasks. Again Task Manager effectively does this, but has the added advantage of allowing a hospital-wide or service specific overview of all the tasks from any computer.

We had investigated a number of options to improve after hours communication. The first used mobile phones to send messages to junior doctors after hours. This was rejected as it was very costly, there were concerns about delays with the phone network, and feedback from junior doctors who had worked with this system was overwhelmingly negative.

We also looked at a product that used text pagers that automatically escalated tasks if there was no response. Again this was rejected on the basis of cost, that it did not necessarily deliver better communication, and it did not provide a hospital-wide view of the pending tasks.

Several studies have tried to estimate the workload after hours, actually shadowing junior doctors as they work. Christchurch Hospital identified that there was wide variability in the activity levels of junior doctors after hours and that most tasks were generic in nature. This is supported by our data. Task Manager has the in-built ability to rapidly generate reports on activity and this has demonstrated for the first time the number and type of tasks undertaken after hours.
The majority (nearly 50%) of after-hours tasks are phlebotomy-related (blood tests and cannulations). We intend to review this in more depth to see whether all the phlebotomy tasks are indicated - especially after hours cannulation.

It is likely that Task Manager does not capture total workload as junior doctors on the wards will be asked to do tasks verbally and these will not be captured in Task Manager. So the workload in Task Manager should be seen as a minimum indication of the total workload. It has however, highlighted some inequalities in workload (such as high rate of phlebotomy tasks), which may be used to better organise the after hours workforce. As the tasks after hours are generic in nature (i.e. not requiring subspeciality expertise) there may be an opportunity to review the traditional roster system for junior doctors.

One of the central tenets of the Hospital At Night work is that routine work is not carried over into the out-of-hours period when there are fewer staff to carry out such work. The Task Manager reports show that such tasks are spilling over into the after-hours. For instance, Warfarin is traditionally charted during the day once the blood monitoring is reviewed, but is given at 1800 hours.

In at least 443 cases, the daytime workers had gone home without charting Warfarin and this was picked up by the after-hours staff. It could be argued that at least some of the IV fluid tasks could have been anticipated by the day staff. Interestingly of note, there are some tasks which are rarely requested such as an ‘Electronic Discharge Summary’ (0.01% of tasks), and ‘Consent Required’ (0.19%). We will be revisiting the list and may delete some of the infrequently requested tasks.

As far back as 1990, it was suggested that "if use of bleepers was restricted to emergencies with the institution of a non-urgent messaging system, the number of interruptions to work and rest, and thus workload, could be reduced considerably".14 We believe that Task Manager is such a system and since its introduction there has been a significant reduction in pagers and ‘page-rage.’ Pager calls for junior doctors have decreased by 30% but the perception is that the reduction is far more (closer to 50%) with junior doctors noticing significantly fewer interruptions.

The reduction for phlebotomy staff is even greater with 40–50% reduction in actual pager calls. They had previously had a fairly rigid work process, starting with a 'ward round' doing four phlebotomy tasks on each ward. With the introduction of Task Manager they were able to see where the most urgent tasks were and to prioritise their work accordingly. At the same time nurses can be reassured when they see that the phlebotomy task has been accepted and are therefore not paging the phlebotomists to check up.

Previous studies have assessed the appropriateness of pager calls to junior doctors. Inappropriate calls have ranged from 17% to 26%.8,9 Task Manager has largely replaced pagers and ward lists for routine tasks but there has been some education of nurses needed for use of 'urgent' priority in Task Manager.

To avoid a really urgent task (e.g. asked to assess a rapidly deteriorating patient) sitting on Task Manager unseen, a fix advocated by junior doctors was instituted. If a nurse assigns an urgent priority to a task, before they can finalise the task, a pop-up box comes up to remind them to page the intended recipient for an urgent task. Urgent tasks make up a small proportion of tasks (just under 7%), but as the risk is there,
we will soon be looking at a forcing function - whereby an automatic page is sent to the on-call house surgeon if an urgent task is entered, and a similar system will work if the nurse requests a Patient At Risk (PAR) team review.

**Limitations**—There are several limitations to our study. We had attempted to get accurate data on junior doctors’ tasks prior to the introduction of Task Manager, but despite hiring people to shadow junior doctors, this provided only very basic data, and was difficult to collect. We have used the number of pagers per junior doctor as a proxy for workload pre and post Task Manager. However, it is not a perfect proxy as we were unable to capture on-the-ward referrals and the use of junior doctors’ mobile phones. Our survey numbers are also very small with only 49 junior doctors and 213 nurses responding, however, we have backed this up with monthly forums for feedback and ongoing discussions about improvements.

**Future directions**—Task Manager has shown its utility in the adult medical/surgical wards and there is now interest from other disciplines (Obstetrics and Paediatrics). However, what has become apparent is that there are multiple 'tasks' that are ordered in a multitude of ways in our hospital and many could be served by Task Manager. We are working on a non-clinical Task Manager for our orderly services. Ward nurses will be able to book an orderly task on Task Manager, the orderly service can then prioritise jobs, direct their staff and keep an overview of activity. Similarly, booking transit nurses could be done in the same way.

**Conclusion**—Task Manager is a simple yet powerful tool for prioritising routine tasks after hours. It allows staff to quickly create tasks, and communicate effectively with other members of the team. It has reduced the number of times junior doctors are paged and they can continue with their work with fewer interruptions. It also provides accurate information on the type of tasks undertaken, the busy shifts and the approximate workload of staff. Whilst it was introduced to improve effective communication after hours it has become apparent that it will also work for other services that respond to tasks 24/7, such as the orderly and transit nurse services.

**Competing interests:** None.

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**Acknowledgement:** Hutt Valley DHB for original idea and for sharing their experiences.

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**References:**


Outcome of patients on azathioprine: need for a better pre-treatment assessment and dosing guideline

Dinar Jabin, Sunil Kumar, Peter J Gow

Abstract

Background Azathioprine (AZA) is a commonly used drug for the management of various rheumatologic disorders. Due to individual variation of the metabolism of AZA, related to genetic polymorphism of the thiopurine methyl transferase (TPMT), serious toxic effects can result if inappropriate dose is administered. AZA dosing according to patients TPMT status can reduce drug-induced morbidity and can be cost effective.

Aim To determine the current local practice of AZA dosing, identify AZA-related toxicity and to compare the local practice with the British Society of Rheumatology (BSR) recommendations.

Methods Retrospective review of patients on AZA for various rheumatologic conditions from inpatient (n=22) and outpatient (n=38) database at Middlemore Hospital, from January 2003 to January 2007. Data were collected on patient’s demographics, treatment history including AZA dosing regimen, TPMT testing, drug-related toxicities and their management.

Results The mean age was 53 years; 73% were females. 43% of European ethnicity; mean weight of patient was 75±25 kg. 42% had SLE, 22% had rheumatoid arthritis, and 13% had systemic vasculitis. Average initial dose of AZA prescribed was 100±37 mg. 45% developed AZA related toxicity. AZA was withdrawn in 35 % of patients due to drug-related side-effects and inefficacy. 15% of the patients required dose reduction. TPMT status was tested in 6 (10%) patients; three had low TMPT level, needing dose reduction. BSR recommendation for AZA dosing was followed in 15% cases.

Conclusion A significant proportion of the studied cohort of rheumatologic patients on AZA had drug-related toxicity resulting in discontinuation of AZA. Our data suggests that better pre-treatment assessment including TPMT testing and the practice of guideline based dosing regimen would reduce the incidence of undue side-effects and discontinuation of such treatment.

Azathioprine (AZA) and its metabolites 6-mercaptopurine (6MP) are thiopurine drugs used widely in the management of various rheumatologic conditions such as rheumatoid arthritis, systemic lupus erythematosus (notably lupus nephritis), systemic vasculitis and other autoimmune connective tissue disorders. It is also used in acute lymphoblastic leukaemia, organ transplantation, inflammatory bowel disease and inflammatory dermatologic disease.

Azathioprine has no indigenous immunosuppressive activity; it is a prodrug. The first step in biotransformation is non-enzymic cleavage to form mercaptopurine which in
Mercaptopurine can be oxidised, methylated, or formed into a variety of active thionucleotide metabolites. Azathioprine, as with all thioguanines, is metabolized to the active metabolites referred to collectively as 6-thioguanine nucleotide (6-TGN), which in turn is inactivated by thiopurine-6-methyltransferase (TPMT).  

TPMT is a cytosolic enzyme that preferentially catalyzes the inactivation (S-methylation) of the active metabolites of the thiopurines (6-mercaptopurine, AZA, and thioguanine).  

TPMT activity in erythrocytes are trimodal; 90% of people exhibit high TPMT activity (homozygous for wild-type alleles), 10% have intermediate activity (mutation on one chromosome), 0.3% have low or no activity (mutation is found on both chromosomes). About 1 in 300 Caucasians are homozygous for TPMT and are at highest risk of life threatening myelotoxicity if standard thiopurine doses are used. This myelotoxicity is thought to be due to elevated concentration of the cytotoxic metabolites, 6-thioguanine nucleotides (6-TGNs), which occur when 6-MP is unable to be metabolized by TPMT to 6-MMP.

British Society of Rheumatology (BSR) recommends the initial dose of AZA should be 1mg/kg/day with dose increment of 0.5 mg/kg every 4–6 weeks until the desired response achieved or a maximum total dose of 2–3 mg/kg/day is achieved. Pre-treatment assessment of TPMT level is also recommended.

AZA treatment discontinuation due to dose-related toxicities has been reported in up to 20% patients. Polymorphism in the TPMT gene predicted haematological adverse drug reactions in 5–10% of patients treated with thiopurine drugs. TPMT testing prior to AZA therapy has been shown to be cost-effective, when modelled in various theoretical situations. British Association of Dermatology (BAD) recommends pre-treatment measurement of TPMT in all patients prescribed azathioprine.

Measurement of TPMT activity prior to initiation of thiopurine therapy can identify the select group of patients at risk of severe myelosuppression with standard dose of the drugs. Adjusting AZA dose on the basis of individual patients’ TPMT activity can potentially minimise this risk. Estimated number of patients who would need TPMT analysis in order to avoid one serious adverse event over 6 months was 20 in one study.

TPMT measurement costs NZ$64.52 per assay in New Zealand and it is performed by Canterbury Health Laboratories.

We undertook this retrospective audit to determine the local practice of AZA dosing and pre-treatment TPMT testing and compared it with the BSR guideline for AZA dosing regimen.

**Methods**

Retrospective review of rheumatology patients receiving azathioprine, between January’ 2003 to January’ 2007, at Middlemore Hospital in Auckland, New Zealand was undertaken. Patients who had a minimum follow-up of 6 months were identified using the Read code MO1C (other DMARDs) from the inpatient and outpatient database.

Data were collected on patient’s demographics, previous and current treatment, AZA dosing regimen, TPMT testing, AZA-related toxicity profile and their management. Major AZA-related side-effects involving gastrointestinal tract, liver and bone marrow, were identified and documented. An increase of
more than twice the upper limit of the normal range in the levels of serum alanine aminotransferase (ALT) was considered as hepatotoxicity. AZA related myelotoxicity was defined as neutrophil count <1.5×10^9 or total white cell count <3.5×10^9. Efficacy was defined as both clinical and biochemical improvement as well as reduction or complete withdrawal of all corticosteroids.

**Statistical analysis**—Data are presented as mean (SD), median (IQR), or percentage as appropriate. Comparisons between groups for categorical data were made using Fishers exact test for 2×2 tables, or chi-square analysis for higher level tables. Normally distributed continuous variables were compared using Student’s t-test. P 0.05 was considered significant, all tests are two tailed.

**Results**

Sixty patients on AZA were identified; majority of the patients were female (73%) and of European ethnicity. 42% of the patients had systemic lupus erythematosis and 22% had rheumatoid arthritis, forming the majority of the cohort (Table 1). Forty-three (72%) patients were on at least one other DMARD prior to initiation of azathioprine—17 patients from group 1 and 22 patients from group 2. Majority were on hydroxychloroquine, methotrexate or sulphasalazine either as monotherapy or combination therapy.

The mean initial dose of prescribed AZA for our patient was 100 mg; the mean patient weight was 70 kg. BSR recommended starting dose (1 mg/kg) and dose incrementation was followed in 32% and 15% cases, respectively (Table 2). TPMT status was tested on six patients; of whom three had low TPMT levels requiring dose adjustment.

Twenty-six patients (43%) of our cohort suffered at least one AZA-related side-effect. 42% suffered hepatotoxicity, 39% had bone marrow toxicity and 19% had gastrointestinal intolerance. AZA was withdrawn in 21 patients (35%) either due to adverse effects or inefficacy. Two patients required hospital admission; one patient required rescue therapy for leucopenia and the other patient was admitted with urosepsis and leucopenia (Table 3).

Comparison of patients who suffered AZA-related toxicity (group 1) with those who tolerated the drug well (group 2), showed no statistically significant difference except group 1 patients were prescribed higher initial dose compared to group 2 (p<0.005) (Table 4).

| Table 1. Patient’s demographics (values are number [%] or mean ± SD) |
|---|---|
| **Sex:** |  |
| Male | 16 (27%) |
| Female | 44 (73%) |
| **Age:** | mean±SD 53 ± 16 |
| **Ethnicity:** |  |
| European | 26 |
| NZ Māori | 10 |
| Polynesian | 9 |
| Fijian | 9 |
| Others | 6 |
| **Disease:** |  |
| SLE | 25 (42%) |
| RA | 13 (22%) |
| Vasculitis | 8 (13%) |
| Inflammatory myopathy | 5 (8%) |
| Others | 9 (15%) |
Table 2. AZA dosing and pre-treatment TPMT testing regimen (values are number (%) or mean ± SD)

<table>
<thead>
<tr>
<th>Initial dose (mean ± SD)</th>
<th>100 ± 38 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimum dosing</td>
<td>19 (32%)</td>
</tr>
<tr>
<td>Under dosing</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Over dosing</td>
<td>28 (46%)</td>
</tr>
<tr>
<td>Escalating dose</td>
<td></td>
</tr>
<tr>
<td>Guideline followed:</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Too rapidly</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>No clear plan</td>
<td>38 (63%)</td>
</tr>
<tr>
<td>Patients weight (mean ± SD)</td>
<td>70 ± 25 kg</td>
</tr>
<tr>
<td>TPMT status</td>
<td>6 (10%)</td>
</tr>
</tbody>
</table>

Table 3. Patient outcome on AZA

<table>
<thead>
<tr>
<th>Interval of adverse reaction</th>
<th>95±40 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>26 (43%)</td>
</tr>
<tr>
<td>Hepatotoxicity:</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Bone marrow toxicity:</td>
<td>10 (39%)</td>
</tr>
<tr>
<td>GIT intolerance:</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Drug withdrawn</td>
<td>21 (35%)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>16</td>
</tr>
<tr>
<td>Inefficacy</td>
<td>5</td>
</tr>
<tr>
<td>Management of adverse reaction:</td>
<td></td>
</tr>
<tr>
<td>Dose reduction:</td>
<td>38%</td>
</tr>
<tr>
<td>Drug withdrawn:</td>
<td>62%</td>
</tr>
</tbody>
</table>

Table 4. Comparison between patients with AZA related toxicity (group 1) and patients who tolerated the drug (group 2)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=26)</th>
<th>Group 2 (n=34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (IQR)</td>
<td>58 (40-67)</td>
<td>53 (39-61)</td>
<td>0.71</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>7:19</td>
<td>9:25</td>
<td>0.99</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>13</td>
<td>13</td>
<td>0.36</td>
</tr>
<tr>
<td>NZ Māori</td>
<td>3</td>
<td>7</td>
<td>0.49</td>
</tr>
<tr>
<td>Polynesian</td>
<td>5</td>
<td>4</td>
<td>0.48</td>
</tr>
<tr>
<td>Fijian</td>
<td>5</td>
<td>4</td>
<td>0.48</td>
</tr>
<tr>
<td>Rheumatological diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>12</td>
<td>13</td>
<td>0.54</td>
</tr>
<tr>
<td>RA</td>
<td>5</td>
<td>8</td>
<td>0.69</td>
</tr>
<tr>
<td>Other DMARDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17</td>
<td>26</td>
<td>0.35</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 ±18 kg</td>
<td>78± 29 kg</td>
<td>0.57</td>
</tr>
<tr>
<td>AZA dose:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended dose</td>
<td>6</td>
<td>13</td>
<td>0.60</td>
</tr>
<tr>
<td>Higher dose</td>
<td>18</td>
<td>10</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Lower dose</td>
<td>2</td>
<td>11</td>
<td>0.37</td>
</tr>
</tbody>
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### Dose escalation regimen:

<table>
<thead>
<tr>
<th></th>
<th>Too quickly</th>
<th>Guideline</th>
<th>No clear plan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>8</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>20</td>
<td>0.60</td>
</tr>
</tbody>
</table>

### WCC:

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post drug exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.5±2.7</td>
<td>2±0.8</td>
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<tr>
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<td>7.5±3</td>
<td>8±3.9</td>
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### Neutrophil:

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<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post drug exposure</th>
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<tr>
<td></td>
<td>5.3±2.6</td>
<td>0.9±0.5</td>
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<td>5±3.5</td>
<td>5.5±3</td>
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### Discussion

This study reviewed local practice of AZA dosing, frequency of pre-treatment TPMT testing, and evaluated AZA-related toxicity in a select group of rheumatologic patients.

Our study shows that BSR guideline for initial dosing regimen was followed in 32% cases and the dose increment regimen was followed in 19% cases. TPMT test was requested in six (10%) patients only; three had low TPMT level requiring reduced dose of AZA.

Available data suggests that by optimizing the maximum dose of AZA (between 0.75 and 3 mg/kg/day), depending on TPMT testing (with a drastic reduction in dosage for patients homozygous for mutant TPMT alleles), considerable cost savings can be made by avoiding hospitalization and rescue therapy for leucopenic events.

In treating rheumatological disease, the commonest cause for withdrawal of AZA is lack of therapeutic effect. This study has shown AZA was prescribed in low dose in 22% of patients and the drug was stopped in five patients (13%) as considered to be ineffective.

One important observation in our study was the high rate of toxicity (43%) necessitating either the withdrawal or dose reduction of the AZA. However, this was not unusually high compared to observations reported in some other published studies.

In all patients, the toxicities were reversible on discontinuation of AZA treatment.

Pre-treatment measurement of TPMT activity has a role in identifying the 1 in 300 patients who are at risk of severe myelosuppression and also to identify the heterozygote intermediate individual who are at risk of early leucopenic episodes when treated with standard thiopurine dosages. Thus knowledge of TPMT status warns of early bone marrow toxicity.

In our study there was no observed consistency in requesting TPMT level prior to initiation of AZA, despite reported benefits of pre-treatment testing and adverse consequences related to non-testing. Of the 6 patients who were tested for TPMT, had AZA dose adjustment accordingly, none had adverse events.

The proportion of patients who could have avoided AZA related toxicities if screening TPMT tests were carried out cannot be inferred from our data. We assume this would be significant and translate into substantial cost saving by preventing toxicity related hospitalizations. Economic analysis has indicated that the prevention of myelo-
suppression in TPMT homozygotes, by adjusting thiopurine dosage is cost-benefitial. 21

Intracellular level of thiopurine metabolites, 6-TGN and 6-MMP can also be used as a guide to optimize drug dose. The therapeutic window of 6-TGN levels for optimal treatment of rheumatic disorders remains to be determined.

In summary, our data suggest a need for greater awareness, both regarding the practice of guideline based dosing regimen of azathioprine as well as TPMT test as a pre-treatment assessment tool to avoid life-threatening myelosuppression.

Competing interests: None known.

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Fibrates plus betaine: a winning combination?

Michael Lever, Peter M George, Sandy Slow, Jane L Elmslie, Brett I Shand, Russell S Scott, Stephen T Chambers

Abstract

Because most of the cardiac risk remains despite successful statin therapy there has been renewed interest in fibrate therapy for persisting hyperlipidaemia. Fibrate therapy lowers triglycerides but causes the urinary loss of betaine, which is an essential metabolite that is involved in osmoregulation, in methyl group metabolism, and which also affects lipid partitioning in the body. Loss of betaine is associated with an elevation of homocysteine and may compromise the potential benefits of fibrate therapy. However, betaine deficiency could be easily and inexpensively corrected by concurrent betaine supplementation. Clinical trials of combinations of betaine and fibrate, to complement statin therapy, are needed to determine the value of these agents in reducing the residual cardiovascular disease risk.

In a 2007 viewpoint article in this Journal, Benatar and Stewart¹ posed the question “Is it time to stop treating dyslipidaemia with fibrates?”. Their main points were that the success of statin therapy for dyslipidaemia made fibrates redundant, and that there was only equivocal evidence for decreased mortality with fibrate therapy.

Although they did not question the safety of fibrates, others have; this safety has been reviewed and affirmed²,³ and the case made for the use of fibrates in conjunction with statins, especially for the treatment of combined dyslipidaemia in patients with the metabolic syndrome or Type 2 diabetes, elevated plasma triglycerides and low HDL-cholesterol.⁴⁻⁸

Statins are well-known to be highly effective, but despite optimal treatment with statins and while achieving LDL-cholesterol treatment goals, 65–75% of the cardiovascular disease risk persists.⁸,⁹ It is now accepted that fibrates reduce the risk in patients with persistent elevated triglyceride and low HDL-cholesterol which persist even with high doses of statins.⁴,⁶,⁹ Prospective studies to quantify the clinical value of these agents are still in progress.

One of the concerns raised about fibrate therapy is the apparent effect on renal function, and in particular the elevation of plasma homocysteine. The commonly observed rise in plasma creatinine and homocysteine has been interpreted to indicate the apparent impairment of renal function, although these changes may not be associated with a change in the glomerular filtration rate.¹⁰

In the FIELD study (on patients with Type 2 diabetes) fenofibrate was found to reduce the incidence of renal complications,¹¹ and fibrates decrease microalbuminuria.¹² Nevertheless the elevation in homocysteine has been suggested as a limitation on the effectiveness of fibrates¹³ although the implied causal connection has been questioned.¹⁴
We have shown that the elevation of homocysteine by bezafibrate is associated with a greatly increased excretion of betaine in the urine. A probable primary renal effect of fibrates is to increase betaine excretion. The fractional clearance of betaine in these patients is often in excess of 100%, implying an active process, and this contrasts with normal betaine excretion which is minimal even after a betaine load (< 2% of dose).

It is likely that the effect on betaine excretion is particularly pronounced in patients with dyslipidemia or other features of the metabolic syndrome, many of whom may lose excessive betaine without drug treatment, and since this population is the one that is most likely to be prescribed fibrates, it is not surprising that New Zealand patients being treated with bezafibrate are losing so much betaine. Although betaine loss from fibrates is variable the daily loss through the urine exceeds the normal dietary intake of betaine in some patients; the median intake of the New Zealand population is about 220 mg/day.

Betaine is probably the most important osmolyte used by tissues for cell volume regulation, and additionally it functions as a store of methyl groups which are needed for the synthesis of creatine phosphate, phospholipids and for the epigenetic control of gene expression. Excessive betaine loss means that more choline must be oxidized to betaine to correct the betaine deficit, thus placing stress on the supply of choline, which in itself is an essential nutrient with many important biological functions.

Betaine can be easily replaced by supplementation. It is a natural by-product of the sugar beet industry, and long-term betaine supplementation is safe and socially acceptable. Health food shops often market betaine, also called “trimethylglycine” (TMG), as a nutritional supplement with extravagant claims for its benefits in a wide range of diseases and although most of these have not been substantiated by controlled trials, there are good grounds for believing that the supply of betaine is relevant to health.

Betaine is widely used in the animal industries as a long-term additive to animal feeds because this decreases body fat and increases the proportion of lean meat. Comparable long-term supplementation data is not available for any human population, but there is cross-sectional evidence that plasma betaine negatively correlates with important lipid cardiovascular risk factors such as plasma triglycerides, percent body fat and especially non-HDL cholesterol.

Betaine appears to affect the partitioning of lipids between tissues and blood, and limitations in the supply of betaine are probably a feature of the metabolic syndrome. It is also well-established that modest betaine supplementation lowers plasma homocysteine in humans. The betaine supply is the main determinant of non-fasting homocysteine, and we believe that the loss caused by fibrates is the main reason why fibrate therapy is associated with elevations in plasma homocysteine.

The interaction between betaine and lipids means that the loss of betaine induces a betaine deficiency which will also compromise the effectiveness of the fibrate in improving the lipid profile. Therefore, we conclude that fibrate therapy combined with betaine supplementation should be an attractive therapeutic option.

The level of supplementation that is added to pig and poultry feed corresponds to about 2 gm betaine a day in a human population, or about ten times the median daily
New Zealand intake. Although the dietary betaine intake can be raised by increasing the consumption of whole wheat products and high betaine vegetables of the beet family, long-term intakes of more than about 850 mg/day cannot be achieved by dietary modification alone (Elmslie, unpublished data).

Large increases in dietary betaine intake are likely to be associated with substantial increases in total energy intakes, but we have shown that dietary betaine and betaine supplied in the form of supplements have similar effects. Much higher levels of supplementation than those proposed have been used in human populations without ill effects. Such modest supplementation would be easy to achieve, and is close to that which has been shown recently to improve athletic performance. The cost of supplementation would be less than $NZ0.50 per day. This level of supplementation may be beneficial by itself, but if combined with fibrate it would be expected to completely compensate for the increased betaine loss.

A predicted marker of compensation should be lowered plasma homocysteine, which in many of these patients is presumed to be a marker of betaine deficiency. This should remove one of the concerns about using fibrates, and could be recommended on the basis of present evidence, however there will still be a need for prospective studies to see if the combination of fibrate and betaine delivers the long-term health outcomes that fibrate treatment would be expected to achieve, but without the equivocation in the results of previous trials. The combination should offer benefits that are complementary to those of statins, and answer the question posed in 2007 by Benatar and Stewart.

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References:


Axillary breast cancer in a Nigerian woman

Emmanuel Sule, Emmanuel Akpo, Afeyodion Akhator, Darlington Obaseki

Abstract

Ectopic breast cancer is rare and diagnosis is commonly delayed. We report the case of a 34-year-old Nigerian woman with a locally advanced invasive ductal carcinoma in the axillary breast. She underwent an axillary mastectomy and is due to receive adjuvant chemotherapy and radiotherapy. The management of this patient is discussed in relation to existing medical literature on the subject.

Ectopic breast cancer arises from aberrant tissue or supernumerary breasts. Ectopic tissue occur along any point of the mammalian ridge following failure of the mammalian ridge regression in embryologic development. It has been estimated that such breast tissue occurs in up to 6% of the general population. It commonly occurs in the axilla and may include pectoral breast components of the glandular tissue, nipple and areola. These areas are subject to all the physiological changes and diseases of the normal breast including malignant change.

Ectopic breast cancer is rare and estimated at 0.3% of all breast cancers. An increased risk for ectopic breast cancer from aberrant breast tissue was suggested by one study. This increased risk has not being reproduced in other studies.

Case report

A 34-year-old southern Nigerian lady presented with a left axillary swelling of 4 months’ duration. The swelling was initially painless but became painful in the last 2 months. Her menarche, age at first confinement, parity, and breastfeeding histories could not be ascertained from the records. She did not use oral contraceptive pills.

There was no family history of breast cancer. The patient had previously received antibiotics for an axillary abscess but with no effect. General examination was unremarkable. She had bilateral axillary breasts with a hard swelling in the left axillary breast (Figure 1).

Swelling involved the entire axillary breast, which was 6 cm in largest diameter, hard, and with some tenderness and fixity. There were palpable axillary lymph nodes around the tumour. An axillary mastectomy with lymph nodes excision was done. Histology showed an invasive ductal carcinoma (Figures 2A and 2B) with positive axillary lymph nodes. Hormonal therapy with tamoxifen was commenced.

The patient will receive chemotherapy and radiotherapy.
Figure 1. Clinical picture of axillary breast cancer

Figure 2A. Malignant epithelial neoplasm with glandular differentiation

Figure 2B. Foci of sweat gland acini and ducts as well as adjacent breast lobular acini
Discussion

The relatively obscure location of ectopic breasts is a contributory factor in the delayed diagnosis of ectopic breast cancer. Its rarity also contributes to a low index of suspicion for the physician. Instead, benign diagnoses of axillary swellings including axillary lymph node, sebaceous cyst and lipoma are commonly entertained.6

In our case, an earlier diagnosis by a primary care physician of an axillary abscess caused a delay in her referral to us. We advocate a low threshold for fine needle aspiration cytology or biopsy for swellings occurring in an ectopic breast to curb delayed diagnosis: as singular reliance on clinical diagnosis may cause delay.7

The tumour commonly presents with axillary lymph node metastases exemplified in our case. This is explained by early dissemination to axillary lymph nodes due to close proximity and delayed diagnosis of this obscure and uncommon disease.7

Evans et al analysed 82 reported cases spanning nearly 6 decades out of which 45 were followed up, half of these patients had recurrences within a year. Only 4 long-term survivors were reported, one of whom had adjuvant chemotherapy.7 Although this review series had largely dismal outcomes, the relative absence of adjuvant chemotherapy in this series must be considered when reporting the high recurrence and low survival. Comparable outcomes are obtained when ectopic breast cancer is matched stage for stage with breast cancer.4

The primary breasts in our case were normal bilaterally. Axillary breast cancer usually occurs at the exclusion of the primary breast.1 However, subsequent cancer in the ipsilateral pectoral breast was noted in three patients previously diagnosed with axillary breast cancer in a series by Marshal et al.1 Although the nature of relationship between the disease entities was not concluded in these cases, the occurrences were exceptionally noted.2

The tumour in our case was attached to the axillary floor and skin with lymph node involvement indicating local advancement. The history indicated an observed duration of 4 months. This brings to the fore the early lymph node involvement and thus metastatic potential of the disease. This is attributed to its proximity to axillary lymph nodes with associated prognostic implications.7

Our case had an axillary mastectomy with excision of lymph nodes. The primary breast was spared. In the large series by Evans et al, radical mastectomy involving the axillary and primary breast did not confer any survival advantage over a more limited axillary mastectomy with lymph node dissection/radiotherapy.7 This usually correlates with non-involvement of the ipsilateral primary breast. However screening of the ipsilateral breast using mammography and MRI is advised.2

Adjuvant chemotherapy is due for this case. Although its role has not being studied in large series, the treatment model for axillary breast cancer is fashioned after that for primary breast cancer, as they are embryologically related. The axillary lymph node involvement in our case necessitated systemic treatment. However chemotherapy and radiotherapy adjuvants has also been advised for node-negative disease.8

Radiotherapy to the breast with a boost to the axilla has been advised by some workers.2 Its significance in the management of this rare cancer is yet to be determined.7
Conclusion

Axillary breast cancer awareness should be promoted among healthcare professionals and the lay public. We advocate a low threshold for fine needle aspiration cytology or biopsy for axillary lumps. Singular reliance on clinical diagnosis may cause delay in diagnosis.

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References:

Pituitary involvement in Langerhans-cell histiocytosis

Daniel Garofalo, Rick Cutfield

A 21-year-old Māori male presented to hospital with a flu-like illness, fever and bilateral otitis externa. On examination he was overweight and hypogonadal (Tanner stage 2) with gynaecomastia. On further questioning he had experienced polyuria and polydipsia since high school.

Over the last few years he had presented to his family doctor with persistent, recurrent scalp lesions resembling an infected eczema. Assessment of pituitary function showed a testosterone level of 0.8 nmol/L (10-28), LH and FSH less than 1 IU/L (1–9), T4 9.6 pmol/L (9–19), T3 2.3 pmol/L (2.5–6), TSH 1.0 mU/L (0.4–4), 9 am cortisol 296 nmol/L (200–700), IGF-1 less than 25 ng/mL (110–350), and prolactin 80 mU/L (10–650). Urine osmolality after overnight water deprivation was 36 mmol/kg (50–1200).

A magnetic resonance (MR) scan showed a hypothalamic mass (Figure 1) for which differential diagnoses included a neoplastic process (primary or secondary) or an infiltrative disorder (such as sarcoidosis or histiocytosis). A chest X-ray was reported as normal, but a computed tomography (CT) scan of the chest revealed multiple cystic lesions compatible with Langerhans-cell histiocytosis (LCH).

Diagnosis was eventually confirmed by biopsy of the scalp lesions. He was treated for his endocrine deficiencies with DDAVP and thyroxine. For his LCH he received vinblastine, prednisone, 6-mercaptopurine and methotrexate, according to international guidelines.¹

Figure 1. Irregular suprasellar mass measuring 1.7 cm in transverse diameter, with diffuse enhancement with gadolinium.
Initially he had a good clinical response and a partial radiological response, but subsequently relapsed, requiring prolonged maintenance therapy with azathioprine. He is currently clinically stable.

A second patient, an 18-year-old Pacific Island male, presented with a flu-like illness, myalgias, polyuria and polydipsia. A routine battery of blood tests showed mildly deranged liver function tests (mixed pattern). An overnight water deprivation test was strongly suggestive of diabetes insipidus (DI), with a urine osmolality of 106 mmol/kg and a serum Na of 148 mmol/L (135–145).

Pituitary function tests showed testosterone 12.9 nmol/L (10–28), FSH 1.9 IU/L (1–9), LH 3.1 IU/L (1–9), T4 11.4 pmol/L (9–19), TSH 1.9 mU/L (0.4–4), 9am cortisol 400 nmol/L (200–700), and prolactin 262 mU/L (10–650).

An MR scan showed loss of normal T1 high signal in the posterior pituitary (Figure 2) consistent with idiopathic DI; however a minimally bulky pituitary stalk with normal signal characteristics and measuring 3.5 mm was also noted. Replacement therapy with nasal DDAVP was started. He was followed in clinic and 11 months later he presented with left-sided headaches and nasal congestion.

Repeat endocrine function was normal except for a significant reduction in the testosterone levels down to 1.1 nmol/L. A repeat MR was carried out, which showed no changes in the pituitary stalk but revealed a lobulated enhancing lesion within the sphenoid sinus and possible early extension into the left cavernous sinus region.

A biopsy of this lesion confirmed the diagnosis of LCH. Treatment with vinblastine and prednisone has resulted in good clinical response and partial reduction in the pituitary stalk (to 2.0 mm) and in the sphenoid mass (currently 2 years since diagnosis).

Figure 2. Loss of normal T1 high signal in the posterior pituitary (arrow) consistent with idiopathic diabetes insipidus
Discussion

Central diabetes insipidus (DI) can be idiopathic (30-50%), familial, or due to physical causes (trauma, fracture, surgery), tumours (germinoma, lymphoma) or, occasionally, infiltrative disorders such as LCH, sarcoidosis, lymphocytic hypophysitis and Wegner’s granulomatosis.

LCH is characterised by a clonal proliferation of histiocytes with a recognised but unexplained predilection for the hypothalamus-pituitary axis (HPA). In autopsies, infiltration of the HPA has been reported in up to 50% of cases of LCH. DI is the most common endocrine abnormality, reported in 15–50% of cases of LCH, followed by growth hormone deficiency. TSH and ACTH deficiency usually only develop in the setting of panhypopituitarism.

Pituitary involvement has been attributed to infiltration by histiocytes, scarring, or antibodies against vasopressin. In 6–40% of cases, DI can predate the diagnosis of LCH by months or years. DI is more common in patients with multisystem disease, bone disease (particularly the skull), and lung, liver and ENT involvement.

Radiological findings include lack of the posterior pituitary bright spot on T1 images (undistinguishable from idiopathic DI) with or without infundibular thickening as in our second case (bearing in mind a normal stalk on MR does not exclude an infiltrative disorder), a partial or completely empty sella or a hypothalamic mass, as in our first case.

Patients presenting with central DI should have a careful clinical history taken that includes questions about otitis externa, skin lesions, and bone pains. The laboratory work-up will include tests for pituitary function, an MR scan of the pituitary and relevant tumour markers (i.e. alpha fetoprotein and beta-HCG).

The search for extracranial lesions should focus on a dermatological survey, ENT exam, bone survey and a chest x-ray. The latter may reveal lesions suggestive of LCH or of other conditions also associated with central DI (Wegener’s granulomatosis, tuberculosis, sarcoidosis).

Extracranial lesions should be biopsied where possible. If no extracranial abnormalities are found, a CSF sample should be obtained for tumour markers and cytology. If the findings are non-contributory and the infundibulum measures more than 7 mm, a pituitary stalk biopsy should be strongly considered. If the infundibulum is less than 7 mm, regular clinical and radiological follow-up may be appropriate.

Treatment should be conducted by a specialised oncology unit, using internationally agreed protocols.

LCH has an unpredictable course, ranging from spontaneous remission to a rapid course with a fatal outcome. In most cases it will behave as a chronic disease with remissions and relapses. Mortality is about 20%. Adverse prognostic factors include older age, multi-organ dysfunction, the number of sites with active disease and response to therapy.

With more frequent and earlier use of chemotherapy in LCH, the incidence of DI appears to be getting lower, indicating a possible preventive effect of cytostatics.
Patients with DI will almost certainly develop multisystem disease, and once DI is established it is irreversible.³

The majority of patients with DI will eventually develop an anterior pituitary hormone defect.⁹ A rare but devastating complication of LCH, neurodegenerative CNS disease, appears to be more prevalent among patients with DI.⁵

In summary, LCH needs to be considered in the differential diagnosis of central DI secondary to infiltrative disorders, especially in younger patients. In these cases, imaging of the chest can yield important diagnostic information. DI in this setting is irreversible and a poor prognostic marker for LCH.

As central DI secondary to LCH can present as ‘idiopathic’ DI, both clinically and radiologically, close follow-up of central DI labelled as ‘idiopathic’ is warranted.

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1. www.histiocytesociety.org
Combination NSAID-codeine preparations and gastrointestinal toxicity

Claire Evans, Teresa A Chalmers-Watson, Richard B Garry

A previously fit and well 35-year-old man was admitted with a haemoglobin concentration of 67 g/L, an albumin of 31 g/L, exertional dyspnoea, and lower leg oedema. He gave a history of daily epigastric pain for a year; worse on eating. He admitted to using over 100 Nurofen Plus per day for back pain.

Gastroscopy revealed an acute gastric ulcer with active bleeding in the pyloric channel, severe gastritis and post-bulbar duodenitis with active bleeding (Figures 1&2).

The patient was prescribed a reducing codeine dose as an opiate substitute for the Nurofen Plus and received counselling for his addiction. Follow-up gastroscopy
showed healing of the ulcer, gastritis and duodenitis, however balloon dilation of the subsequent pyloric stenosis was required.

**Discussion**

Here we present one of four patients who have presented to our Service over the last 2 years with significant gastrointestinal pathology secondary to the gross overuse of combination non-steroidal anti-inflammatory drug (NSAID)/codeine products.

It is well documented that NSAIDs cause a plethora of adverse effects, including NSAID-induced enteropathy, but the addition of codeine to NSAIDs in such products increases their addictive nature.

In the 2007/08 New Zealand Alcohol and Drug Use Survey, the lifetime prevalence of prescription opiate abuse was estimated to be 2.3%. While data are not available regarding the abuse of over the counter codeine-containing products, addiction to these products has been of increasing concern.

In November 2009, in response to this concern, the Medicines Classification Committee recommended a change in the classification for all products containing under 15 mg codeine in combination with another pharmacologically active substance from pharmacy-only to a restricted product.

This reclassification as a pharmacist-only medication is hoped to reduce the availability of these products as a drug of abuse and thus reduce the clinical consequences such as were seen in this patient. This information was included in the Prescriber Update February 2010.

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**Correspondence:** Associate Professor Richard Gearry, Department of Medicine, University of Otago, Christchurch, Consultant Gastroenterologist, Christchurch Hospital, PO Box 4345, Christchurch 8140, New Zealand. Fax: +64 (0)3 3640935; email: Richard.Gearry@cdhb.govt.nz

**References:**

2. Ford C. Dependence on OTC drugs, Over the counter drugs can be highly addictive; Letters BMJ. (5 May) 2007;334:917–918
3. Drug Use in New Zealand: Key Results of the 2007/08 New Zealand Alcohol and Drug Use Survey; Ministry of Health; 2010.
4. Minutes of the November 2009 Medicines Classification Committee Meeting, www.medsafe.govt.nz
A Case of Caesarian Section

By Drs P. W. Hislop, M.D. (Geraldine) and P. Clennell Fenwick, F.R.C.S.E. (Christchurch). Published in a NZMJ 1910 issue.

In April, 1908 I performed caesarian on this patient and tied and divided the fallopian tube on each side. The patient made an uninterrupted recovery and left the home three weeks after operation in excellent health. She returned to consult me at the end of 1909 believing that she was again pregnant.

On examination the fact was established without doubt and caesarian section was recommended as she laid undergone the operation so well before. On July 2nd, 1910, she was admitted into the nursing home and a bougie was passed into the uterus. The following morning slight labour pains had commenced, and Dr. Mill gave chloroform and we opened the abdomen through the old scar. A firm adhesion between the anterior abdominal wall and the uterus was found and divided. Several wide adhesions between the omentum and uterus required careful attention and then a search was made for the old cicatrix in the wall of the uterus. We could not discover this so the uterus was opened and the child extracted.

The placenta was peeled off easily and the uterine wound closed with fourteen silk sutures. After an injection of ernutin the uterus contracted well and the tubes were then examined to discover the reason for the recurrence of pregnancy. Apparently they were both normal. It was not possible to detect the scar where they were divided at the first operation. To make things certain, both ovaries were removed.

The child, a female, weighed 6 ¼ pounds. It took the breast the same evening. There was no sickness after operation but the patient complained of very severe after-pains for which morphia was required. A rise of temperature occurred on the 6th day due apparently to one small stitch abscess.

The interest of this case was the recurrence of pregnancy after the fallopian tubes had been carefully divided. My colleague was sceptical and suggested that I had not divided the tubes on both sides but I recalled to his memory an incident which proved that we had taken especial care to perform this measure properly as I remembered that we had each divided one tube.
Increased incidence of hypospadias and cryptorchidism in the sons of dibutylphthalate-exposed NZ war veterans

MB Carran & IC Shaw. Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch.

Dibutylphthalate (DBP) is an endocrine disrupting compound (EDC). EDCs have been implicated in human exposure effects including cryptorchidism, hypospadias and precocious puberty in girls\(^1\); however there is no definitive cause/effect evidence.

Members of the NZ Army stationed in Malaysia in the 1950’s and 60’s used DBP as an acaricide to prevent bush typhus which is transmitted by several ticks, including Tronbicula akamushi. DBP was painted onto the seams of the soldiers clothing before military operations and inevitably contaminated their skin from where it is known to be well absorbed. DBP-exposed NZ Malaysian veterans are therefore an interesting exposure cohort in which to study EDC effects.

A questionnaire survey of NZ Malayan Veterans’ Association members was conducted which sought to determine the frequencies of selected EDC exposure-associated disorders including cryptorchidism and hypospadias in the veterans, their children and grandchildren. The data were compared to the frequencies of the same disorders in the NZ population as a whole.

Eighty-six questionnaires were returned, of these 73 of the respondents were exposed repeatedly to DBT. The DBT-exposed veterans had a total of 77 male children. The incidence of hypospadias, and cryptorchidism in the male offspring cohort were 1.3% (i.e. 1 case) and 5.2% (i.e. 4 cases) respectively. The corresponding incidences in the NZ population are 0.28%\(^2\) and 3%\(^3\) therefore the incidence of EDC-associated disorders is greater in the male children of exposed veterans. This is the first evidence of a causal link between exposure of human males to an EDC and biological effects.

Acknowledgement: MBC was supported by a Summer Scholarship 2009-2010 jointly funded by the University of Canterbury and the Tertiary Education Commission of New Zealand (TEC).

References:

A new multipurpose cancer zapper

TF Cronje¹, PT Gaynor¹, G Lau². ¹Department of Electrical and Computer Engineering, University of Canterbury, ²Department of Radiology, Dunedin Public Hospital, Dunedin.

A cancer cell zapper under development will offer two modalities of therapy, namely electroporation (EP) and radio frequency ablation (RFA). RFA has been used in surgical practice successfully for small liver tumours. EP renders cells temporarily permeable to dosing of large molecules including chemotherapy drugs like bleomycin and cisplatin, or genetic materials. EP is still mainly in an experimental phase, although some standard treatments for superficial cancers have been adopted (and defined as electrochemotherapy). EP is also used quite regularly in vitro for cell fusion, cloning and genetic manipulation. We believe that EP as an additional modality during the RFA procedure will raise the success rate of the treatment.

The main thrust of the project currently is in the design of the electroporator. This will also enable design of new RFA apparatus, due to similarities in circuit structure. Our electroporator will be ultimately used to treat a volume of tissue in vivo, thus is required to generate high voltages of up to several thousand volts. We also want to make it unique in its ability to work across a wide range of frequencies (up to several MHz) and voltages, be both bipolar or monopolar (in terms of voltage) and also offer different waveforms. Commercial electroporators lack the majority of these features as they mostly offer only monopolar rectangular pulses. The ability to vary frequency will also benefit RFA effectiveness, where commercial RFA systems operate at fixed frequencies.

Several development circuits have been built and tested electrically. We are currently working on a prototype half-bridge pulser as major building-block. Completion of the prototype will allow in vitro testing on agglomerations of cultivated cancer cells, attempting to show an improvement in efficacy of chemotherapy using a rather unique regime of bipolar pulses at several frequencies compared to previous studies by other groups.

Optimisation of energy thresholds in spectral X-ray imaging for biological material discrimination


Discrimination of materials in computed tomography (CT) is based on their different X-ray attenuation, displayed in the shades of gray in normal CT images. Exploiting the energy dependency of these attenuation profiles, dual-energy CT provides an improved characterisation of tissues by applying two distinct X-ray spectra, typically generated using different kV settings of the X-ray tube. Modern photon counting X-ray detectors with energy resolving capabilities are able to record the energy in addition to the spatial positions of the detected photons. One of the appealing features
of these detectors is the intrinsic energy thresholds that enable the classification of photons into multiple energy bins. Multi-energy or spectral X-ray CT hence promises a better delineation of materials by accessing the extra information currently unavailable to the conventional and dual-energy CT.

It has been shown that the choice of binning can affect the performance of material decomposition [1, 2]. In this work, the accuracy of discriminating different biological materials upon optimising the positions and widths of the energy bins is investigated. A way of describing the conspicuity of materials by assessing the standard deviations associated with thickness measurements is proposed. A metric is setup and tested against simplistic cases before being applied to realistic examples. Our initial results indicate that optimal energy threshold arrangement can improve the ability to discriminate materials substantially (about 20% reduction in the standard deviations of thicknesses) compared to equidistant windows. In the future, the results will be verified using Monte Carlo simulations and by means of physical measurements.

References:


A highly predictive metabolic model for glycemic control of critically ill patients

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Hyperglycaemia is prevalent in critical care due to the stress of patient’s condition, even without a previous history of diabetes. Model-based and model-derived tight glycemic control (TGC) methods, such as SPRINT, have shown significant reductions in ICU mortality, organ failure and cost. However, as computational capability and access improve, model-based TGC offers avenues for significant improvement if they can provide highly accurate predictions of the glycaemic outcome of an intervention.

This study presents a new highly predictive and comprehensive glucose-insulin dynamic system model for real-time TGC. Identification of critical population parameters is carried out parametrically, optimizing one hour forward prediction error. Validation is performed using clinical data from 173 critically ill patients on the SPRINT TGC protocol that received insulin while in the ICU and stayed for more than 72 hours. The model is assessed for both its fitting and, more critically for TGC, predictive performance, as measured in absolute percentage error.
The model achieves fitting error < 1% in all data from 173 patients. Median per-patient one hour ahead prediction error is a very low 3.05% [IQR 1.26, 6.54]% All identified population parameter values are within reported physiological ranges. Parameter sensitivity analysis further confirms the validity of limiting time-varying parameters to insulin sensitivity, \( S_{I}(t) \) only.

The model is capable of accurately capturing long term dynamics and evolution of critically ill patient’s glucose insulin response. It has a stronger physiological relevance and more detailed insulin kinetics in particular than prior models. All predictions up to the 90th percentile are within measurement error. These results indicate the model’s suitability as a platform for developing robust TGC strategies.

**Oxidation versus hyperoxidation of peroxiredoxins in human endothelial cells exposed to inflammatory oxidants**

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Typical 2-cys peroxiredoxins (Prxs 1-4) have a low-pK\(_{a}\) peroxidatic cysteine residue that is rapidly oxidised by hydrogen peroxide (H\(_2\)O\(_2\)) to a sulfenic acid. The oxidised cysteine can either hyperoxidise (to a sulfinic or sulfonic acid) or most often forms a disulfide bond with the resolving cysteine of an adjacent Prx molecule. This homodimer is reduced by the thioredoxin/thioredoxin reductase system while the hyperoxidised form is re-reduced in an ATP-dependent process by sulfiredoxin.

Few studies have investigated how Prxs might be specifically oxidised by other thiol-targeting oxidants, such as chloramines. Chloramines are formed as a result of the neutrophil oxidative burst. Neutrophil-derived HOCl reacts with amines to produce chloramines, which can in turn oxidise biological targets and contribute to inflammatory tissue damage. Prxs could act as favoured targets for chloramines and potentially protect cells from these inflammatory oxidants. We have characterized and compared the oxidation, hyperoxidation and regeneration of Prxs 1, 2 and 3 in human umbilical vein endothelial cells (HUVEC) treated with cell-permeable chloramines, HOCl or H\(_2\)O\(_2\).

Our findings show that HUVEC peroxiredoxins are readily oxidised by each oxidant examined, but are hyperoxidised only with H\(_2\)O\(_2\) treatments. A lack of Prx3 oxidation by glycine chloramine suggests that this oxidant does not easily gain access to the mitochondria. Minimal losses in cell viability and thioredoxin reductase activity indicate that Prx oxidation is likely via a direct mechanism. Recovery of the thiol from the disulfide requires less than 30 minutes, while the hyperoxidised form is recycled after several hours in medium.

Thus, exposure of endothelial cells to inflammatory oxidants results in reversible Prx oxidation; this could implicate the Prx family in potentiating cellular responses during inflammation.
Validation of a virtual trial method for tight glycemic control in intensive care

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Virtual trials based on a metabolic system model and clinical data have been used by our research group to develop tight glycemic control (TGC) strategies. Virtual patients are created from retrospective data [1, 2], upon which new strategies can be tested. While clinically tested in several cases, the underlying method has never been fully validated. The aim is to validate the model and methods used for virtual trials using clinical data from two matched cohorts from an independent TGC trial.

A retrospective analysis using a 211 patient subset from the Glucontrol trial conducted in Liege, Belgium. Glucontrol-A (N=142) targeted 4.4-6.1 mmol/L and Glucontrol-B (N=69) targeted 7.8-10.0 mmol/L. Cohorts were matched by APACHE II score. The Glucontrol-A cohort was slightly older (p=0.0352). Virtual trial methods are used for self-validation (A protocol on Group A virtual patients; and B protocol on B virtual patients) and cross-validation (A protocol on Group B virtual patients; and B protocol on A virtual patients). These tests show whether virtual trials accurately capture individual patients.

Intra-patient metabolic variability was very similar across median, IQR and 90% CI of the model-based insulin sensitivity range for both cohorts. Model fit errors were very small (<0.25%) for both cohorts, indicating model fitness. Cohort median blood glucose was within 5% (0.3-0.5 mmol/L) of the clinical values for self and cross-validation tests on both cohorts. Distributions were within 1-10% across all glycaemic levels.

Self-validation indicated clinically insignificant errors due to model and/or clinical compliance. Cross-validation showed that virtual patients created from clinical data are independent of the clinical inputs used to generate them and can represent any similar cohort. Thus, virtual patients and in-silico virtual trials are validated in their ability to accurately simulate, in advance, the clinical results of a TGC protocol, enabling rapid in-silico protocol design and optimisation.

References:
Skin peptide defences of African Clawed Frogs (*Xenopus laevis*) and New Zealand *Litoria* frogs against bacterial dermatosepticemia

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An important mechanism of the innate immune defence of frogs is secretion of antimicrobial peptides. The activity of frog skin peptides was investigated against seven bacterial pathogens associated with bacterial dermatosepticemia, a fatal, infectious disease of frogs. These frog pathogens are also considered as potential zoonotic pathogens of humans and are: *Aeromonas hydrophila*, *Chryseobacterium meningosepticum*, *Citrobacter freundii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Serratia liquefaciens*. Activity was also assessed against a frog bacterial saprophyte *Lactococcus lactis* and human clinical isolate of *E. coli* (ATCC 25922). Natural peptide mixtures and single peptides from skin secretions of three frog species: African Clawed Frogs (*Xenopus laevis*), Green and Golden Bell Frogs (*Litoria aurea*) and Southern Bell Frogs (*Litoria raniformis*) were tested for antibacterial activity.

The peptide mixtures and single peptides of all three tested frog species showed inhibitory activity against *C. freundii*, *C. meningosepticum*, *K. pneumoniae* and *P. aeruginosa* and *L. lactis* and *E. coli* (ATCC 25922) in vitro indicating a likely protective function (1,2). Three pathogens *A. hydrophila*, *P. mirabilis* and *S. liquefaciens* are abundant components of the skin microbiota of healthy frogs and were found to be resistant to the peptide mixtures of all three frog species tested (1). It was shown that one pathogen, *A. hydrophila*, had the ability to secrete proteases which could inactivate skin peptides (3). Thus while skin peptides could function against several pathogens, some pathogens might have co-evolved to resist skin peptides.

The potential for use of such peptides and their derivatives in human medicine is worthy of consideration.

References:

Antidepressants and pregnancy

The authors of this study and an editorial commentator agree that pregnancy is often complicated by depression. This may require pharmacological treatment and the issue addressed here is whether antidepressant drugs increase the risk of spontaneous abortion. They used a nested case-control design, whereby they obtained data on 5124 women who had a spontaneous abortion. Of the 5124 women, 284 (5.5%) had had a prescription filled for an antidepressant. Each case was matched by randomly selecting 10 controls from their data bank. They report that the use of antidepressants (especially paroxetine, venlafaxine or the combined use of different classes of antidepressants) during pregnancy was associated with an increased risk of spontaneous abortion.

The overall odds ration (OR) was 1.68, but the OR for combined use of antidepressants was 3.51. The editorial commentator was not overimpressed pointing out that a filled prescription does not necessarily mean that the drug was taken. On the other hand she mentions a prospective randomised trial, which featured her as an author, which reached identical results.

CMAJ 2010;182, 1031–7, & 10107–18.

Screening mammography—benefit and harm analysis

This paper reports the results of the Norwegian breast cancer screening programme which was started in 1996. Screening was offered every 2 years to women aged 50–69 years. The authors report that the death rate from breast cancer has been reduced by 7.2 deaths/100,000 person years. However they produce data to show that only one-third of this is due to screening, the other two-thirds is due to advances in breast cancer awareness and treatment.

An editorial commentator offers a benefit-harm analysis based on the relative reduction in mortality reported in this paper (10%). His analysis—if 2500 women have screening over 10 years, one woman would avoid dying of breast cancer. Up to 1000 women will have at least one false alarm and about half of these will have a biopsy.

And breast cancer will be overdiagnosed in 5–15 women and treated needlessly.


Various treatments for rotator cuff tears

A common complaint in the elderly. The authors of this review suggest that more than half of all adults over 60 years of age may have a partial or complete rotator cuff tear at some time.
Their review is based on 137 studies in which patients with imaging-confirmed lesions were treated in a variety of ways. They conclude that functional outcomes did not differ between open versus mini-open repair, mini-open versus arthroscopic repair, arthroscopic repair with versus without acromioplasty, or single-row versus double-row fixation, whatever that means.

However non-operative treatment involving analgesia and physical therapy had similar outcomes. So they reach the conclusion that evidence on the comparative effectiveness and harms of various operative and nonoperative treatments for rotator cuff tears is limited and inconclusive.


Exposure to oral bisphosphonates—a cause of oesophageal pathology?

Bisphosphonates inhibit osteoclast-mediated bone resorption and are mainly used to prevent or treat osteoporosis, especially in postmenopausal women. Consequently, a lot of older women are on such treatments, alendronate most commonly. It is known that this medication can cause serious oesophagitis in some.

Indeed, crystalline material that resembles ground alendronate tablets has been found on biopsy in patients with bisphosphonate-related oesophagitis. It is known that these abnormalities persist after the inflammation has subsided. It has been suggested that this may predispose the patient to develop oesophageal cancer.

This review of data from the UK General Practise Research Database compares the incidence of oesophageal cancer in more than 40,000 subjects who were taking oral bisphosphonate with the incidence in a similar number not taking bisphosphonate. They found no significant association between the use of oral bisphosphonate and oesophageal cancer.


Homeopathy and the UK National Health System (NHS)

In February this year the House of Commons Science and Technology Committee concluded that homeopathy is a placebo treatment that deceives patients and could therefore damage the implicit trust between doctor and patient (BMJ 2010;340:c1091). Furthermore they recommended that the NHS should no longer fund such treatments and that such products should no longer be licensed.

The government noted the report but passed the buck to the local primary care trusts. And there the matter rests, with the homeopaths happy and others outraged. In particular, Professor Ernst, the professor of complementary medicine at the Peninsula College of Medicine is quoted as saying—“This is utterly incomprehensible and makes a mockery of the principles of evidence based medicine.” Gilbert and Sullivan could make something of this.

BMJ 2010;341:c4073.
Very cheap drinking in New Zealand: some alcohol is more affordable than bottled water and nearly as cheap as milk

There is a wealth of scientific evidence that policies affecting alcohol price are effective in influencing alcohol consumption, and hence reducing adverse outcomes due to hazardous alcohol use.\textsuperscript{1,2}

Lowered alcohol prices encourage consumption and can increase alcohol-related harms, as was found in Finland, where a decrease in excise tax in 2004 led to increased deaths from alcohol-related causes.\textsuperscript{3} Policies such as raising excise taxes, minimum pricing, incentives for low alcohol beverages/taxes on strength of alcohol and restriction on below cost sales and price based promotions can reduce consumption.

The public and taxpayers should particularly welcome such measures to reduce alcohol-related harm given that some of the interventions may be cost saving to government (e.g., alcohol taxation and advertising restrictions)\textsuperscript{4,5} or at least be relatively cost-effective.\textsuperscript{6}

This issue is pertinent for New Zealand, as these policies can be effective tools targeting the binge drinking culture that is placing strain on the health care system (especially emergency departments), the justice system and the private lives of many New Zealanders who live with the impacts of hazardous drinking.

Controls on price are particularly effective in targeting heavy drinkers, and youth, but are unlikely to significantly impact on the relatively ‘responsible’ drinker who consumes a glass or two of wine with dinner.\textsuperscript{7}

\textbf{Methods}—To better understand changes in the drinking culture in New Zealand over time, and how price could be an effective policy strategy in this country, we investigated temporal trends in alcohol affordability, using data collected by Statistics New Zealand (SNZ) for the Consumers Price Index (CPI). We also considered data on average hourly earnings from the New Zealand Income Survey, which collects detailed annual information on gross income from working age New Zealanders.\textsuperscript{8} For the CPI data, prices are collected monthly for alcoholic beverages. Data collectors from SNZ personally gather alcoholic beverage prices from outlets within the 15 main urban areas during a week-long period that ends around the mid-point of each month.\textsuperscript{9}

For comparison data on discounted beverage prices, we accessed a specific website which documents specials and discounts on alcohol offered from outlets throughout New Zealand (\url{www.lips.co.nz}), on 20 September, 2 October, and 9 October 2010.

The price per unit was calculated using the formula: “volume of container (litres) × % alcohol by volume (mL/100mL) × 0.789 = number of standard drinks” (obtained from a NZ Government website: \url{http://www.nzfsa.govt.nz/consumers/food-safety-topics/food-processing-labelling/food-labelling/fact-sheets/fs-2003-04-alcohol-labelling.htm}).
Results—The data show that the average price of alcohol has increased over the past ten years (Table 1) and the highest increase in percentage terms has been for a glass of beer at a licensed premise and for cask/white wine.

For comparison, the price of 2 litres of milk has also increased over this time, proportionately a little more than a litre of whisky or a dozen bottles of beer.

Table 1. Average cost ($) of alcohol, milk and bottled water in New Zealand 1999–2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Whisky (liquor store, 1L*)</th>
<th>Cask / white wine (supermarket &amp; liquor store, 3L, 30sd*)</th>
<th>Beer—1 dozen bottles (supermarket &amp; liquor store, ~3.96L, 12sd*)</th>
<th>Beer glass (licensed premises, 0.4L, 1.3sd*)</th>
<th>Milk—standard homogenised (2L*)</th>
<th>Bottled water, (0.75L*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>34.87</td>
<td>16.03</td>
<td>16.34</td>
<td>3.16</td>
<td>2.64</td>
<td>NA</td>
</tr>
<tr>
<td>2000</td>
<td>35.41</td>
<td>16.24</td>
<td>16.53</td>
<td>3.21</td>
<td>2.67</td>
<td>NA</td>
</tr>
<tr>
<td>2001</td>
<td>35.92</td>
<td>16.73</td>
<td>16.68</td>
<td>3.33</td>
<td>2.91</td>
<td>NA</td>
</tr>
<tr>
<td>2002</td>
<td>37.05</td>
<td>17.03</td>
<td>17.31</td>
<td>3.47</td>
<td>3.02</td>
<td>NA</td>
</tr>
<tr>
<td>2003</td>
<td>36.94</td>
<td>17.41</td>
<td>17.65</td>
<td>3.62</td>
<td>2.80</td>
<td>NA</td>
</tr>
<tr>
<td>2004</td>
<td>37.34</td>
<td>18.17</td>
<td>18.31</td>
<td>3.80</td>
<td>2.87</td>
<td>NA</td>
</tr>
<tr>
<td>2005</td>
<td>37.68</td>
<td>18.44</td>
<td>18.52</td>
<td>3.98</td>
<td>3.02</td>
<td>NA</td>
</tr>
<tr>
<td>2006</td>
<td>38.28</td>
<td>18.71</td>
<td>18.33</td>
<td>4.15</td>
<td>2.91</td>
<td>1.81</td>
</tr>
<tr>
<td>2007</td>
<td>39.41</td>
<td>19.39</td>
<td>18.43</td>
<td>4.33</td>
<td>2.80</td>
<td>1.85</td>
</tr>
<tr>
<td>2008</td>
<td>40.58</td>
<td>20.16</td>
<td>18.02</td>
<td>4.57</td>
<td>3.27</td>
<td>1.88</td>
</tr>
<tr>
<td>2009</td>
<td>42.01</td>
<td>20.83</td>
<td>18.98</td>
<td>4.84</td>
<td>3.22</td>
<td>2.00</td>
</tr>
<tr>
<td>2010</td>
<td>42.94</td>
<td>21.80</td>
<td>19.50</td>
<td>4.95</td>
<td>3.41</td>
<td>2.02</td>
</tr>
<tr>
<td>Overall % change (1999-2010)</td>
<td>18.8%</td>
<td>26.5%</td>
<td>16.2%</td>
<td>35.1%</td>
<td>22.8%</td>
<td>10.4% (2006-2010)</td>
</tr>
</tbody>
</table>

*Average over the quarters; sd = standard drink; NA = data not available for these years

Although the price of alcohol has increased over the past decade, the affordability of alcohol has actually increased, due to increases in average hourly earnings outstripping the percentage increases in alcohol prices. This is shown in Table 2 and Figure 1, which presents the minutes taken to earn sufficient alcohol to reach the legal blood alcohol limit (currently a blood alcohol limit of 80mg/dL), based on a conservative value of four standard drinks in each alcohol category for an average individual adult.

For example, in 1999, it would have taken a working person 16.4 minutes to earn enough money (if earning the average hourly wage) to buy sufficient whisky to become intoxicated, but in 2009, it would have only taken 13.2 minutes to achieve this.

Of particular note is the absolute affordability of cask wine—if this type of alcohol is used to achieve intoxication, it is particularly cheap, costing only $2.78 for an average working adult to be legally unfit to drive in 2009.
Table 2 Alcohol affordability in New Zealand over time (1999–2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>Average hourly earnings (gross)*</th>
<th>Minutes taken to earn enough wages to pay for sufficient alcohol to reach the legal limit for intoxicated driving** ($ needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$</td>
<td>Minutes $</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Whisky</td>
</tr>
<tr>
<td>1999</td>
<td>15.33</td>
<td>16.38 (4.18)</td>
</tr>
<tr>
<td>2001</td>
<td>16.30</td>
<td>15.87 (4.31)</td>
</tr>
<tr>
<td>2002</td>
<td>16.65</td>
<td>16.02 (4.45)</td>
</tr>
<tr>
<td>2003</td>
<td>17.82</td>
<td>14.93 (4.43)</td>
</tr>
<tr>
<td>2004</td>
<td>18.19</td>
<td>14.78 (4.48)</td>
</tr>
<tr>
<td>2005</td>
<td>19.24</td>
<td>14.10 (4.52)</td>
</tr>
<tr>
<td>2006</td>
<td>19.99</td>
<td>13.79 (4.59)</td>
</tr>
<tr>
<td>2007</td>
<td>21.35</td>
<td>13.29 (4.73)</td>
</tr>
<tr>
<td>2008</td>
<td>22.26</td>
<td>13.13 (4.87)</td>
</tr>
<tr>
<td>2009</td>
<td>22.98</td>
<td>13.16 (5.04)</td>
</tr>
</tbody>
</table>

* New Zealand Income Survey; **for the average person 4 standard units (120ml of whisky, 4 glasses (4 x 100ml) of cask wine at 12.5% alcohol, 4 x 330ml beer bottles at 4% alcohol).

Figure 1. Time trends in alcohol affordability in New Zealand (data as per Table 2)

Discussion—These results indicate how alcohol has become more affordable in this last decade and it is probably the cheapest recreational drug on the New Zealand market (though we do not have good data on average cannabis prices). However, our results for average affordability are somewhat simplistic in that we considered “gross hourly earnings” and New Zealand adults are subject to variable income tax rates.
(albeit with relatively little change in tax structures over this last decade). So it is likely that a few extra minutes would need to be added to the results in Table 2 for the “average” working adult to purchase the “average” priced beverage to reach intoxication levels.

But countering this is that price-sensitive consumers (especially youth) can easily purchase alcohol at way below the average prices in Table 2. For example, our searches (using the website www.lips.co.nz, see Methods) showed that 3 litres of white cask wine can be bought for as little as $16.99 (62c per standard drink at 11.5% alcohol; other specials on 13% alcohol content cask wine translate to 63c per standard drink) and a standard 750ml bottle of wine can sometimes be bought for $5 (65c per drink). Similarly, a litre of spirits can be bought for $25 (in two for $50 specials, 78c per standard drink for spirits containing 40% alcohol) and 12 bottles of 5% beer for $9.99 (64c per standard drink).

By way of comparison, a glass of milk (250ml) costs 43c using the average 2010 CPI prices and a glass of bottled water costs 67c. Thus a glass of wine or a bottle of beer can cost not much more than a glass of milk, and less than a glass of bottled water. Ready-to-drink (RTD) alcohol drinks, premixed with soda, and highly laden with sugar, flavours and sometimes caffeine, are a more recent phenomenon that have not been monitored by SNZ in their data collection for the CPI. These commonly retail at around $1 to $1.50 per standard drink although discounts occasionally offer these at less than a dollar per unit of alcohol.

Given this background we favour a situation where the negative externalities of alcohol use (to public health and society) are better reflected through higher alcohol prices (via taxation). We certainly do not need a situation where the affordability of alcohol keeps increasing and is as affordable as bottled water and nearly as affordable as milk. We favour government action on raising alcohol excise tax, as recommended by the Law Commission’s Review document. Consideration should also be given to:

- Bans on below cost discounts and any marketing around beverage pricing;
- Having a minimum price per alcohol unit (which would help address the issue of relatively cheap cask wine and RTDs). But we acknowledge that much higher alcohol taxes and bans on price-related marketing may obviate the need for minimum prices;
- Possibly other restrictions on RTDs, given their likely key role in fuelling the binge drinking culture in New Zealand.

These actions should ideally be done in conjunction with other particularly cost-effective interventions of restrictions on alcohol marketing and sponsorship; restrictions on alcohol availability through limiting the density and opening hours of off licence premises and reducing the legal blood alcohol level for driving. Ultimately New Zealand society might wish to strive to create an environment where the pattern of alcohol use is as per the traditional one of such European countries as Spain and Italy, where alcohol is generally consumed with meals. Perhaps a citizen jury or citizen panel could be convened to explore if this type of direction should be pursued?

Finally, New Zealand needs to have an alcohol price surveillance system for collecting all relevant price data and regularly reporting it to the public and policy
makers. Ad hoc unfunded research (as in this study) should be replaced by a routine government-funded surveillance system.

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Disclaimer: Both authors have taken advantage of low cost alcohol prices during the conduct of this study.

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References:

Answer to NZMJ about Ron Jones’ research

Dr R W Jones was a co-author of the 1984 ‘McIndoe Paper’,¹ which became the principal catalyst of the 1987 Judicial Inquiry into treatment of cervical dysplasia at National Women’s Hospital. The 1984 McIndoe Paper states that of the 948 women with grade 3 cervical dysplasia reviewed, 1955–76, 923 had principal initial treatment of hysterectomy or cone excision of cervix and 25 punch or wedge biopsies.²

Dr R W Jones is also a co-author of a 2010 article in the ANZJOG,³ which claims to be the ‘final word’ to silence all critics of the 1984 McIndoe Paper. This 2010 article states that of the 948 women reviewed by McIndoe in the years 1955–76, 428 women, in the years 1965–74, had initial management in which treatment of ‘curative intent’ was deliberately withheld in unethical experiments. This era was selected to prove that the 1966 NWH ‘more conservative dysplasia management protocols were an added cancer risk’.

Simple arithmetic confirms that it is not possible to have 422 women with treatment of “curative intent withheld” in 948 women which the 1984 McIndoe Paper states 923 had initial treatments of cone excision or hysterectomy, i.e. on their own 2010 definition ‘treatment of curative intent’.

The 1984 McIndoe statistics are correct; the 2010 statistics are damaging fiction in my opinion.

Elizabeth Overton
Wife of Graeme Overton (Senior Consultant associated with National Women’s Hospital 1960–99)

References:

Hype around high-dose vitamin C is unjustified

Vitamin C needs little introduction—it is an essential vitamin found in many fruits and vegetables. Shortages can cause scurvy as it is needed for healthy skin, soft tissues, bones and blood vessels, but eating a balanced diet gives more than enough vitamin C. Higher doses of 1000 mg per day have been shown to reduce the chances of catching a cold in some situations, and can also probably reduce the duration of colds. In addition, there is some evidence that a diet rich in vitamin C can help reduce the chances of getting cancer.

There is currently a great deal of media hype, particularly in New Zealand, around the use of massive doses of vitamin C for people with serious illnesses. This can be traced back to Linus Pauling, a brilliant physicist and winner of two Nobel prizes, who claimed that massive doses of vitamin C, 10,000 mg per day, could help to treat cancer. This claim was based on a study he was involved with of 100 patients with advanced cancer, which concluded that those given huge doses of vitamin C survived 3 to 4 times longer than those who were not given the supplement.

It would be a huge breakthrough in cancer treatment if it was true, but his study was seriously flawed and three similar but scientifically valid studies undertaken later at the Mayo Clinic found no benefits from the same doses of vitamin C in similar patients. As well as being shown not to work in good studies, Cancer Research UK strongly advise against the use of high-dose vitamin C as it can reduce the effectiveness of radiation therapy and some forms of chemotherapy, and can cause kidney damage.

Recently published research from the University of Otago found that some types of tumour were less able to accumulate vitamin C compared with healthy tissues ...“and that this related to the ability of the tumour to survive and grow”. However, this work was carried out on tissue, not people, and whilst interesting in terms of increasing our knowledge, it is wrong to claim based on this research that high-dose vitamin C can help people with cancer, or that this is proof of the effectiveness of vitamin C, as a number of media reports and vitamin C proponents have claimed.

The hype continued when in August of 2010, popular New Zealand TV current affairs shows reported a case of a man who was in all likelihood about to die from swine flu. His family insisted that he receive high-dose vitamin C and they eventually got their wish after using legal threats. These threats were made after doctors refused to administer it on the basis that there was no good research evidence that it would help. The man went on to make a remarkable recovery and the result is likely to be that, based on this single case, seriously sick patients and their relatives are going to demand high-dose vitamin C in the future. This is already happening—an oncologist told me that 7 patients who attended a recent clinic asked about receiving intravenous vitamin C. Perhaps more importantly, the hype is giving unjustified false hope to vulnerable patients and relatives. Optimism whilst dealing with a serious illness is beneficial, but unrealistic expectations can be harmful.
It is possible that future studies may find high-dose vitamin C to be an effective and safe treatment for people with serious illnesses, including cancer, and that previous trials have not shown a benefit because they have, for example, used the wrong dose or method of delivery. If it did work, it would be very easy to demonstrate this in clinical trials and there would be no shortage of willing participants. But the evidence currently available tells us that it almost certainly does not help and there is a real chance of harm.

High-dose vitamin C is not recommended for any condition and the current media hype is unjustified and unhelpful.

Shaun Holt
Tauranga

References:

Thomas Guy Hawley

MB CHB FAFPHM DPH (11 September 1925 – 9 August 2010)

Guy was born in Coventry, Warwickshire, England. His father and grandfather were both doctors and he followed their medical careers. His initial education was at Ascham St Vincent’s, Eastbourne, and Malvern, near Oxford.

Secondary schooling was at Christ’s College, Christchurch, New Zealand, as he, a brother and their mother were sent to safety away from the developing war in Europe. There he won a Boarding Bursary and a Ralph Barnett Scholarship, entering Otago Medical School in 1943.

In addition to medical studies he was active in rowing, debating (leader of the 1944 winning faculty team), and President of the Otago University Union debating club. He edited “Critic”, the Student Association newspaper.

Drama was another interest and he was a member of Ngaio Marsh’s touring drama group. There he was paid for the parts played, minor though they were.

He also joined the Otago Dramatic Society where he met his wife, Suzette Ann (Toni) Bilton. They married in 1947. Toni died in 2008 and he is survived by his daughter Therese, and sons Bilton and Guy.

Guy’s early career began in Samoa in 1950 where his intense interest in the Pacific Islands and Public Health started and diverted him from the intended return to England. He joined the Colonial Service in Fiji in 1953, spent some months in Tonga and then went to the UK studying for the Diploma in Public Health, 1956–57.

He returned to Fiji, worked as Medical Officer in Suva, Lautoka, Labasa and Sigatoka. He was tutor in charge of Social & Preventive Medicine Fiji School of Medicine, Senior Tutor, then Principal of the School, 1969–1974. The Fiji School of Medicine was the central medical school for all the English-speaking Pacific nations and also offered refresher courses to their medical staff; for example, those working in the field of leprosy.

In 1974 he was appointed Deputy Superintendent in Chief of the Auckland Hospital Board (later Auckland Area Health Board) where his special interest in Public Health, the health of Pacific peoples in Auckland, and community health developed further. As part of his duties he was appointed Medical Superintendent of the Wilson Home, Takapuna, where children with long-term physical disabilities received the best
treatment possible, while having their educational needs met. He retained this position until his retirement.

Guy was committed to ensuring the links between hospital treatment, rehabilitation and home care were provided effectively. The then Extramural Hospital with its four bases in Greater Auckland, led by a medical practitioner, provided the District Nursing Service and allied health professionals (social workers, physiotherapists, occupational and speech language therapists) which complemented the in hospital services. He also had responsibility for chairing the Health of Older People Advisory Committee.

Under his guidance representatives from the religious and welfare and private sectors met to plan services and set standards for the care of older people in residential care. His vision for the improvement of residential care services for older people led to the establishment of a team of social workers who developed a register of all such homes that were then monitored. This was a very useful accommodation register providing individuals and families with essential information as they made their choice.

His last appointment, 1988, was as Chief Medical Officer of the Auckland Area Health Board, prior to retirement in 1990. Despite his increasing deafness Guy continued to maintain his interest and enjoyment in bridge, reading and philately, all interests maintained from his student years.

Guy had a deep and wide knowledge of the medical fields he studied and worked in. A quiet, modest, compassionate man he contributed much to the understanding and treatment of the diseases and illnesses of the Pacific region and then assisted in the delivery of health services to the people of Greater Auckland. He will be remembered for his intellect, humour and wisdom.

Contributed by Therese Hawley, Dr Desmond Beckett and Judith MacKenzie
Erratum


The authors advise that the study population in fact included people aged 15 and older and there was no upper limit of 65 years as previously advised and published. Hence a sentence was changed in the Abstract and Methods sections. The authors apologise for any inconvenience caused.

Please see the webpage and PDF links above for the corrected copy.
Saunders Essentials of Medical Assisting (2nd edition)


This American-based book is meant to provide the knowledge and skills needed to become a medical assistant in the United States. A position equivalent to the nurse practitioner and secretary role in the New Zealand system.

It has chapters about physiology and anatomy, although the level of knowledge remains basic. In addition there are chapters on how to organise and design a medical office/waiting room; performing office tasks (for example a detailed instruction list on how to send a confidential fax is included); and ethics/how to behave and communicate correctly (e.g. don’t chew gum and cover up your tattoos).

It also explains in great detail how to perform minor medical chores like phlebotomy, recording an ECG, or assisting in minor surgical procedures.

The tone of the book is patronising and reads in parts more like an instruction manual. It is thorough in detail of even the obvious leaving no space for one’s own initiative or alternative opinions. A lot of emphasis centres on the legal consequences of your actions, with the notorious lawsuit always threatening around the corner. It feels like the book itself needed to be so thorough in detail to prevent a lawsuit for missing information. The book includes a two-page English-Spanish translation of the most common medical questions. The chapters about office managing, still relying on a lot on paper and pencil, already feel outdated.

The book delivers what it intends to do: providing the essentials of medical assisting (in the US!). If you want to be a medical assistant outside the US a lot of the regulations and insurance details will be of no value. And if a more profound knowledge of medicine or organising a practice is needed, this is not the book to buy.

Edwin Beenen
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