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An 88-year-old woman with a history of ischaemic heart disease, chronic kidney disease, type II diabetes mellitus and gastritis presented to the emergency department of an Australian tertiary hospital with melaena, symptomatic anaemia, haemoglobin of 61 g/L. Three weeks prior to the presentation she had been changed by her general practitioner from warfarin, on which she had previously been well controlled for more than 10 years, to dabigatran for stroke prevention for her atrial fibrillation. Why did this previously stable patient experience significant haemorrhagic complications so shortly after commencing the new medication?

Dabigatran has been approved for use in Australia by the Therapeutic Goods Administration (TGA) for the prevention of stroke and systemic embolisation in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke. It has been recommended for listing on the Pharmaceutical Benefits Scheme (PBS) by the Pharmaceutical Benefits Advisory Committee (PBAC) for this indication. Despite the PBAC’s recommendation the Department of Health and Ageing (DOHA) has delayed its decision on the matter, commissioning further inquiry into the use of the drug. The Department’s concerns included that the benefit of dabigatran observed in the landmark trial may not be reflected in the general Australian population, and that this may lead to over-prescription without adequate education for doctors, pharmacists or patients. Between June 2009 and October 2011 the TGA has received reports of 297 adverse events with the use of dabigatran, 70 of which were serious bleeding events. A similar picture has emerged in New Zealand. The TGA has subsequently issued two warnings, one on the bleeding risk of the dabigatran, and the other on the necessity of assessing renal function in those taking the drug. The Department’s concerns included that the benefit of dabigatran observed in the landmark trial may not be reflected in the general Australian population, and that this may lead to over-prescription without adequate education for doctors, pharmacists or patients. The TGA has subsequently issued two warnings, one on the bleeding risk of the dabigatran, and the other on the necessity of assessing renal function in those taking the drug.

Impaired renal function

As dabigatran is 80% renally excreted, care must be taken in its use in patients with impaired renal function. It is contraindicated in people with a creatinine clearance (CrCL) less than 30 mL/min. The company suggests considering the reduced dose of 110 mg twice daily for those with moderate renal impairment (CrCL of 30–50 mL/min), but it would be logical to make this recommendation mandatory. In the RE-LY trial the risk of bleeding events increased with decreasing CrCL, although this did not meet significant criteria. Impaired renal function was a likely contributor to the bleeding event in the our case. Accurate estimation of renal function is important for drug dosing. The Cockcroft-Gault equation and the Modification of Diet in Renal Disease equation (estimation of glomerular filtration rate (eGFR)) have both been validated for use in people of average age, weight and size, but are less robust for use in those in the extremes of those categories. Neither method has been validated for use in those over 80, particularly if lean body mass is not taken into account as with the eGFR. Our patient, described earlier, was significantly underweight. It is important to keep these inaccuracies in mind when deciding on drug use or dosing.

The elderly

The bleeding rates with dabigatran increase with increasing age. In the RE-LY trial those over 75 on dabigatran...
had greater rates of major bleeding, extracranial bleeding, and gastrointestinal bleeding than those <75 years. Patients >75 years had significantly higher rates of gastrointestinal bleeding with both doses of dabigatran compared with warfarin like the case in question. Age did not have a significant effect on the lower rates of intracranial bleeding seen with both doses of dabigatran.

Reversal

Unlike warfarin, one of the major drawbacks of dabigatran is the lack of an effective antidote for use in the event of a severe bleeding event. Prothrombin complex concentrate did not correct prolonged coagulation assays in healthy volunteers, and there is no evidence to support its use in bleeding patients. It is not clear whether recombinant factor VIIa will be effective. This becomes a critical issue when urgent surgery is required.

Monitoring options

At present there are no available laboratory tests that have been validated for monitoring of dabigatran. Situations do exist in which the ability to monitor its therapeutic effect would be potentially beneficial. In the case described monitoring dabigatran activity may have allowed for dose adjustment or cessation of the medication to prevent the haemorrhagic complication.

The commonly used APTT and PT are not suitable for the measurement of dabigatran effect. The thrombin clotting time is a sensitive test for determining if any dabigatran is present in a sample, however, because of great variation of results with different reagents used by different laboratories it has not been validated for use as a monitoring test. The test can only be used to tell if there is any dabigatran activity present, but not how much.

Perioperative and acute coronary syndrome (ACS) settings

Like all the new anticoagulants and new anti-platelet drugs on or about to be available on the Australasian market, the treating team has to recognise these new medications (and their trade names) and stop them for an appropriate time before surgery or before conventional anticoagulation can start (in the case of ACS). Failure to identify these agents or surgery in the emergent situation will be extremely hazardous.

Drug interactions

Dabigatran is given as the prodrug dabigatran etexilate, and this prodrug is a substrate for the efflux p-glycoprotein transporter. Inhibitors of p-glycoprotein, such as ketoconazole (most azoles), protease inhibitors, macrolides, calcineurin inhibitors, amiodarone and verapamil, can increase dabigatran plasma concentrations by decreasing the efflux of the drug into the gastrointestinal lumen. Strong inducers of p-glycoprotein, such as rifampicin, carbamazepine and phenytoin can reduce plasma concentrations and coadministration should be avoided. Given its indication for use in atrial fibrillation, particular caution must be used with the potential interactions with verapamil and amiodarone. Simultaneous initiation of dabigatran and verapamil is contraindicated, but the product information does recommend verapamil can be given 2 h after the dabigatran. The company does not recommend dose alterations in dabigatran with pre-existing treatment with amiodarone or verapamil, but it is likely less dabigatran will be required. No significant interaction was seen with digoxin, also a p-glycoprotein substrate.

Approximately 40% of patients in the RE-LY trial took concomitant aspirin on enrolment, and about half of these continued to take it throughout the study. The combination of aspirin and dabigatran was associated with higher bleeding rates. Bleeding rates were also higher among people who received the combination of aspirin and clopidogrel throughout the study compared with those who did not receive combination antiplatelet therapy.

Different international normalised ratio (INR) groups

The comparison of efficacy and safety between dabigatran and warfarin is altered by the success in achieving a therapeutic international INR with warfarin therapy. Overall the patients in the warfarin arm of the RE-LY trial had a mean Time in Therapeutic Range (TTR) of 64%. In centres with a high mean TTR (greater than 57.1%) there was no significant difference in the primary endpoint (the composite of stroke or systemic embolisation) or non-haemorrhagic stroke between either dose of dabigatran when compared with warfarin. Australian subjects had a mean TTR of 74%, which was exceeded only by Sweden. A similar picture emerges for major bleeding when comparing the high dose dabigatran (150 mg b.d.). The lower 110 mg dose of dabigatran maintained a slightly lower total bleeding rate even in those with a high TTR, though all other bleeding subgroups were not significantly different. The lower rates of intracranial bleeding with dabigatran compared with warfarin were maintained for all populations of TTR.
Who should not and who should?

Those who have been prescribed with dabigatran should match the inclusion criteria of the major trial that proved the efficacy and safety of that drug. The RE-LY trial excluded those with creatinine clearance <30 mL/min, those with active liver disease, pregnancy and any patient with a condition that placed them at an increased risk of bleeding, including a history of gastrointestinal ulcer disease, recent or planned surgery, uncontrolled hypertension, a history of intracranial or gastrointestinal bleeding. Patients with a history of heart valve disease were also excluded. A knowledge of these exclusion groups is crucial as not only has dabigatran not been demonstrated to be efficacious in these groups, it has also not been proven to be safe.

In the trial the elderly and patients with impaired renal function had higher rates of bleeding and those with stable INRs did well with warfarin. So if well controlled on warfarin it makes no sense in changing these patients to dabigatran. There is an advantage for intracranial haemorrhage for dabigatran; however, we are unaware of any validated predictive model that is available to distinguish this group from the general bleeding risk.

There is a role for the use of dabigatran in patients with atrial fibrillation. We would propose that dabigatran would be useful in patients <75 years, who have normal renal function, few co-morbid medical conditions (i.e. not many concurrent medications), limited additional risks for bleeding. Here the decreased risk of intracranial bleeding is clinically advantageous and the lack of regular INR testing is convenient. Patients whose INR control is poor should also be considered for dabigatran.

Conclusion

No doubt this era of new anticoagulants and new antiplatelet medications is an advance. Despite the marketing it is the opinion of the authors that all anticoagulants must be considered to have a narrow or critical therapeutic range. In view of all the issues why would one market this new medication in general practice?

We require an effective antidote, clear national guidelines about who should be considered for dabigatran therapy, and a reliable, widely available laboratory monitoring test. Its cost-effectiveness is uncertain. The drug interaction story is yet to be played out in full. Guidelines on how clinicians deal with the multiple issues that patients on dabigatran can present with are now being produced.

As more new medications are potentially held up by DOHA, pharmaceutical companies are considering PFPs or other forms of Medicines Access Programs. In our new world of Medicare Locals and Local Health and Hospital Networks, strict oversight of these programmes is essential.

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Advances in gastrointestinal endoscopy

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Abstract

Gastrointestinal endoscopy has undergone a remarkable expansion in its capabilities as a result of sophisticated technological advances in recent years. New imaging technologies, novel ablation and resection techniques, cutting-edge endoscope development and creative extraluminal applications have taken gastrointestinal endoscopy to an exciting new level. An update on some of these advances is presented for the physician audience.
Introduction
Endoscopy remains an essential complement to the clinical management of patients with gastrointestinal disorders. Recent technological advances have broadened the horizons of possibility for endoscopic therapies. Several recent advances that may be encountered by the general physician audience are reviewed here.

Advances in imaging
Standard endoscopy uses white light to provide images of the gastrointestinal tract mucosa. Image-enhanced endoscopy has evolved over the past decade with the development of several modalities to increase the amount of visual data above what can be obtained with white light alone.

Four main techniques have been developed: (i) high resolution and magnification white light endoscopy; (ii) contrast enhancement; (iii) in vivo histology; and (iv) autofluorescence.

High resolution and magnification endoscopy
High-resolution images can now be achieved with endoscopes containing new generation charge-coupled devices (CCD), which allow the capture of more than a million digital pixels, as compared with conventional endoscopes that capture around 300 000 pixels. This increase in resolution improves image quality and results in better discrimination of detail. The application of this new CCD technology has important clinical implications – previously, dysplastic changes in Barrett’s oesophagus were essentially endoscopically ‘invisible’, making random biopsy protocols the only way to detect abnormalities. However, high-resolution endoscopes now make it possible to specifically target biopsies of endoscopically visible abnormalities within Barrett’s segments, with detection rates of up to 80% of the lesions present.1,2

Magnification results in enlargement of images, without necessarily increasing resolution. The new generation magnification endoscopes have an adjustable focusing mechanism that enables enlargement of the image size from 1.5 to 150 times.3 As some mucosal abnormalities, such as intestinal metaplasia, are translucent, the addition of a tissue stain to magnification endoscopy can improve visualisation. Again, one of the major roles of these visualisation enhancements is to improve the targeting of biopsies to areas containing dysplasia: several studies suggest that this can be achieved accu-
evolution of this technique. Confocal laser endomicroscopy (CLE) and endocytoscopy are the two techniques that permit in vivo histology.

CLE integrates a confocal laser microscope within the tip of a standard videoendoscope or can be used as a probe passed through the channel of a standard endoscope. The technology uses a laser that penetrates the mucosal surface and illuminates a microthin layer of tissue. The endomicroscope provides 7-μm thick cross-sectional tissue images parallel to the mucosal surface to a depth of 250 μm. The initial clinical trials of CLE found close to 100% accuracy for detecting neoplastic lesions at surveillance colonoscopy. Subsequently, other disorders have been studied with CLE, including Barrett’s oesophagus, gastric adenocarcinoma and oesophageal squamous cell carcinoma. Overall, reported results are very good, with accuracy rates often greater than 90%. However, it should be noted that the patients were highly selected and the studies were performed in expert centres.

Endocytoscopy is based solely on high-level magnification using optical lenses. Therefore, because of a lack of a confocal plane, only the most superficial mucosal layer can be imaged and the lens must come into direct contact with the tissue. The development of endocytoscopy devices has not been as rapid and prolific as for the CLE technology, and less data have been published. It is likely that CLE will surpass endocytoscopy in this field of technological advancement.

Autofluorescence

Autofluorescence uses natural tissue fluorescence emitted by endogenous molecules (fluorophores), such as collagen, flavins and porphyrins. After excitation by a short wavelength light source, the fluorophores emit light of longer wavelengths (fluorescence). The total fluorescence emission differs between tissue types due to differences in fluorophore concentration, metabolic state and/or spatial distribution. The colour differences in fluorescence emission can be demonstrated in real time during endoscopy and provide a basis for differentiation between normal and abnormal tissue.

Initial studies demonstrated that neoplastic lesions within the colon could be accurately detected by virtue of the longer wavelength autofluorescence emitted in comparison to surrounding normal tissue. However, it subsequently became apparent that the relatively inferior resolution of this technology, among other shortcomings, limited its utility as a stand-alone technique. The recent coupling of autofluorescence with other forms of image enhancement now offers a multimodal technique that addresses these limitations. Olympus Corporation have developed a trimodal imaging system consisting of autofluorescence followed by NBI with magnification – this has significantly improved the accuracy of Barrett’s neoplasia detection, as well as increased the diagnostic yield of neoplasia detection in screening of patients with ulcerative colitis. Accurate results have also been found in the analysis of colonic polyps.

Advances in ablation

Once neoplastic tissue has been detected through the above imaging enhancement technologies, eradication of the tissue using minimally invasive techniques is a highly sought-after goal. While surgery remains the definitive curative treatment option, it may be associated with significant morbidity and mortality. Therefore, endoscopic ablation techniques represent an important technological advance.

Three major advances have been made in this arena in recent years: (i) radiofrequency ablation (RFA), (ii) argon
plasma coagulation (APC) and (iii) cryotherapy. All of these techniques represent important treatment options for treating premalignant lesions in a non-surgical fashion, with the major application being for Barrett’s oesophagus.

Radiofrequency ablation

RFA is the most significant advance in this field. RFA applies an alternating electrical current to tissue through an electrode array. This current creates an electromagnetic field, causing electrons and other charged ions to oscillate and create molecular friction, thereby resulting in a rapid rise in tissue heat and subsequent injury. A commercially available RFA system for oesophageal treatment is produced by BARRX Medical Inc (Sunnyvale, CA, USA), the HALO360 and HALO90 ablation catheters. The HALO360 catheter is passed through the working channel of an endoscope and applies a 360-degree treatment to the circumference of the oesophageal wall (Fig. 2). RFA has been demonstrated to be effective for the treatment of both high- and low-grade dysplasia in Barrett’s oesophagus. In a randomised sham controlled trial, complete eradication of dysplasia was achieved in 90.5% of low-grade dysplasia patients as compared with 22.7% of controls ($P < 0.0001$), and 81% of high-grade dysplasia patients as compared with 19% of controls at 12 months ($P < 0.0001$).24 With the ability to use standard endoscopes to employ these single-use catheters, this technology is being increasingly employed and long-term data are being generated.

Argon plasma coagulation

APC uses argon gas as the medium of transfer for electrical current, creating non-contact thermal coagulation of target tissue. The coagulation is delivered by the passage of a probe through the working channel of a standard endoscope. APC is capable of ablating a superficial area of mucosa, although prolonged application can result in deeper tissue injury.25 Variable results have been reported for APC in the eradication of Barrett’s mucosa, ranging from complete ablation rates of over 98% and no relapse at 12 months26 to ablation rates of approximately 60% and recurrence in approximately half.27,28 ‘Buried Barrett’s’, the recurrence of intestinal metaplasia beneath squamous reepithelisation, is also a significant problem. For these reasons, APC is not considered to be an adequate stand-alone technique for the long-term destruction of neoplastic tissue.

Cryotherapy

Cryotherapy causes tissue destruction by spraying a cryogen (liquid nitrogen or carbon dioxide) as a gas onto tissue. It can be delivered through a catheter passed into the working channel of a standard endoscope. Cell death is caused by the production of extracellular ice. Current data are limited, with small numbers and short follow-up times, but promising early experiences have been described in the oesophagus, stomach and rectum. Perhaps its most important use is in Barrett’s oesophagus. A multicentre retrospective study found a 97% eradication rate for high-grade dysplasia, but ‘buried Barrett’s’ was found in 3%.29

Advances in resection

Surgery is the most established curative treatment modality for gastrointestinal tract lesions containing high-grade dysplasia. However, it carries with it significant morbidity and mortality, especially in elderly patients with comorbidities.

Endoscopic resection has evolved significantly in recent years, with sophisticated techniques now permitting even the largest lesions to be endoscopically resected. Resection techniques carry a significant advantage over ablation techniques: histological assessment can be performed on the resected specimen, confirming histological subtype and staging.

Two major technical categories exist: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR refers to the resection of mucosal tissue using a snare, whereas ESD is the direct dissection of the submucosal layer beneath the lesion. An exhaustive review of the techniques is beyond the scope of this publication.

Endoscopic mucosal resection

Three main methods have been developed to facilitate snare resection of abnormal tissue: multiband ligation, cap-assisted, and lift and cut (Fig. 3). Variations of these techniques can be employed at all levels of the
gastrointestinal tract. In Eastern populations, the majority of published literature pertains to early lesions in the stomach. In contrast, local data are dominated by the more common Western entity of colonic polyps, with multicentre Australian data demonstrating the success of EMR technique for large laterally spreading tumours.30

Endoscopic submucosal dissection

Three main steps form the basis of ESD: injection of fluid into the submucosal plane to elevate the area of abnormality, cutting of the mucosa surrounding the lesion and then dissecting the submucosa beneath the lesion to remove it. It has been developed and refined in Japan where its initial use was for the treatment of early gastric cancer. ESD has subsequently been extrapolated to use in the colon for the en bloc resection of laterally spreading colonic tumours.

Excellent technical and short-term follow-up results have been reported with ESD. Perhaps of greater importance are long-term outcomes, results of which are emerging from Japan. For gastric ESD, disease-specific 5- and 10-year survival rates of 99% and 99% have been reported;31 ongoing endoscopic surveillance is prudent, however. Complications include bleeding, both immediate and delayed, stricture formation and perforation. These occur at variable rates depending on the location of resection.

Advances in endoscopes

Colon capsule endoscopy

The demand for colonoscopy remains high, with screening programmes, such as the Australian National Bowel Cancer Screening Program, providing an ever-increasing demand for services. The quest for an alternative colonic investigation that is less invasive and requires less manpower, yet remains equally accurate, continues.

Wireless capsule endoscopy, the ingestion of a pill-sized battery-powered camera device that captures images of the gastrointestinal tract as it moves with peristalsis, was originally developed to visualise the small intestine. In recent years, this technology has been extrapolated to the development of the colon capsule endoscopy, marketed by Given Imaging Ltd as the PillCam Colon. A second generation device, the PillCam Colon 2, has now been developed (Figs 4, 5). This new generation capsule has a wider angle of view than its predecessor and conserves battery energy by adapting the frame rate of image capture according to the speed of movement.

A recently published multicentre European trial compared the performance of the PillCam Colon 2 with colonoscopy, demonstrating relatively high sensitivities
of 84% and 88% for colonic polyps ≥6 mm and ≥10 mm respectively, and specificities of 64% and 95%. While these results are promising (and represent an improvement upon previous meta-analysis for the first generation colon capsule33), conventional optical colonoscopy remains the gold standard as it is currently the only tool that offers both diagnostic and therapeutic capabilities. The main role for colon capsule endoscopy is likely to remain with indications, such as inability to perform complete colonoscopy and where contraindications to performing colonoscopy exist (e.g. anaesthetic risk).

Remote control and magnetic capsule endoscopy

The major limitation of all forms of capsule endoscopy to date has been the inability to control its movement and administer therapeutic intervention. Movement of the device through the gut is passive, relying on peristaltic waves for propulsion. To address these shortcomings, current advances are directed at developing a controllable device by use of techniques, such as magnets and remote control locomotion.

Currently, information transfer is unidirectional: images are captured by the device and transmitted to a data recorder. The ability to reciprocate, transmitting instructions to the capsule from an external controller, is yet to be fully realised. However, advances are being made in this regard, with magnet control currently under development. The ability to steer the capsule quickly through areas that are not of interest (e.g. the oesophagus and stomach, regions that can already be easily viewed through standard gastroscopy) to the region in question (e.g. the small bowel) has been achieved with a capsule containing neodymium boron iron cylindrical magnets – its movement can be manipulated by an external hand-held magnet.34 A paddling-based locomotion device is also in current development.35 In a porcine model, researchers were able to completely direct stable and active movement, both in vitro and ex vivo, without complications. Both of these developments represent promising advances towards the ultimate goal of a fully steerable device capable of delivering directed therapy.

Colonoscopy advances

Given that conventional colonoscopy remains the current gold standard in clinical practice, refining the art to improve its accuracy is of paramount importance. Many of the imaging developments discussed in the first section of this article apply to colonoscopy. Further advances specific to colonoscopy have also been developed.

Water immersion colonoscopy

The filling of the colon with water, instead of air, has the benefit of straightening the sigmoid colon, resulting in an easier-to-traverse angle. For patients undergoing colonoscopy with light or ‘on-demand’ sedation, this technique results in lower sedation requirements.36 It may also improve adenoma detection rate.37–39

Cap-fitted colonoscopy

The addition of a transparent cap or hood to the tip of the colonoscope may improve ease of colonoscope advancement by maintaining a distance between the tip of the colonoscope and the colonic mucosa, thereby avoiding obscuration of view by the collapse of the mucosa over the instrument tip.40 This simple technical modification shortens time taken to reach the caecum in randomised controlled trials.41–43

Third Eye Retroscope

The accuracy of colonoscopy is measured by its ability to detect polyps during withdrawal of the colonoscope. Standard colonoscopy withdrawal techniques only provide views of the distal side of the mucosal folds. The Third Eye Retroscope (Avantis Medical, Sunnyvale, California, USA) has been developed to address this problem. It is a separate device that is passed through the working channel of the colonoscope and advanced into the colonic lumen and retroflexed (Fig. 6), ‘hooking’ behind the folds to provide images of these areas. The proceduralist watches both the images from the forward and retroflexed views simultaneously on two separate screens.
Prospective studies have demonstrated improved adenoma detection rates using the Third Eye Retroscope, but at the expense of increased procedure duration.44–46

**Advances beyond the gut**

Venturing beyond the gastrointestinal tract wall has become a true endoscopic reality as a result of the advances in two techniques: EUS (endoscopic ultrasound) and NOTES (natural orifice transluminal endoscopic surgery).

**EUS-guided therapies**

EUS was originally developed to provide imaging of organs that lie in close proximity to the gastrointestinal tract wall, particularly the pancreas. A modified endoscope containing an ultrasound component at its tip provides detailed images of extraluminal structures, and also allows real-time visualisation of a needle passed through the echoendoscope to perform fine needle aspiration. Extrapolating further, the technique can be used for the drainage of pancreatic collections, such as pseudocysts and infected pancreatic necrosis. It is also emerging as a vehicle for the oncological treatment of pancreatic and other extraluminal cancers.

**Pancreatic therapies**

Pseudocysts complicate approximately 10% of cases of acute pancreatitis.47 While many will resolve spontaneously, occasionally significant clinical sequelae may develop, including gastric outlet obstruction and infection. Infected pancreatic necrosis is a more sinister complication, with systemic sepsis and multiorgan failure being life-threatening complications. Laparotomy and drainage/necrosectomy is an invasive procedure, for which these patients are often too unwell to undergo. For collections lying in close proximity to the gastric or duodenal wall, endoscopic drainage provides a minimally invasive alternative (Fig. 8). Under real-time EUS guidance, the peripancreatic collection can be punctured, and stents placed between the collection and the gastric/duodenal lumen to facilitate drainage into the gastrointestinal tract (Figs 9–11). Furthermore, where there is solid necrotic debris within the collection, the endoscope can be passed through the gut wall and into the collection to perform debridement with excellent clinical outcomes (Fig. 12).48

**Injection**

Extrapolating further upon the ability to pass a needle across the gut wall into adjacent organs, several oncological applications have been developed for EUS.

The EUS-guided injection of fiducial markers to guide stereotactic radiotherapy is a novel, minimally invasive way to improve the accuracy of treatment. It is potentially more comfortable and accurate than the percutaneous route, and has been used for pancreatic, prostate and mediastinal cancers.49–51
EUS fine needle injection of various antitumour agents into pancreatic and other malignancies is also advancing. Ethanol and paclitaxel have been injected into pancreatic cystic lesions with resolution rates of over 60%.52,53 Dendritic cells, potent antigen-presenting cells for the induction of T-cell responses, have been injected under EUS guidance into advanced pancreatic cancers, with preliminary results showing mixed outcomes but no serious toxicity.54 Likewise, reports of EUS injection of mixed lymphocyte culture, adenovirus vectors and conventional chemotherapeutic agents have reported minimal toxicities and variable early results.55–59

Natural orifice transluminal endoscopic surgery

NOTES has generated significant interest in recent years. Accessing the peritoneal or thoracic spaces through internal, transvisceral incisions instead of transabdominal incisions offers potential benefits of decreased postoperative pain, fewer wound complications and better cosmetic outcome. The transgastric route has been used to perform procedures including peritoneoscopy, cholecystectomy, appendicectomy, repair of percutaneous endoscopic gastrostomy tube complications and cystogastrostomy.60–65 However, at this time, the majority of experience and literature remains in animal models, with human experience remaining limited. The development of dedicated NOTES equipment and the resolution of challenges, such as suturing and anastomotic...
techniques, need to be addressed before this technology reaches prime time human use.

**Conclusion**

Significant advances have been made in endoscopic technology in recent years. Endoscopists now have multiple techniques with which to visualise, resect and ablate abnormalities within and beyond the gastrointestinal tract. The judicious use of these new technologies is of paramount importance; the success of any new technology will always be dependent upon its use in appropriately selected patients.

**References**

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Governance approval for multisite, non-interventional research: what can Harmonisation of Multi-Centre Ethical Review learn from the New South Wales experience?


Abstract

Background: In 2007, New South Wales Health mandated the separation of ethical and scientific review from research governance at all New South Wales public health sites based on their distinction in the National Health and Medical Research Council National Statement. This separation allowed for single-site ethical review of multicentre studies.

Aims: To investigate the time taken for governance approval of multicentre studies through the site-specific approval (SSA) process.

Methods: A retrospective audit of the SSA process for five non-interventional studies proposed by a university cancer research unit.

Results: The median total governance approval time for all submissions \( (n = 28) \) was 12 weeks (range 2.5–64); median time from starting the SSA to submission was 8 weeks (range 1–48) and median time for governance approval was 5 weeks (range 0.3–40). Approval times were shorter for public compared to private institutions. Reasons for delays in finalising submissions for approval were the absence of institutional governance officers, lack of clarity regarding signatories, the need to identify a principal investigator employed by the institution, and lack of recognition of ethical approval by private institutions. The need to develop legal agreements between the university and hospital was the main reason for lengthy delays in obtaining approval.

Conclusions: The advantages of a harmonised single ethical review process were undermined by the coexistence of a fragmented, complex and lengthy governance approval process. This experience has implications for the success of the national Harmonisation of Multi-Centre Ethical Review (HoMER) model. A harmonised and fully supported national approach to research governance should be developed contemporaneously with HoMER.

Introduction

Recent years have seen marked changes internationally in the institutional review of human research. In Australia, the National Health and Medical Research Council (NHMRC) updated the National Statement on Ethical Conduct in Human Research (National Statement) in 2007 and released an online, standardised national ethics application form (NEAF). While viewed by many as cumbersome, the NEAF has reduced the effort required by researchers to obtain ethical approval for multisite research proposals.\(^1\) In July 2007, the New South Wales (NSW) Health Department mandated the separation of ethical and scientific review from research governance at all NSW public health sites. The separation of these two processes was based on their distinction in the National Statement and allowed for the single-site ethical review of multicentre studies.

The centralised, state-based system and policies on ethical and governance review were established as a framework in which the public health institutions were to operate. These procedures were a welcome initiative...
designed to protect research participants, researchers and institutions, whilst reducing duplication by both researchers and institutions, in accordance with the National Statement. In the new system, the ethical and scientific review of multisite research proposals is performed by a single accredited Human Research Ethics Committee (HREC), and the governance review is performed by each institution at which the research will be carried out. In undertaking research governance review an institution considers local resources, including space and staffing required to implement the project, as well as project budgets, support service costs, indemnity, insurance and compliance with relevant regulatory agencies and applicable laws. Private institutions, which account for approximately one-third of all hospital separations in NSW,2 are not included in the system and independently determine the mechanisms for authorising the conduct of research within their facility.

The NHMRC Harmonisation of Multi-Centre Ethical Review (HoMER) model is a national approach to single ethical and scientific review of multicentre health research. Governments, institutions and researchers are collaborating to develop standardised procedures, policies and forms. The model is expected to be operational at some institutions in 2011. The initiative is expected to substantially reduce the efforts and resources of researchers and HRECs in the conduct and ethical and scientific review of cross-jurisdictional health research. However, the HoMER model does not currently include national harmonisation of research governance procedures. The model explicitly retains institutional autonomy to determine whether a research proposal should be conducted within a particular facility.

Here we highlight our experience with research governance approval in the context of a newly initiated standardised state-based ethical, scientific and governance review system in NSW. Specifically, we examine the time to research governance approval for non-interventional research projects at public and private hospitals in NSW. We document the local factors that contributed to delays and highlight the potential implications for the HoMER model.

### Materials and methods

Researchers at a university-based cancer research unit compiled retrospectively the information on the time taken for governance approval of all new non-interventional (non-clinical trial), investigator-initiated research proposals submitted for review in NSW after July 2007. Five studies requiring 28 individual governance approval applications were identified (Table 1). Two studies were designed to include private institutions. In each study there were no substantive delays in obtaining HREC approval from a lead Committee.

<table>
<thead>
<tr>
<th>Study</th>
<th>Timing of first SSA application</th>
<th>Type of study</th>
<th>Local method of data collection</th>
<th>Funding agency</th>
<th>Time taken for HREC approval (weeks)</th>
<th>Number, location and type of sites</th>
<th>Informed patient consent</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>September 2007</td>
<td>Retrospective clinical research</td>
<td>Medical record abstraction</td>
<td>Cancer Institute NSW</td>
<td>1</td>
<td>7 hospitals Major metropolitan, regional and rural Public only</td>
<td>Waived</td>
</tr>
<tr>
<td>B</td>
<td>December 2007</td>
<td>Prospective clinical research with on-site patient recruitment</td>
<td>In-person interview and medical record abstraction</td>
<td>NHMRC</td>
<td>5</td>
<td>12 hospitals Major metropolitan, regional and rural Public and private</td>
<td>Required</td>
</tr>
<tr>
<td>C</td>
<td>December 2008</td>
<td>Retrospective population health research</td>
<td>Medical record abstraction</td>
<td>NHMRC</td>
<td>3</td>
<td>3 hospitals Major metropolitan only Public only</td>
<td>Waived</td>
</tr>
<tr>
<td>D</td>
<td>April 2009</td>
<td>Prospective clinical research with on-site patient recruitment</td>
<td>Collection of fresh primary tumour tissue and medical record abstraction</td>
<td>Cancer Council NSW</td>
<td>7</td>
<td>4 hospitals Major metropolitan only Public only</td>
<td>Required</td>
</tr>
<tr>
<td>E</td>
<td>September 2009</td>
<td>Prospective, clinical research with on-site patient recruitment</td>
<td>Treating clinician, medical record abstractions, and in-person interview</td>
<td>NHMRC</td>
<td>6</td>
<td>2 hospitals Major metropolitan only Public only</td>
<td>Required</td>
</tr>
</tbody>
</table>

HREC, Human Research Ethics Committee; NHMRC, National Health and Medical Research Council; NSW, New South Wales; SSA, site-specific assessment.
The time from starting the site-specific governance approval process to submission of the site-specific assessment (SSA) form (public institutions) or the equivalent (private institutions), and the time from submission to institutional approval, were abstracted for each study and institution. The time prior to submission is an essential component of the total time as it reflects the time taken to prepare the submission to meet the stated requirements of the research office; applications were only submitted when they were considered to be complete. Each institution was classified as public or private and as major metropolitan, regional or rural. The mean and median times for approval were calculated for each study and by institution type. Statistical differences in median times were examined using the Mann–Whitney test and the level of statistical significance was set to \( \alpha = 0.05 \). Also extracted were the local reasons for any delays in either the governance submission or approval process.

**Results**

Of the 28 research governance applications submitted for the five studies, 24 have been approved to date. A private rural hospital was removed from Study B 40 weeks after the first approach because the necessary signatures could not be obtained. Study D has been approved by only one of four institutions, and negotiations are continuing with the three remaining sites some 23, 39 and 39 weeks after submission of the governance application.

The governance approval times varied both between and within studies. The median total approval time from the start of the application process until receipt of approval was 10 weeks (range 2.5–17) for Study A, 19 weeks (range 6–45) for Study B, 18 weeks (range 13–48) for Study C, 4 weeks (range 4-ongoing) for Study D and 8 weeks (range 5–10) for Study E. Study A commenced submissions shortly after the new system was initiated, and therefore both researchers and governance officers were unfamiliar with the system requirements. Nevertheless, variation between studies appeared to be related to the type of research, with longer approval times for studies requiring the collection of human tissue (Study D) and possibly for studies requiring on-site patient recruitment (Studies B, D and E). Some of the variation within studies appeared to be related to institution type, with longer approval times observed for private compared to public institutions in major metropolitan locations, and for rural compared to major metropolitan locations within the public system; however, these differences did not reach statistical significance (Table 2). Reasons for lengthy periods of time to submit governance applications included the absence of governance officers, variation in interpretation of the required supporting documentation, lack of clarity on behalf of the researchers, site investigators and governance officers regarding the appropriate signatories, and the need for principal investigators to be employed by the institution. In addition, some private institutions did not recognise the lead HREC ethical approval. The main reasons for lengthy delays in the institutional review process were the requirement to develop legal agreements between the university and the institution, and negotiation around the requirement for individual investigator contracts.

**Discussion**

In the context of a newly initiated state-based research ethical, scientific and governance review system, this retrospective audit shows that the time taken to obtain governance approval can exceed that for ethics approval, even in the case of non-interventional research. These results question the net benefits to be obtained under the HoMER system in the absence of a truly harmonised governance review system. Our findings support the use of a compulsory, standardised governance approval process, and raise concerns about the validity of

<table>
<thead>
<tr>
<th>Hospital type</th>
<th>Number of proposals submitted</th>
<th>Number of proposals approved</th>
<th>From start of governance application process to submission</th>
<th>To approve governance application</th>
<th>From start of application process to approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major metropolitan, public</td>
<td>14</td>
<td>13</td>
<td>5 (1–40)</td>
<td>4 (0.3–12)</td>
<td>9 (2.5–48)</td>
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<tr>
<td>Major metropolitan, private</td>
<td>5</td>
<td>3</td>
<td>5 (5–7)</td>
<td>16 (1–40)</td>
<td>21 (8–45)</td>
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<tr>
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<td>3</td>
<td>6 (2–10)</td>
<td>7 (4–18)</td>
<td>17 (10–20)</td>
</tr>
<tr>
<td>Regional, private</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Rural, public</td>
<td>4</td>
<td>4</td>
<td>8 (4–18)</td>
<td>7 (4–9)</td>
<td>15 (13–26)</td>
</tr>
<tr>
<td>Rural, private</td>
<td>1</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>24</td>
<td>5 (1–48)</td>
<td>5 (0.3–40)</td>
<td>12 (2.5–64)</td>
</tr>
</tbody>
</table>
population health research if specific institutions are under-represented because governance approval is not sought or cannot be obtained. The timelines and reasons for lengthy approval times also demonstrate that introducing a new system requires local resourcing and training, otherwise substantial obstacles to health research will be generated.

Although our experience represents only a small fraction of the research governance applications submitted since the initiation of the new system, it is likely that it is reflective of other research groups in NSW. In our experience, the details of the new system for governance approval were poorly understood by researchers, research governance officers and senior hospital executives responsible for approving studies at their institution. The SSA form was standardised, but open to local interpretation. Progress was achieved by trial and error, and regular contact with governance officers, but inconsistency between institutions meant requests for supporting information could not always be reliably predicted. From our experience, many of these issues remain even after the initial and understandable teething problems. A major concern is the requirement for a Principal Investigator to be employed by the hospital where the research is to be undertaken. This requirement is not a policy of NSW Health and yet has the potential to be a major impediment to future multisite, investigator-initiated non-interventional health research.

Our findings mirror those observed in the UK after the introduction of a centralised and harmonised ethical review service with local institutional research governance approval. In the UK, research governance approval times impeded both clinical trials and non-interventional research. Interestingly, the obstacles encountered in the UK and here in NSW are remarkably similar. Common amongst these are staff shortages, diverse local interpretation, delays in obtaining the appropriate signatories and the requirement for site-specific honorary contracts for researchers. Of concern is that the research governance delays in the UK resulted in the ethics of the research governance process itself being questioned, and research governance being labelled the ‘weak link’ in the research approval process. The relatively rapid HREC approval times for our peer-reviewed proposals fully endorse the HoMER approach. Together, our experiences suggest that the HoMER model will succeed in reducing only some of the duplication and delays experienced by researchers conducting multicentre research. Furthermore, it indicates that barriers and challenges are likely to be experienced during the transition from the old to the new system.

In 2009, the National Health Service in the UK introduced a coordinated system with imposed approval timelines for gaining clinical research governance approval with the objective of ‘reducing both approval times and bureaucracy’ (http://www.ukcrn.org.uk/index/clinical/csp.html). The harmonisation being pursued through the HoMER model presents a timely opportunity for Australia to develop a nationally consistent framework and policies for ethical, scientific and governance review that can be adopted by institutions throughout the country, irrespective of local legislation. Such a development would redress the current imbalance between local risk mitigation and the conduct and support of health research in Australia. It will require goodwill and cooperation by the Commonwealth and jurisdictional health agencies, private health institutions and academic institutions. Continuing delays in obtaining research governance approval will delay the initiation of research and the dissemination of research findings. These delays may also directly reduce the amount of health research conducted in Australia, limiting access to new therapies, opportunities for the development of intellectual property, and academic research competitiveness. Our data support harmonising and streamlining the entire human health research approval process in Australia.

**Conclusion**

Our experiences suggest that for the full benefits of HoMER to be realised, health institutions must be adequately resourced, governance officers trained, researchers educated, and harmonised governance approval procedures developed and integrated with the HoMER model for research at both public and private institutions. Development of governance guidelines similar to the National Statement would help ensure more consistent interpretation of the requirements for governance approval, while allowing for local issues to be addressed. Once bedded down, a system developed to achieve clarity, transparency and uniformity in governance requirements would maximise the protection of research participants, researchers and institutions and facilitate health research in Australia.

**References**

Early implementation of antifungal therapy in the management of febrile neutropenia is associated with favourable outcome during induction chemotherapy for acute leukaemias

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Key words
acute leukaemia, induction chemotherapy, fungal infection, empirical, outcome.

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Abstract

Background: Mortality related to induction chemotherapy during the treatment of acute leukaemias (AL) has been estimated at 5–20%, and this increases with age. Fungal infection remains one of the major causes of morbidity and mortality and is considered an obstacle to the successful management of acute leukaemias.

Methods: We retrospectively analysed all patients treated for acute leukaemias at a single institution between July 2006 and January 2009, to assess the impact of early antifungal therapy on outcome during induction chemotherapy. There were 44 episodes of induction chemotherapy, with a median age of patients of 61 years (range 18–81), including 29 patients with acute myeloid leukaemia, 9 with acute lymphoblastic leukaemia and 6 with relapsed AL. The median age was 61 years (range 18–81), and 20 patients were over the age of 60 years.

Results: All patients who developed febrile neutropenia received broad-spectrum antibiotics. Early empirical antifungal treatment was commenced with voriconazole (15 patients) or caspofungin (12 patients) if the febrile neutropenia did not resolve after 72 h of antibiotic therapy, in conjunction with radiological changes consistent with possible fungal infection. None of the patients succumbed during induction chemotherapy. The 120-day mortality rate after the induction therapy was 2.2%, without any incidence of invasive fungal disease.

Conclusion: Our analysis shows that early empirical treatment for fungal infection with voriconazole or caspofungin is associated with a favourable outcome of induction therapy for acute leukaemias. Further studies to confirm this finding are warranted.

Introduction

One of the major obstacles in the management of acute leukaemia is a high treatment-associated mortality rate. Infection remains one of the leading causes of morbidity
and mortality in acute leukaemia patients, accounting for up to 70% of deaths.\textsuperscript{1,2} Prior to 1990, Gram-negative bacteria were the primary organisms responsible for infections. However, fungi are increasingly problematic pathogens, and the incidence of invasive fungal infection is rising among neutropenic patients. Moulds and yeasts, predominantly aspergillus and candida, are among the most common fungal pathogens affecting these immunocompromised patients.\textsuperscript{1-3}

Induction chemotherapy in many haematological malignancies results in a prolonged, severe myelosuppression for several weeks with concomitant significant infectious complications requiring immediate intervention.\textsuperscript{4-6} The treatment-related mortality rate of patients undergoing induction chemotherapy for acute myeloid leukaemia (AML) has been estimated at 5 to 10% for young adult patients and increases to 30% for patients over 60 years old.\textsuperscript{7,8}

Antifungal management during neutropenia can be divided into three indications. First, antifungal prophylaxis with low doses of conventional or liposomal amphotericin B, or with itraconazole or flucanazole and most recently posaconazole, are used when there is an expected prolonged period of neutropenia, based on the underlying disease or the chemotherapy regimen, such as in acute leukaemia or in bone marrow transplantation.\textsuperscript{9-12} Second, antifungal therapy in full treatment doses is administered when there is radiological or microbiological evidence strongly suggesting fungal disease. This strategy is considered pre-emptive treatment when it is used early in the treatment of high-risk patients. Thirdly, anti-fungal treatment as empirical therapy is commenced when fever in neutropenia does not resolve after about 5–7 days of initial and subsequently extended broad-spectrum antibiotics, even if there is no microbiological evidence of fungal disease.\textsuperscript{9-11}

It is often difficult to confirm a suspected diagnosis of fungal disease,\textsuperscript{12-15} and therefore patients may be undertreated with prophylactic or late empirical treatment strategies. With the development of newer and more effective antifungal drugs, such as voriconazole, posaconazole or caspofungin, such strategies may need to be revised and standardised for the best outcome in cohorts of severely immunocompromised patients, particularly patients with prolonged severe neutropenia secondary to induction chemotherapy for acute leukaemia. Our study provides a retrospective analysis of the fungal infection risk and clinical outcomes in a cohort of patients with acute leukaemias that were treated with early empirical antifungal therapy using newer generation antifungals, and provides a new perspective on the treatment options available in febrile neutropenia.

Patients and methods
All patients treated for acute leukaemias during the period July 2006 to January 2009 at Launceston General Hospital were retrospectively analysed. The aim of this analysis was to study the early implementation of treatment with newer antifungals on the outcome of induction chemotherapy in acute leukaemia. There were 38 patients undergoing induction or re-induction chemotherapy (44 episodes) for acute leukaemia during this period. The diagnostic subgroups in the patient population comprised 29 cases of AML and nine cases of acute lymphoblastic lymphoma (ALL) or Burkitt lymphoma. Six patients had relapsed disease (three with AML, three with ALL), and these underwent re-induction chemotherapy (Table 1). Induction therapy was defined as the first course of chemotherapy that was commenced to control acute leukaemia disease, while re-induction chemotherapy was defined as the first course of chemotherapy that was commenced in relapsed cases. The male to female ratio was 22:16 (Table 1). Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) status, where score 0 is fully active and score 4 is completely disabled.\textsuperscript{16} All patients were treated in single rooms, but without high-efficiency particulate air filters.

Pretreatment factors that may influence outcome were analysed, such as patient age, performance status, disease risk stratification, co-morbidities, intensive care unit (ICU) admission at presentation and complications of disease at presentation (e.g. organ failure or infections). Established post-treatment factors that may affect outcome included complications as a result of treatment (mainly tumour lysis, bacterial, viral and fungal infections), the severity and duration of neutropenia, frequency of blood component requirements and treatment-associated complications, such as bleeding, venous thromboembolic disease and other complications. The type of induction chemotherapy and intensity of treatment were recorded. Bacterial, viral and fungal prophylaxis and treatment strategies were considered in the analysis.

Radiological criteria for probable or possible fungal infection in high-resolution computed tomography (HRCT) scans were used as suggested by other authors; these were presence of multiple or single lung nodules, diffuse infiltrates, consolidation, ground-glass opacities and increased interstitial markings, as assessed by an expert radiologist.\textsuperscript{17-19}

Results
A total of 44 episodes of induction or re-induction chemotherapy in 38 patients were analysed. The median
The median age of patients was 61 years (range 18–81 years), and 20 patients were over the age of 60 years. Most of the patients presented initially with pancytopenia caused by leukaemia itself before commencement of any treatment, and seven patients had an existing infection at the time of presentation; this included two cases of pneumonia, one case of lower limb cellulitis and one case of sinusitis. Two patients were admitted at first presentation to the ICU with severe pneumonia requiring intubation and ventilation. One of these patients presented with multi-organ failure (acute renal failure, bone marrow failure, acute respiratory distress syndrome and acute intestinal obstruction) because of Burkitt lymphoma. This patient received induction chemotherapy in the ICU and recovered well to go home in remission after 8 weeks of hospitalisation (4 weeks in the ICU).

Patients in 26 episodes received high-dose cytarabine-containing regimens. The patients in the other 18 episodes received low- to intermediate-dose cytarabine in conjunction with anthracycline with a median duration of hospital stay of 30 days (range 18–58). Most of the patients received daily filgrastim (29 patients) at a dose of 5 mcg/kg body weight that was started 24 hours after completion of chemotherapy and continued until neutrophil recovery to $>0.5/nL$ for at least two consecutive days, while only nine patients received peg-filgrastim.

All patients received prophylactic nystatin mouth washes and prophylaxis with oral antifungals, consisting of either itraconazole capsules 200 mg b.d. (36 episodes), fluconazole 200 mg daily (three episodes) or posaconazole 200 mg three times daily (five episodes). In addition, all patients received Pneumocystis jirovecii pneumonia prophylaxis with double-strength sulfamethoxazole and trimethoprim on alternate days. Eleven patients received ciprofloxacin prophylaxis. Antiviral prophylaxis was commenced with famciclovir in the majority of patients, but valaciclovir (one patient) and aciclovir (two patients) were also used.

All patients were well hydrated with intravenous saline and received allopurinol for tumour lysis prophylaxis, except one patient who required rasburicase for the treatment of tumour lysis in conjunction with acute renal failure during his first presentation in the ICU.

Eleven patients were transferred to the ICU after commencement of treatment for acute leukaemia, either with sepsis or with respiratory compromise. All returned to ward-based care shortly after stabilisation of their condition. Two of these patients (2 out 11) also developed severe tumour lysis syndrome requiring ICU admission. Both were complicated by acute renal failure, necessitating intravenous rasburicase and dialysis treatment. Both recovered with normal kidney function after treatment.

The median period of neutropenia following induction therapy was 24.5 days (range 14–56). Three patients experienced prolonged neutropenia for more than five weeks. All patients developed febrile neutropenia. For 32 episodes, infections were clinically, radiologically or microbiologically established as the likely cause of fever. This included 27 pneumonias, one cystitis, two cases of sinusitis, as well as eight cases of blood culture-positive septicemias (with bacteria). For 12 patients and episodes, the cause of febrile neutropenia could not be established. In our series, most of the patients with respiratory distress syndrome and acute intestinal obstruction because of Burkitt lymphoma.

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of inductions (including re-induction for re-induced disease)</td>
<td>44 episodes, 38 patients</td>
</tr>
<tr>
<td>Age</td>
<td>Median 61 (Range 18–81)</td>
</tr>
<tr>
<td>No. of patients aged &gt;60</td>
<td>20</td>
</tr>
<tr>
<td>Sex</td>
<td>Male-to-female ratio 22:16</td>
</tr>
<tr>
<td>Disease (no. of episodes)</td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukaemia</td>
<td>29</td>
</tr>
<tr>
<td>Acute lymphoblastic lymphoma</td>
<td>9</td>
</tr>
<tr>
<td>Re-induction for relapsed disease</td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukaemia</td>
<td>3</td>
</tr>
<tr>
<td>Acute lymphoblastic lymphoma</td>
<td>3</td>
</tr>
<tr>
<td>Cytogenetic analysis</td>
<td></td>
</tr>
<tr>
<td>Ph+ chromosome</td>
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</tr>
<tr>
<td>Monosomy (5, 20 or 21)</td>
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</tr>
<tr>
<td>Translocations (e.g. 5,17; 8,21)</td>
<td>3</td>
</tr>
<tr>
<td>Complex karyotype</td>
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</tr>
<tr>
<td>Normal karyotype</td>
<td>28</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group at presentation (no. of episodes)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>LDH at presentation (N &lt; 225 U/L)</td>
<td>Median 385 (range 163–6590)</td>
</tr>
<tr>
<td>Neutrophils at presentation (N 2–7/nL)</td>
<td>Median 0.9/nL (range &lt;0.1–4.5)</td>
</tr>
<tr>
<td>Type of induction therapy (no. of episodes)</td>
<td></td>
</tr>
<tr>
<td>Regimen containing high-dose Ara-C</td>
<td>26</td>
</tr>
<tr>
<td>Regimen containing low dose Ara-C</td>
<td>14</td>
</tr>
<tr>
<td>Intermediate dose Ara-C</td>
<td>3</td>
</tr>
<tr>
<td>All-trans retinoic acid /idarubicin</td>
<td>1</td>
</tr>
<tr>
<td>Duration of hospital admission during induction therapy</td>
<td>Median 30 days (range 18–58)</td>
</tr>
<tr>
<td>Duration of hospital admission during induction therapy</td>
<td>Median 24.5 days (range 14–56)</td>
</tr>
<tr>
<td>Episodes requiring intensive care unit admission</td>
<td>11</td>
</tr>
<tr>
<td>Duration of intensive care unit admission</td>
<td>Median 8 days (range 4–28)</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase.
febrile neutropenia underwent a chest X-ray that was not conclusive, and therefore an HRCT scan of the chest and sinuses was conducted according to our hospital protocol.

At induction, all patients who developed febrile neutropenia received broad-spectrum antibiotics, including Gram-negative cover (ticarcillin clavulanate with or without gentamicin, ciprofloxacin or meropenem), and most (27 patients) received antifungal treatment if the fever did not resolve after 72 hours of antibiotic therapy. Patients were commenced on antifungal therapy with either voriconazole (15 patients) for a median period of 17 days (range 10–48) or caspofungin (12 patients) for a median period of 9.5 days (range 7–26). Caspofungin was commenced in patients who had elevated liver enzymes as a likely transient effect of chemotherapy. The dose of voriconazole was 400 mg IV twice daily for the first day, followed by 200 mg IV twice daily until discharge. The dose of caspofungin was 70 mg IV loading dose on the first day of treatment, followed by 50 mg IV daily until discharge. In both regimens, oral voriconazole was continued for 2–4 weeks with 200 mg twice daily after discharge. All patients recovered with normal liver function during the induction therapy. There were no significant differences between the two groups of patients who received either voriconazole or caspofungin, with resolution of fever and improvement of radiological findings in the further follow up.

Among the 27 patients who received antifungal therapy for persistent febrile neutropenia, the HRCT scans of the chest indicated that nine patients had consolidation in both lung fields, four patients showed pleural effusions, three had multiple nodules and two had a single nodule. Four patients had ground-glass opacities and three had increased interstitial markings. Two patients had bilateral maxillary sinusitis; one of them had additional ethmoidal sinusitis. The CT scans showed features of sinusitis, including mucosal thickening, soft tissue attenuation and air-fluid levels, which are considered suggestive of fungal disease. It is worth noting that about 50% of patients had some radiological changes that may suggest fungal disease, with a possible categorisation depending on CT findings to a ‘probable’ grading of fungal disease.

None of the patients died during the induction chemotherapy. The outcome was measured by the overall survival of patients at 30 days after recovery from neutropenia post induction therapy, and this was 100%. Furthermore, the 120-day survival rate after induction therapy was 97.8%. There was one patient with AML who succumbed at day 90 because of further disease progression after the second cycle of chemotherapy.

Discussion

The incidence of invasive fungal infections in patients with AML has been reported in some studies as 12% overall, and this is increased during induction therapy.20,21 The incidence of probable or proven aspergillosis in patients with AML was 7.1% in a study by Nosari et al.,22 and most patients (92%) were neutropenic at the time of diagnosis. Pagano et al.21 reported that the attributable mortality rate (AMR) of patients with hematologic malignancies caused by yeast infections were 33% for candidaemia, 50% for cryptococcosis, and 29% for trichosporonosis. The AMR for candidaemia ranged from 19% in lymphoma to 36% in ALL. Furthermore, the same study showed that the AMR in hematologic malignancies were 42% for aspergillosis, 64% for zygomycosis and 53% for fusariosis. The AMR for aspergillosis was 38% in AML. An analysis of the AMR caused by aspergillosis revealed that 28% of deaths (31 of 112) occurred during the induction treatment of hematologic malignancies and the AMR increases up to 50% in patients who are treated for relapsed disease, which may be attributed to the increased incidence of fungal disease among this cohort of patients.21 Thus, reducing the risk of fungal infections, particularly in the induction phase, is a high priority.20–25

The new antifungals have been directly associated with an improved outcome of systemic or invasive fungal disease in immunocompromised patients.26 Simultaneously, there has been a significant decline in the administration of the antifungal amphotericin B deoxycholate, which has been used for several decades and has widely known side effects.27 Cordonnier et al.24 compared empirical versus pre-emptive antifungal therapy with amphotericin B deoxycholate in high-risk, febrile neutropenic patients. Empirical therapy was defined as antifungal treatment after 4 days of fever and antibacterial treatment, and pre-emptive therapy was defined as antifungal therapy after 4 days of fever and antibacterial treatment plus any other clinical, radiological or laboratory sign that is commonly associated with invasive fungal infection. Pre-emptive treatment was non-inferior to empirical treatment with regard to patient survival; however, the rate of invasive fungal infections was higher in the pre-emptive group (9.1% vs 2.7%). It is worth noting that antifungal treatment in the study of Cordonnier et al.24 was different to our study in that amphotericin B deoxycholate (1 mg/kg/day) and liposomal amphotericin (3 mg/kg/day) was used according to creatinine clearance.24 The probability of fungal infection in the severely immunocompromised patients treated at our institution can be considered high. Furthermore, it was difficult to clinically justify a bronchoalveolar lavage
procedure under suboptimal conditions with low oxygen saturation or other respiratory compromise, high risk of bleeding complications, in addition to the difficulties in culturing fungi. Recently however, HRCT scanning has been considered an acceptable diagnostic criterion for fungal disease.12,13,25

In our series, we commenced early empirical treatment with either voriconazole or caspofungin during acute leukaemia induction therapy when febrile neutropenia did not respond to broad-spectrum IV antibiotics after only 72 h (10 patients), or as a pre-emptive antifungal treatment when there were pulmonary changes in the HRCT scan (17 patients). Patients with positive HRCT findings suggestive of fungal disease (17) received voriconazole (9) and caspofungin (8) with excellent response thereafter and resolution of the fever and pneumonia. The remainder of the febrile neutropenic patients were treated as early empirical antifungal treatment with voriconazole (6) and caspofungin (4) with resolution of their fever and improvement of their wellbeing. Antifungal medications were well tolerated by all patients.

It is worth noting that none of the patients who underwent induction or re-induction chemotherapy for their acute leukaemia or lymphoblastic lymphoma succumbed to infection during the induction therapy. In fact, patients who were significantly ill with a poor ECOG status between 2 and 4 (15 cases) that was associated with life-threatening infections responded well to treatment, with improvement in their ECOG status to 0 and 1, and were discharged from hospital in good clinical condition. Twenty patients in total were aged over 60 years of age, which is considered a separate high risk factor.

The most significant change in our series compared with other studies is that we have employed the new antifungals voriconazole and caspofungin during induction chemotherapy for patients with febrile neutropenia not responding to broad-spectrum antibiotics, and that this was commenced after 72 hours of unresolved fever. These patients were considered to be at high risk of developing fungal infections, and this risk was enhanced when considering the radiological findings that may suggest fungal disease. Such an early treatment strategy has the potential to further reduce the mortality rate below the rates of 10% previously reported during induction therapy for younger patients with acute leukaemia, and below the rates of up to 30% for elderly patients (>60 years).7,8 In accordance with other recent reports, HRCT played an important role in diagnosing or suggesting fungal infection.28

Our study has a few shortcomings, as it is based on a retrospective analysis of patients that have been treated at our institution. Therefore, there is no dedicated control group of patients who have not received early antifungal treatment in febrile neutropenia, so that published mortality rates from other cohorts have to be used as a point of reference.

In conclusion, early empirical antifungal treatment in line with the published Australian and New Zealand guidelines,12,13 was associated with significantly lower treatment-related mortality during the induction therapy for acute leukaemia in our cohort of patients than in other published studies. Furthermore, there was no indication that any of our patients had progressed to severe invasive fungal infection. This suggests that further studies of early antifungal therapy in febrile neutropenia are warranted, particularly in high-risk patients with prolonged episodes of neutropenia after chemotherapy.

Acknowledgement

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Clinical utility of molecular and flow cytometric markers in chronic lymphocytic leukaemia

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Key words
B-cell chronic lymphocytic leukaemia, prognosis, CD38, ZAP-70, Ig somatic hypermutation.

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Abstract
Background: Chronic lymphocytic leukaemia (CLL) is a clinically heterogeneous disease. While immunoglobulin variable region heavy chain (IgVH) mutational status remains the ‘gold standard’ in molecular prognostication, a range of additional markers is increasingly being used in clinical trials. As awareness of trial data increases, requests to determine these prognostic markers for new CLL patients are becoming more prevalent in Australia.

Aim: To explore the clinical utility of currently available prognostic markers for CLL in an Australian cohort.

Methods: IgVH mutational status and gene usage was determined and compared with other reported immunophenotypic markers, cytogenetics and clinical outcome as defined by treatment-free survival (TFS), lymphocyte doubling time and clinical stage in a cohort of 65 CLL patients.

Results: An unmutated IgVH gene, high expression of CD38, ZAP-70, CD25, CD49d, CD54 or low expression of CD49c was associated with shorter TFS indicating an adverse clinical prognosis in our cohort. High expression of each of CD38, ZAP-70, CD49d and CD54 was significantly associated with an unmutated IgVH gene; however, associations were not absolute. IgVH and CD25 expression retained their significance in multivariate analysis. Concordant CD25high/IgVH unmutated CLL patients had the shortest median TFS interval (40 months) in our cohort.

Conclusions: Molecular and immunophenotypic markers remain useful as adjuncts to clinical prognostication; however, as single parameters they are unable to dictate the timing of therapeutic intervention. The combined use of CD25 and IgVH mutational status may be clinically relevant to CLL prognostication while also providing insight into the biological pathways involved in disease progression.

Introduction

Chronic lymphocytic leukaemia (CLL) is the most common lymphoid malignancy in western countries, including Australia, accounting for approximately 25% of all leukemias.1 Data from the Australian Cancer Registry note that approximately 720 new cases of CLL are diagnosed each year. Diagnosis is often made incidental to a routine full blood examination. A high B-lymphocyte count of greater than 5 x 109/L with a phenotype determined by flow cytometry of CD5, CD19 and CD23 positivity with weak monoclonal light chain expression and low levels of CD20 are characteristic of the disease. The advent of multi-parametric flow cytometry has meant that all of these expression markers may be analysed in a single tube allowing highly specific characterisation of the malignant clone.

CLL displays heterogeneity in biology and clinical outcome, where survival can range from months to decades. Several prognostic markers for CLL exist, including the degree of somatic mutation in the immunoglobulin (Ig) variable region (V), heavy chain (H) genes (IgVH).2,3 An unmutated IgVH gene (≥98% concordance with the germline sequence) is generally associated with a shorter time to therapeutic intervention, poorer overall survival and the presence of unfavourable
cytogenetic abnormalities; reviewed in Kharfan-Dabaja et al. However, the process of determining IgVH mutational status requires specialised laboratory techniques, is time-consuming and expensive. This has led to a search for the identification of reliable surrogate markers for IgVH.

The cytoplasmically expressed ZAP-70 protein was identified as potentially one such marker. However, there is considerable technical variation in the flow cytometric assay for ZAP-70 protein expression with generally poor reproducibility restricting its general application. Other surface membrane markers also have limited published prognostic potential in CLL, including CD11b, CD20, CD25, CD49c, CD49d and CD54. Cytogenetic abnormalities, in particular, deletion of 11q22 and 17p13 also define a poor prognostic outcome for the patient. Clinicians are increasingly being requested to determine prognostic markers, in particular IgVH mutational status, CD38 and ZAP-70 expression and cytogenetics. These markers are regularly used in clinical trials and until recently have not been widely available in Australia. Here we present data on cytogenetic anomalies, IgVH mutational status and other prognostic markers, including the expression of CD38 and ZAP-70 for an unselected cohort of CLL patients presenting to an Australian teaching hospital.

Materials and methods

Patients and patient characteristics

Whole blood samples were collected from 65 patients diagnosed with B-CLL. Written informed consent for the collection of blood from patients and normal donors was obtained in compliance with institutional ethical guidelines. The diagnosis of B-CLL was based on standard morphologic and immunophenotyping criteria. Routine laboratory studies consisted of complete blood count with leukocyte differential, platelet count and blood chemistry, including lactate dehydrogenase (LDH). Lymphocytes were isolated from whole blood by density gradient centrifugation using Ficoll-Paque PLUS (GE Healthcare, Uppsala, Sweden) and stored in liquid nitrogen for subsequent use.

Antibodies

Directly conjugated CD11b-PE, CD20-APC and CD25-PE antibodies were from BD Biosciences (San Jose, CA, USA). CD5 PECy7, CD19-APCCy7, CD27-FITC, CD45 PEcy5, CD49d-PECy5 and CD54-PECy5 were from BD Pharmingen (San Diego, CA, USA). CD38-A647, CD49c-PE and CD79a-A647 were from AbD Serotec (Kidlington, UK). Upstate Anti Zap-70 FITC (clone 2F3.2) was from Millipore (Bedford, MA, USA).

Genomic DNA extraction and IgVH mutational status

Genomic DNA was extracted from 5 × 10⁶–1 × 10⁷ cells using the Illustra Blood GenomicPrep Mini Spin Kit (GE Healthcare, Buckinghamshire, UK) as per manufacturer’s instructions. Amplification and sequencing of IgVH genes was performed using Framework1 and JH consensus primers, as previously described. CLL cases were classified as IgVH unmutated if there was ≥98% concordance between the leukaemic DNA and the respective V-germline sequence, and IgVH mutated if there was <98% concordance with sequence data obtained from the IMGT database.

Interphase fluorescent in situ hybridisation

Lymphocytes from six normal donors and 38 CLL patients were incubated with hypotonic solution (0.075 M KCl for 30 min at 37°C) and fixed with three changes of 3:1 methanol/acetic acid. Slides for fluorescent in situ hybridisation (FISH) were made by hybridising probes for del(17)(p13.1), del(13)(q14.3), del(11)(q22.3) and centromere 12 using commercially available probes from Abbott Molecular Inc (Des Plaines, IL, USA). For each sample, 100–200 interphase nuclei were scored by two independent scorers. Results were considered clonal when the percentage of cells with any given chromosome abnormality exceeded the normal cut-off value. Cut-off values were determined by calculating the average scores plus three times the standard deviation for six normal samples: for the 13q14 probe, the cut-off level was 4%; for the centromere 12 probe, the cut-off level was 3.5% and for the 17p13 and 11q22 probes, the cut-off level was 4.5%.

Flow cytometry

Cells were labelled with combinations of directly conjugated antibodies using standard protocols. Lymphoid cells were gated on FSC-A and SSC-A, and further gated on CD5 and CD19 expression. Dual CD5+/CD19+ populations were selected, and the mean fluorescence intensity (MFI) of each surface marker (CD38, CD25, CD27, CD11b, CD20, CD45, CD49d, CD49c, CD54 and CD79a) was recorded. CD38 expression was also determined as per cent positivity by gating on unstained cells in the

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sample. Voltage settings were kept constant between all tubes/samples. For the intracellular protein ZAP-70, fixation and permeabilisation procedures were performed using the Dako IntraStain Kit (Glostrup, Germany) according to manufacturer’s instructions. Cells were analysed on a FACS Canto with FACS Diva software (BD Biosciences, San Jose, CA, USA). For ZAP-70 analysis, dual CD5/CD19 positive cells were conservatively gated and MFI recorded. ZAP-70 expression in CD5 positive CD19 negative T cells was also recorded as MFI. ZAP-70 expression was calculated as the ratio of MFI in CLL cells/MFI in T cells.18

Statistical analysis
The associations between variables were tested by Spearman’s correlation test for continuous variables. Differences in the cellular and clinical characteristics of good and poor prognostic populations were evaluated by χ² statistics. A Kruskal–Wallis test (one-way ANOVA) with a Dunn’s post-hoc test for multiple comparisons was used to test differences between two or more groups. To identify antigens whose expression was directly related to prognosis, univariate Cox proportional hazards analysis was performed with treatment-free survival (TFS) as the dependent variable. Values of cell surface and intracellular markers were also tested for possible cut-offs by means of maximally selected log–rank statistics.19 TFS curves were plotted according to the Kaplan–Meier method and compared with the log–rank test. To evaluate the simultaneous impact of variables on duration of TFS, a multivariate analysis was performed using the Cox regression model. A P-value of less than 0.05 was considered significant for all statistical calculations.

Results
Patient characteristics
A summary of the clinical and laboratory characteristics of the cohort is displayed in Table 1. Patients were referred to Flinders Medical Centre directly from general practice. Of note, the average age of diagnosis in our cohort (60.1 years) was younger than the average age of diagnosis in Australia (65–70 years).20 Evaluation of laboratory prognostic markers (IgVH mutational status, expression of surface and intracellular markers) was performed within the first 24 months of initial diagnosis for 24/65 (37%) patients. For the remainder of patients, these markers were determined at an interval of between 25 and 107 months (median 68 months) post diagnosis. The median follow-up time was 5 years (range 10 months to 11 years and 1 month) and the survival rate was 100%. Twenty (31%) patients demonstrated progressive disease requiring treatment. Of this group, the median TFS interval from diagnosis was 36 months (range 1–132 months).

As the overall survival rate in our cohort was 100% at the time of analysis, the risk of all clinical and laboratory prognostic markers, including age at diagnosis, lymphocyte doubling time (LDT), LDH and clinical stage, was evaluated in our cohort as TFS. Advanced clinical stage (Binet stage B/C) and a LDT of <12 months were predictors of a shorter TFS (P < 0.01, univariate Cox proportional hazard model). In contrast, age at diagnosis, high LDH and male sex were not predictive of shorter TFS in univariate analysis.

IgVH mutation frequency and VH gene usage
IgVH mutation frequency and V gene usage was determined in 61/65 patients. Of these, 17/61 (27.9%) patients had an unmutated and 44/61 (72.1%) had a mutated IgVH gene. The VH3 family was the most commonly used (48.4%) followed by VH1 (28.1%), VH4 (14.1%), VH2 (6.3%) and VH5 (3.1%). VH6 usage was not detected in our cohort. VH gene usage was widely distributed with a total of 28 VH gene segments used. VH3-7 was the most commonly used VH segment (7 patients) followed by VH1-69 (5 patients), VH3-21 (4 patients) and VH3-23 (4 patients). Two patients in our
cohort had more than one CLL clone present; one patient used the VH1 family only (VH1-2 and VH1-69, both unmutated) and the second used VH1-36, VH2-5, VH3-7 and VH4-31 gene segments (all mutated).

Patients with an unmutated IgVH gene displayed a significantly higher proportion of Binet stage B/C patients and had a significantly higher proportion of patients with a short LDT (<12 months) compared with the IgVH mutated group (P < 0.001, χ² statistic). Kaplan–Meier analysis also demonstrated that TFS was significantly shorter in patients with an unmutated IgVH gene (median TFS 53 months) compared with patients with a mutated IgVH gene (median TFS 132 months) (Fig. 1, P = 0.014, log-rank test). However, it is important to point out that 22% of patients with a mutated IgVH gene also had advanced clinical stage disease and 13.6% had a LDT of <12 months. Furthermore, 47% of patients with an unmutated IgVH gene were of early clinical stage disease and a large proportion of IgVH unmutated patients (64.7%) had a LDT of >12 months.

Expression of surface and intracellular markers and relationship to prognosis

The prognostic value of surface and intracellular markers, including CD38, ZAP-70, CD25, CD27, CD11b, CD20, CD49d, CD49c, CD54 and CD79a, were assessed in our cohort. Because of the homogeneous (unimodal) staining of surface markers, expression was defined as MFI and ZAP-70 was reported as a ratio of the MFI on T cells. For CD38, expression was also determined as per cent positivity using unstained cells in the sample to apply a threshold gate. As shown in Figure 2, there was a positive correlation between CD38 expression determined as MFI and per cent positivity (r = 0.746, P < 0.01, Spearman’s correlation test).

Maximally selected log–rank statistics plots were used to identify the optimal cut-off points yielding the best separation of CLL patients into two subgroups with different TFS probabilities. The selected cut-points were MFIs of 1137 (CD38), 997 (CD25), 1155 (CD49d), 579 (CD54) and 237 (CD49c), a ratio of 0.49 (ZAP-70) or ≥3% positive cells (CD38).

An assessment of the Kaplan–Meier curves demonstrated that the median TFS was significantly shorter in patients with high CD38, ZAP-70, CD25, CD49d or CD54 expression compared with patients with low expression of each of these antigens (Fig. 3). Conversely, patients with high CD49c expression had a significantly longer TFS interval compared with patients with low CD49c expression (Fig. 3). No association was found when the higher reported cut-off values for CD38 were analysed with respect to TFS (5%, 7%, 20% and 30%) (P > 0.05, log-rank test). Expression of CD11b, CD27, CD20 or CD79a was not associated with TFS in our cohort.

The association between patients with high and low CD38, ZAP-70, CD25, CD49d or CD54 expression was also compared with IgVH mutational status and other clinical parameters. A short LDT (<12 months) and advanced clinical stage was associated with high expression of each of CD38, CD25, CD49d, CD54 and low

![Figure 1](image1.png)

**Figure 1** Kaplan–Meier plot of treatment-free survival (TFS) in chronic lymphocytic leukaemia (CLL) patients subdivided on the basis of immunoglobulin variable region heavy chain (IgVH) mutational status. Median TFS was 132 vs 53 months for IgVH mutated (n = 41) vs IgVH unmutated (n = 17) CLL cases, respectively (P = 0.014, log-rank test).

![Figure 2](image2.png)

**Figure 2** Correlation between CD38 expression measured as mean fluorescence intensity (MFI) and per cent positivity. A positive correlation was observed between CD38 expression reported as MFI and per cent positivity (n = 65) (r = 0.746, P < 0.01, Spearman’s correlation test).
Kaplan–Meier plots for surface and intracellular markers associated with treatment-free survival (TFS) in chronic lymphocytic leukaemia (CLL). Kaplan–Meier curves were assessed for CD38 (a), ZAP-70 (b), CD25 (c), CD49d (d), CD54 (e) and CD49c (f) using cut-off values as determined by maximally selected log-rank statistics. High expression of CD38, ZAP-70, CD25, CD49d and CD54 and low expression of CD49c was associated with significantly shorter TFS. Median TFS intervals were as follows: CD38 (132 vs 63 months for patients with low vs high expression, respectively), ZAP-70 (132 vs 53 months for patients with low vs high expression, respectively), CD25 (132 vs 63 months for patients with low vs high expression, respectively), CD49d (132 vs 53 months for patients with low vs high expression, respectively), CD54 (median TFS not reached vs 97 months for patients with low vs high expression, respectively) and CD49c (63 vs 132 months for patients with high vs low expression, respectively). MFI, mean fluorescence intensity.
expression of CD49c. High ZAP-70 expression was significantly associated with short LDT but not advanced clinical stage. There was a significantly higher proportion of IgVH unmutated cases in patients with high CD38, ZAP-70, CD49d and CD54 expression compared with patients with low expression of these markers \((P < 0.05, \text{Table 2})\). However, it must be noted that these associations were not absolute. For example, a small proportion of patients with low CD38 expression also had an unmutated IgVH gene (11.3%), a LDT of <12 months (15.9%) or advanced clinical stage (25%) (Table 2 and Fig. 4a). When considering patients with low ZAP-70 expression, 16.2% had an unmutated IgVH gene and 14.2% had a short LDT (Table 2 and Fig. 4b). Similar observations were also made for CD25, CD49d, CD54 and CD49c (Table 2).

Given that all markers besides CD25 and CD49c were significantly associated with IgVH mutational status (Table 2), we only evaluated the simultaneous impact of CD25 and CD49c with IgVH mutational status on the duration of TFS in multivariate analysis (Cox regression model). IgVH mutational status \((P = 0.03)\) and CD25 \((P = 0.002)\) (but not CD49c) retained their significance in multivariate analysis. The combined impact of these two variables on TFS was therefore assessed. Thirty-six patients had a concordant pattern and 23 patients had a discordant pattern. The differences in the TFS of these four groups were statistically significant with median TFS intervals of 132 months (CD25 low/IgVH mutated, \(n = 27\)), not reached (CD25 low/IgVH unmutated, \(n = 8\)), 97 months (CD25 high/IgVH mutated, \(n = 15\)) and 40 months (CD25 high/IgVH unmutated, \(n = 9\)) (log–rank test for trend, \(\chi^2 = 17.853, df = 1, P < 0.001, \text{Fig. 5}\)).

Cytogenetics/FISH

Thirty-eight patients with available cytogenetic (FISH) data were stratified into four groups according to major cytogenetic categories \((13q14 as a sole aberration (n = 18), normal karyotype (n = 11), 12q trisomy (n = 4), 11q22 or 17p deletion (n = 5))\). Where more than one anomaly was detected, patients were placed into cytogenetic categories according to the most aggressive risk factor present: 17p deletion (most aggressive) → 11q deletion → trisomy 12 → 13q deletion (least aggressive). The percentages of cells carrying abnormalities for each group were as follows: 13q14 deletion (12%–98%, mean 73%), trisomy 12 (6%–86% deleted, mean 51%), 11q22 deletion (one patient demonstrating a deletion in 86% of cells) and 17p deletion (7%–76%, mean 24%).

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**Table 2** Association of surface and intracellular antigen expression with clinical and laboratory features and IgVH mutational status in CLL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age‡ Binet stage B/C</th>
<th>LDT &lt;12 months</th>
<th>IgVH UM</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with characteristic</td>
<td>All patients</td>
<td>46.1%</td>
<td>33.3%</td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD38low</td>
<td>47.7%</td>
<td>25%</td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD38high</td>
<td>42.8%</td>
<td>42.8%</td>
</tr>
<tr>
<td>(P)-value†</td>
<td>0.6</td>
<td><strong>0.029</strong></td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>% with characteristic</td>
<td>ZAP-70low</td>
<td>54.7%</td>
<td>28.5%</td>
</tr>
<tr>
<td>% with characteristic</td>
<td>ZAP-70high</td>
<td>33.3%</td>
<td>42.8%</td>
</tr>
<tr>
<td>(P)-value†</td>
<td><strong>0.019</strong></td>
<td>0.099</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD25low</td>
<td>48.7%</td>
<td>20.5%</td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD25high</td>
<td>42.3%</td>
<td>50%</td>
</tr>
<tr>
<td>(P)-value†</td>
<td>0.463</td>
<td><strong>0.001</strong></td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD49dlow</td>
<td>49%</td>
<td>25.5%</td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD49dhigh</td>
<td>46.1%</td>
<td>61.5%</td>
</tr>
<tr>
<td>(P)-value†</td>
<td>0.758</td>
<td><strong>&lt;0.001</strong></td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD54low</td>
<td>40.9%</td>
<td>18.1%</td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD54high</td>
<td>51.2%</td>
<td>41.4%</td>
</tr>
<tr>
<td>(P)-value†</td>
<td>0.297</td>
<td><strong>0.003</strong></td>
<td><strong>0.042</strong></td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD49clow</td>
<td>52.9%</td>
<td>52.9%</td>
</tr>
<tr>
<td>% with characteristic</td>
<td>CD49chigh</td>
<td>46.5%</td>
<td>25.5%</td>
</tr>
<tr>
<td>(P)-value†</td>
<td>0.549</td>
<td><strong>0.002</strong></td>
<td><strong>0.001</strong></td>
</tr>
</tbody>
</table>

†The significance of differences between low and high patient groups was determined by \(\chi^2\) statistics (significant comparisons indicated in bold and italics). ‡Age at diagnosis. Cut-off values to define high and low expression of each marker were determined by maximally selected log–rank statistics and are shown in Figure 3. No differences were detected between low and high patient groups for any marker with respect to sex or LDH (data not shown). CLL, chronic lymphocytic leukaemia; IgVH, immunoglobulin variable region heavy chain; LDH, lactate dehydrogenase; LDT, lymphocyte doubling time; UM, unmutated.

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No significant differences in FISH risk distributions were found in subsets of patients classified by laboratory and clinical markers of prognosis ($P > 0.05$ for all comparisons, Kruskal–Wallis test); however, we acknowledge that this is most likely due to the low numbers of patients with available cytogenetic data.

**Discussion**

The clinical utility of prognostication in CLL lags considerably behind the technical possibilities. Although IgVH mutational status has been considered the ‘gold standard’ in CLL prognostication, potential surrogate prognostic markers have been used in clinical trials, two of which are ZAP-70 and CD38. Additionally cytogenetic analysis and FISH appear important for treatment decisions and prediction of response to certain therapies. As awareness of trial data increases, requests to determine these prognostic markers for new CLL patients are becoming more prevalent in Australia. We have profiled an Australian cohort from a single institution using currently accepted prognostic markers for CLL to add to the discussion regarding their relevance in the clinical setting. While the overall survival rate of our cohort (100%) most likely reflects the younger average age of our cohort at diagnosis,$^{21,22}$ the characteristics of our cohort were representative of the heterogeneous nature of CLL.

In our study, the frequency of IgVH subgroup usage was typical of other western cohorts. Consistent with the literature, our cohort demonstrated preferential use of VH3-7 and VH4-34 gene segments. VH3-21 usage is reported to be associated with significantly shorter survival, regardless of mutational status$^{23}$ and in our series most were unmutated. The identification of 2/61 patients (3.2%) having multiple clones is consistent with published literature.$^{24}$

The median TFS of patients with an unmutated IgVH gene of 53 months in our cohort is in line with another study examining this relationship.$^{25}$ While having an unmutated IgVH gene was also significantly associated...
with a shorter LDT and advanced clinical stage, it was not absolutely predictive of clinical outcome. This is the case for almost every study of IgVH mutational frequency in the literature highlighting the need for either additional prognostic markers in CLL or an algorithm for the current prognosticators. The association between high CD25 expression and a shorter TFS observed in our cohort has previously been recognised and as the receptor for interleukin-2, high CD25 expression may potentially contribute to immunodeficiency in CLL by reducing the levels of free interleukin-2 available to normal immune cells. To our knowledge, this is the first study to report the additive prognostic potential of CD25 expression and IgVH mutational status in CLL. Therefore, further consideration of CD25 as a prognostic variable may be warranted and any impact on immune status further explored.

The use of immunophenotypic prognostic markers has its limitations. This is especially evident when considering CD38 and ZAP-70 expression, two of the most widely used prognostic markers. Much criticism for the use of ZAP-70 as a prognostic marker comes from a lack of standardisation in the methods employed to detect and analyse ZAP-70 expression. While many studies use a percentage cut-off value to define ZAP-70 positivity, we and others found this method to be unreliable and that employing a ZAP-70 ratio allowed for more reproducible results. This is in line with an increasing number of reports indicating that discrimination between ZAP-70 positive and negative cases should be based on a population derived parameter, such as the fluorescence ratio of two cell populations. Furthermore, the use of a ratio allows for the incorporation of an internal control in each sample, reducing day-to-day variability. Our proposed cut-off value of 0.49 (MFI ratio) for defining high and low ZAP-70 expression should therefore be tested in a larger prospective study.

Determination of CD38 expression also has limitations and cut-off values from 5% to 30% have been reported in the literature. In our own study, 3% appeared most discriminatory, although should be validated in a larger cohort. The low cut-off value in this study is in line with another report suggesting that any detectable level of CD38 is a marker of poor prognosis. However, the determination of a cut-off value is somewhat arbitrary without a bimodal cell population. Our experience and the wide range of cut-off values reported in the literature for CD38 demonstrate a need for each laboratory to establish and validate their own cut-off values for this marker. This may also apply to other molecular markers as demonstrated in this study. Furthermore, given that the expression of CD38 varies with time it is here recommended that the expression of CD38 be viewed speculatively and in conjunction with clinical disease.

The clinical utility of CD49d, CD54 and CD49c as prognostic markers in CLL deserves further attention. There is no evidence in the literature to suggest that the expression of any of these markers changes over time and given their relative ease of measurement these markers have the potential to serve as robust prognostic variables in CLL. In agreement with our study, others found determination of CD49d expression to be highly reproducible and not subjected to variations in fresh versus frozen samples or over time.

**Conclusion**

We have retrospectively evaluated the prognostic significance of several molecular markers on predicting TFS in CLL. IgVH mutational status and CD25 expression were strong predictors of TFS in multivariate analysis and we have demonstrated a potential for their combined use. Our results highlight the need for individual laboratories to fully define and validate their own cut-off values for molecular markers. However, given the relatively small numbers and young age of our cohort at diagnosis, a larger prospective study with longer follow up will be needed to evaluate fully the significance of the cut-off values proposed for all immunophenotypic markers found to be significant by univariate analysis in this study (CD25, CD38, ZAP-70, CD49d, CD49c and CD54).

Clearly, molecular markers are necessary for the evaluation of outcome in clinical trials. These data suggest that chromosome or FISH analysis has the greatest prognostic impact for response to therapy. However, even with the strongest of these predictors, aberrations of the tumour suppressor gene TP53, initiation of therapy remains a clinical decision. Molecular markers may add science to the art of clinical-based decision making; however, as single parameters they are unable to dictate the timing of therapeutic intervention. The question remains as to whether a combination of prognostic markers or an algorithm for the current markers may be more clinically relevant, also providing insight into the biological pathways involved in disease progression. Certain biochemical pathways will eventually hold the keys to variation in primary disease behaviour, others to response to therapy. In time, research will hopefully close the gap between our understanding of this heterogeneous disease and our observations.

**Acknowledgements**

The authors acknowledge Ms Olja Saran and Ms Tram Vu (Department of Immunology, Allergy and Arthritis, Flinders Medical Centre) for their assistance with the immunophenotyping of CLL patients.
Insulin resistance and coronary flow velocity reserve in patients with autosomal dominant polycystic kidney disease

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Abstract

Background: Cardiovascular problems are a major cause of morbidity and mortality in patients with autosomal dominant polycystic kidney disease (ADPKD).

Aim: The aim of this study was to investigate coronary flow velocity reserve (CFVR) as a marker of endothelial dysfunction, carotid intima media thickness (CIMT) as a marker of subclinical organ damage and insulin resistance (IR) as a cardiovascular risk factor in patients with ADPKD.

Methods: Twenty-two normotensive ADPKD patients with well-preserved renal function and 19 healthy subjects were included in the study. Creatinine clearances were calculated by the Cockcroft-Gault formula. The homeostasis model of IR (HOMA-IR) was used to measure IR. CIMT was measured by high-resolution vascular ultrasound. CFVR was calculated as the ratio of hyperaemic to baseline diastolic peak velocities by echocardiography.

Results: There was no significant difference between the two groups regarding age, gender, body mass index, systolic and diastolic blood pressures, cholesterol and triglyceride levels. However, CIMT and HOMA-IR were significantly increased and CFVR significantly decreased in patients with ADPKD compared with healthy subjects.

Conclusions: The findings of decreased CFVR, increased CIMT and increased IR suggest that cardiovascular risk is elevated even in the early stages of ADPKD.
Introduction
Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease. Patients with ADPKD have an increased incidence of cardiovascular complications. Hypertension, a common finding of ADPKD, often occurs before the onset of renal insufficiency and is associated with a faster progression to end-stage renal disease and increased cardiovascular mortality. Left ventricular hypertrophy (LVH) also occurs frequently in patients with ADPKD. Increased left ventricular mass index (LVMI) and biventricular diastolic dysfunction even before the development of hypertension in patients with ADPKD with preserved renal function were reported. Moreover, endothelial dysfunction in patients with ADPKD with preserved renal function and normal blood pressures and normal renal functions were recently reported in young patients with ADPKD who have normal blood pressures and normal renal functions.

Insulin resistance, an independent predictor of cardiovascular disease, was reported in patients with ADPKD. The mechanisms of insulin resistance in ADPKD were detailed in previous studies. An association between insulin resistance and LVH was also found in these patients, independent of other factors known to increase LVMI. The aim of this study was to investigate the association of insulin resistance with CFVR and CIMT in normotensive patients with ADPKD who have preserved renal function.

Methods

Subjects
Twenty-two normotensive patients with ADPKD (7 men, 15 women) with a mean age of 38.8 ± 12.1 years and 19 healthy controls (8 men, 11 women) with a mean age of 36.2 ± 6.6 years were included in this cross-sectional study. Healthy subjects and ADPKD patients were selected randomly from the Nephrology Department of Istanbul University Faculty of Medicine, Istanbul, Turkey. The diagnosis of ADPKD was reached by the ultrasonographic criteria described by Ravine and positive family history of ADPKD in all the patients.

Creatinine clearances were calculated by the Cockcroft–Gault formula. All patients had a creatinine clearance greater than 60 mL/min/1.73 m².

Subjects with diabetes mellitus, established cardiovascular disease, chronic diseases that could affect endothelial function, a creatinine clearance lower than 60 mL/min/1.73 m² or a family history of premature atherosclerosis were excluded. Thyroid and liver functions were checked and subjects with thyroid or liver function abnormalities were also excluded. During the testing period, all subjects were asked to keep their normal diet and physical activity.

Five patients with ADPKD and six healthy subjects were smokers. None of the subjects had a history of ethanol intake. Three patients with ADPKD and two healthy subjects were postmenopausal women. None of the subjects received any medications.

The study protocol was approved by the institutional medical ethics committee and written informed consent was obtained from all the subjects included in the study.

Systolic and diastolic blood pressures were measured on the right arm of subjects in an upright sitting position after at least 5 min of rest using an Erka sphygmomanometer (PMS Instruments Ltd, Berkshire, UK) with appropriate cuff size. Two readings were recorded for each individual. The average of two readings was defined as the subjects’ blood pressure. Ambulatory blood pressure monitoring was performed in all patients over a 24-h period by the oscillometric method using a fully automatic non-invasive recorder (Spacelabs 90207, Redmond, Washington, USA). The monitor was programmed to measure blood pressure and heart rate at 20-min intervals between 07.00 and 22.59 and at 30-min intervals between 23.00 and 06.59. The patients were advised to pursue their usual daily activities; none was on nightshift duty, and they all slept during the night. All data were transferred into a software program.

Venous blood samples were drawn after an overnight fast of 12 h. All biochemical analyses, including glucose, creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride concentrations, were performed with an oxidase-based technique using Roche/Hitachi Modular System (Japan) in our central biochemistry laboratory. Fasting plasma insulin levels were determined from blood samples stored at −70°C by means of a commercial double-antibody solid-phase radioimmunoassay (Phadeseph Insulin RIA 100; Pharmacia Diagnostics AB, Uppsala, Sweden). In this study, the homeostasis model of insulin resistance (HOMA-IR) was used as a measure of insulin resistance. HOMA-IR was calculated with the following formula: fasting plasma glucose (mmol/L) times fasting serum insulin (mU/L) divided by 22.5.

Echocardiographic examinations
Echocardiographic examination was performed using a Vingmed System Five, Norway echocardiographic system.
equipped with 2.5-MHz transducers (Vingmed Sound, Norway). M-Mode and two-dimensional measurements were performed in accordance with methods recommended by the American Society of Echocardiography.²¹,²² Cardiac mass was calculated by means of the formula derived by Devereux and Reichek.²³ LVH was defined as left ventricular mass index (LVMI) >125 g/m² for men and >110 g/m² for women.

**Carotid intima media thickness measurements**

The carotid arteries were evaluated with the Vivid 7 echocardiography device (General Electrics, Milwaukee, WI, USA) by using a 10-MHz linear probe. The acquired images were recorded for playback analysis and were later measured off-line. The common carotid artery, the carotid bulb, internal and external carotid arteries were visualised on both sides. The IMT of the carotid arteries were measured in the distal common carotid artery at a level 15–20 mm proximal to the carotid bulb. The two bright echogenic lines in the arterial wall were identified as the intima and the media. Three measurements were made for each side of the body; separate means were calculated and recorded as the right and left IMT. None of the patients had stenosis, atheroma plaque or local thickening in excess of 2 mm in the carotid arteries. Two different operators measured the carotid intima media thickness (CIMT) and the intra-observer coefficient of variation for CIMT was 2.5%.

**Coronary flow velocity measurements**

The coronary flow velocity recordings were performed by a single investigator (H.O.) who was blinded for the two groups. CFVR recordings were performed with the Vivid 7 echocardiography device (General Electrics, USA) using a middle range frequency (3–8 MHz) broadband transducer.

CFVR recordings were performed in the left anterior descending coronary artery (LAD) by transthoracic Doppler echocardiography, as previously described.²⁴ The acoustic window was around the midclavicular line in the fourth and fifth intercostal spaces in the left lateral decubitus position. The left ventricle was imaged in the long-axis cross-section and the ultrasound beam was inclined laterally. The coronary blood in the mid-to-distal LAD was searched by colour Doppler flow mapping guidance with the optimal velocity range (+12 to +15 cm/s). The sample volume (1.5 or 2.0 mm wide) was then positioned on the colour signal in the LAD artery. Variables of LAD artery velocity were measured using fast Fourier transformation analysis. After baseline recordings of flows, dipyridamole (Persantin, Boehringer Ingelheim, 0.56 mg/kg) was infused over a 4-min period. An additional infusion of dipyridamole (0.28 mg/kg over a 2-min period) was used if the heart rate did not exceed a 10% increase from the baseline. One patient with ADPKD and one subject in the healthy control group needed a second dose of dipyridamole injection. Two minutes after the end of the infusion, hyperaemic spectral profiles in the LAD artery were recorded. All images were recorded for playback analysis and were later measured off-line. Average peak diastolic velocity (APDV) and average mean diastolic velocity (AMDV) were measured at baseline and under hyperaemic conditions. The number of cardiac cycles from which the average APDV and AMDV were derived was three and the variations of APDV and AMDV between each cycle were lower than 3%. CFVR was defined as the ratio of APDV at hyperaemia: APDV at baseline. The intra-observer variability of CFVR measurement was 3.1% in the current study.

All of the measurements were performed between 8:00 and 9:00 AM and all of the subjects abstained from smoking and caffeine-containing drinks for at least 12 h before testing.

**Statistical analyses**

Data are expressed as mean ± SD. Comparisons between groups were performed by t-test. Relationship between variables was calculated with Pearson correlation test. Differences were considered significant when P-values were less than 0.05.

**Results**

Table 1 illustrates the demographic and anthropometric data of the groups. There was no significant difference between groups regarding age, sex, body mass index, creatinine clearance, microalbuminuria and lipid levels. Twenty-four-hour ambulatory blood pressure results were recorded and showed in Table 2. There was no statistically significant difference regarding both mean systolic and diastolic blood pressure results between patients and healthy subjects.

CIMT was significantly increased in patients with ADPKD compared with healthy controls (0.81 ± 0.31 vs 0.52 ± 0.13 mm, P < 0.001) as shown in Figure 1. LVMI was also significantly higher in ADPKD patients (92 ± 21 vs 80 ± 15 g/m², P = 0.04). A significant correlation between CIMT and LVMI was determined (Fig. 2a, r = 0.458, r² = 0.21, P = 0.003). Regarding the coronary flow data, there was no significant difference in APDV and AMDV values between the groups (Table 2). CFVR values were significantly lower in patients with ADPKD than controls (1.84 ± 0.41 vs 2.65 ± 0.64, P < 0.001) (Fig. 3).
There was an inverse correlation between CIMT and CFVR values in all subjects, which was statistically significant (Fig. 2b, \( r = -0.312, r^2 = 0.097, P = 0.047 \)). Both CIMT and CFVR results were independent of blood pressure values. Insulin resistance determined by HOMA-IR equation was significantly higher in patients with ADPKD patients than healthy subjects (1.81 ± 0.97 vs 0.85 ± 0.27, \( P < 0.001 \)). There was a significant correlation between HOMA-IR and LVMI (Fig. 2c, \( r = 0.309, r^2 = 0.095, P = 0.049 \)). Although not statistically significant, there was a reverse correlation between CFVR and HOMA-IR (Fig. 2d, \( r = -0.293, P = 0.06 \)). There were no correlations between microalbuminuria and CFVR, LVM, LVMI, HOMA-IR and CIMT (\( r < 0.2, P > 0.05 \) for all). There was an inverse correlation between microalbuminuria and creatinine clearance, which is statistically significant \( r = -0.33, P = 0.03 \).

**Discussion**

Cardiovascular disease remains the most common cause of death in patients with ADPKD.\(^2\) Pathological findings of subclinical organ damage, such as ED, LVH, increased CIMT and microalbuminuria, may be seen early in the

### Table 1  Clinical characteristics and laboratory findings of patients with ADPKD and healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients with ADPKD ((n = 22))</th>
<th>Healthy subjects ((n = 19))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38 ± 8</td>
<td>33 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167 ± 9</td>
<td>166 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 12</td>
<td>68 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>25 ± 3</td>
<td>25 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.66 ± 2.0</td>
<td>4.33 ± 0.33</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.84 ± 0.96</td>
<td>4.16 ± 1.27</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.29 ± 0.34</td>
<td>1.11 ± 0.36</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.77 ± 0.91</td>
<td>2.56 ± 1.09</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.64 ± 0.96</td>
<td>1.16 ± 0.87</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>0.079 ± 0.019</td>
<td>0.072 ± 0.011</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>113 ± 22</td>
<td>114 ± 26</td>
<td>NS</td>
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<tr>
<td>Microalbuminuria (mg/day)</td>
<td>78 ± 165</td>
<td>17 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>95.8 ± 46.5</td>
<td>45.8 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.81 ± 0.97</td>
<td>0.85 ± 0.27</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ADPKD, autosomal dominant polycystic kidney disease; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of insulin resistance; LDL, low-density lipoprotein; NS, not significant.

### Table 2  Blood pressures, pulse rates and echocardiographic findings of patients with ADPKD and healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients with ADPKD ((n = 22))</th>
<th>Healthy subjects ((n = 19))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline systolic BP (mm Hg)</td>
<td>116 ± 14</td>
<td>119 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperaemic systolic BP (mm Hg)</td>
<td>118 ± 15</td>
<td>117 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline diastolic BP (mm Hg)</td>
<td>73 ± 8</td>
<td>75 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperaemic diastolic BP (mm Hg)</td>
<td>74 ± 18</td>
<td>72 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline pulse rate (per min)</td>
<td>73 ± 12</td>
<td>70 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperaemic pulse rate (per min)</td>
<td>87 ± 11</td>
<td>90 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Mean 24-h SBP (mm Hg)</td>
<td>125 ± 10.5</td>
<td>123 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Mean 24-h DBP (mm Hg)</td>
<td>82 ± 9.6</td>
<td>81 ± 8.7</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline AMDV (cm/s)</td>
<td>27 ± 7</td>
<td>24 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperaemic AMDV (cm/s)</td>
<td>49 ± 27</td>
<td>60 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline APDV (cm/s)</td>
<td>33 ± 10</td>
<td>29 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperaemic APDV (cm/s)</td>
<td>63 ± 33</td>
<td>78 ± 30</td>
<td>NS</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>166 ± 53</td>
<td>135 ± 31</td>
<td>0.03</td>
</tr>
<tr>
<td>LVMI (g/m(^2))</td>
<td>92 ± 21</td>
<td>80 ± 15</td>
<td>0.04</td>
</tr>
</tbody>
</table>

ADPKD, autosomal dominant polycystic kidney disease; AMDV, average mean diastolic velocity; APDV, average peak diastolic velocity; BP, blood pressure; DBP, diastolic blood pressure; LVM, left ventricular mass; LVMI, left ventricular mass index; SBP, systolic blood pressure.
course of ADPKD and was reported in several studies in patients with ADPKD with well-preserved renal function.\textsuperscript{2,11–13} ED, which is an early manifestation of vascular injury, has been used to predict future coronary artery disease prior to atherosclerotic changes in arteries.\textsuperscript{25,26} Wang et al.\textsuperscript{11} and Kocaman et al.\textsuperscript{12} previously reported that both normotensive and hypertensive patients with ADPKD have impaired endothelial-dependent relaxation of small resistant vessels.

LVH is also very common in patients with ADPKD. The frequency of LVH in patients with ADPKD may be related to the high prevalence of hypertension reported in these patients.\textsuperscript{2,27} Increased LVM is also associated with a worse renal and patient outcome in patients with ADPKD.\textsuperscript{28} Systolic blood pressure is correlated with LVM in patients with ADPKD.\textsuperscript{6,7} Moreover, Bardaji et al.\textsuperscript{13} reported that systolic blood pressure was the most important factor related to LVH in dialysis and nondialysis patients with ADPKD. Both hypertension and LVH were the consequences of increased renin-angiotensin-aldosterone system (RAAS) activation in these patients. However, a high prevalence of LVH was also reported in normotensive patients with ADPKD.\textsuperscript{3} Therefore, factors other than elevated blood pressure may be important in the development of LVH in patients with ADPKD.

The CFVR represents the capacity of the coronary circulation to dilate following an increase in myocardial oxygen demands and can be expressed by the difference between the hyperaemic flow and the resting flow curve.\textsuperscript{13,24} Decreased CFVR reflects coronary ED and is associated with a significantly higher incidence of cardiovascular events during long-term follow up of patients with coronary heart disease.\textsuperscript{25,26} In patients with dilated cardiomyopathy and hypertrophic cardiomyopathy, a reduced CFVR is a strong and independent predictor of clinical deterioration and death.\textsuperscript{30,31} Reduced CFVR was also demonstrated in diabetic patients without overt coronary heart disease and in patients with syndrome X.\textsuperscript{32,33}

Presence of insulin resistance and compensatory hyperinsulinaemia were shown in patients with ADPKD.\textsuperscript{14} The polycystic kidney disease 1 (PKD1) gene product is a membrane protein involved in cell–cell and cell–matrix interactions and has a widespread tissue distribution. Insulin resistance found in ADPKD might be due to this abnormal gene membrane protein and to the abnormalities of membrane cytoskeleton that occurs in this disease.\textsuperscript{15} Abnormal membrane fluidity in erythrocytes and mononuclear cells from ADPKD patients is due to altered membrane proteins and these might be related to whole body insulin sensitivity.\textsuperscript{14,16} Therefore, the main pathogenesis of insulin resistance includes altered membrane fluidity in erythrocytes, mononuclear cells and other cells in patients with ADPKD.\textsuperscript{14} Lumiaho et al.\textsuperscript{17} showed that insulin resistance, determined by using the homeostasis model assessment, was significantly associated with LVM in patients with mutations in the PKD1 gene and their relatives independent of other factors known to increase LVM, such as age, weight, systolic blood pressure and albuminuria. Thus, the authors hypothesised that insulin resistance could also be an important determinant of LVM because of increased compensatory hyperinsulinaemia that occurs in patients with ADPKD without renal failure.\textsuperscript{17}

We have previously reported significantly decreased CFVR, significantly increased CIMT and presence of inverse correlation between CIMT and CFVR in patients with ADPKD.\textsuperscript{13} In the present study we showed a significant relationship between increased CIMT, LVM, LVM and insulin resistance in normotensive ADPKD patients. Several mechanisms can be considered regarding insulin resistance that contributes to LVH in patients with ADPKD. First of all, the relationship between RAAS, hypertension and hyperinsulinaemia should be underlined. Activation of the RAAS caused by cyst expansion and local ischaemia has been proposed to play an important role in the development of hypertension in ADPKD.\textsuperscript{34} Furthermore, hyperinsulinaemia induced angiotensin II-stimulated aldosterone production may aggravate hypertension.\textsuperscript{35} Furthermore, angiotensin II and hyperinsulinaemia have cardiac growth-promoting effects independent of blood pressure.\textsuperscript{36,37} Insulin activates the sympathetic nervous system in patients with essential hypertension, and LVH was suggested to be related to high sympathetic nervous system activity.\textsuperscript{28,38} Insulin was also suggested to inhibit myocardial protein
degradation and this antiproteolytic action may be a mechanism by which hyperinsulinaemia could contribute to the development of LVH.39

The findings mentioned above reflect coronary artery ED and derangement of coronary microcirculation even in the early stages of the disease. ED of the epicardial vasculature and hyperinsulinaemia may be a factor for the decreased CFVR and increased CIMT in the present study. Left ventricular diastolic dysfunction occurring early in the course of ADPKD may be another factor responsible for impaired CFVR. Impaired CFVR reported in the present study is consistent with the previous findings of subclinical organ damage and underscores the increased cardiovascular risk in these patients. Interventional studies would be helpful in determining the pathogenesis of decreased CFVR. We have recently reported that the angiotensin receptor blocker, telmisartan, significantly improved CFVR in patients with ADPKD.40 This finding suggests that the stimulation of the RAAS contributes to the ED in these patients.

The correlations between insulin resistance and LVMI and CFVR were weak and had borderline significance in this study. The small sample size may explain the borderline significance and may be overcome by increasing the number of subjects. However, we think that the weak correlations existed because of the presence of factors.

**Figure 2** (a) The relationship between left ventricular mass index (LVMI) and carotid intima media thickness (CIMT) of the two groups. (b) The relationship between carotid intima media thickness (CIMT) and coronary flow velocity rate (CFVR) of the two groups. (c) The relationship between left ventricular mass index (LVMI) and homeostasis model (HOMA) of the two groups. (d) The relationship between coronary flow velocity reserve (CFVR) and homeostasis model (HOMA) of the two groups.
other than insulin resistance underlying left ventricle hypertrophy and impaired CFVR in these patients. Although HOMA-IR is one of the easiest methods to determine insulin resistance, the euglycaemic-hyperinsulinaemic clamp technique, although more cumbersome, is the gold standard method and could be used to assess insulin resistance with better accuracy.41

**Conclusion**

Normotensive patients with ADPKD with well-preserved renal function have significantly increased CIMT and significantly decreased CFVR compared with healthy subjects. These patients also have hyperinsulinaemia and insulin resistance. Complicated pathological events mentioned above may be the responsible for the increased CV mortality and morbidity even in the early ages of patients with ADPKD.

**References**


Insulin resistance and CFVR in ADPKD patients


Smoking cessation post-discharge following nicotine replacement therapy use during an inpatient admission

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Key words
Smoking, cessation, post-discharge, inhaler, patch.

Abstract

Background: Cigarette smoking remains a health issue despite declining prevalence in Australia. The burden of tobacco-related morbidity affects hospitals, particularly those in lower socioeconomic areas where prevalence is highest.

Aim: We have shown that nicotine replacement therapy (NRT) use during hospitalization increases motivation to quit post-discharge. We postulated that subjects using the nicotine patch post-discharge, in comparison to the inhaler, would have higher rates of abstinence at 12 months after discharge. The aim was to compare the efficacy of the nicotine patch or inhaler formulation for cessation post-discharge, following use during admission.

Methods: Post-discharge, subjects chose their preferred formulation (patch or inhaler) based on their experience with NRT during admission. Tailored, medium-intensity support was provided with subsidized NRT during outpatient visits. Subjects were followed for 12 months. Exhaled breath CO confirmed non-smoking.

Results: Of 123 subjects enrolled, 37 elected to use the inhaler, 50 the patch and 36 no NRT. At 12 months continuous abstinence rates were 38%, 38% and 25% respectively.

Discussion: This study built upon the ‘teachable moment’ provided by hospitalization and the inpatient use of NRT, encouraging cessation post-discharge. Both NRT formulations provided similar 12 month cessation rates, and were superior to those achieved by subjects electing not to use NRT. Although the patch was the most popular formulation, the inhaler provided an equally efficacious alternative which addressed other facets of cigarette addiction. Subjects electing not to use NRT were less successful. Continuous abstinence rates were equivalent to community-based studies using NRT. We recommend a similar programme to other hospitals.

Introduction

Cigarette smoking remains the leading cause of preventable morbidity and mortality in Australia, despite declining prevalence in recent decades.¹ Current morbidity and mortality rates reflect smoking patterns in previous decades, due to the long lag time between initiation and the onset of disease. Smoking increases the incidence of diseases that result in a substantial burden to the healthcare system, particularly respiratory diseases (especially chronic obstructive airways disease), cancer (especially lung cancer) and cardiovascular disease (especially ischaemic heart disease).² In Australia smoking-related diseases contribute to more hospitalizations and deaths than alcohol and illicit drug use combined and result in more than 15 000 deaths annually.³⁴

Prevalence of cigarette smoking is not uniformly distributed across society but varies by socioeconomic status.⁵ The estimated financial impact of tobacco-related diseases incurred by hospitals in 2008 exceeded $223 million.⁶ While this burden affects all hospitals, it is likely to impact greatest on public hospitals situated in lower socioeconomic areas, where prevalence is typically higher.¹⁴

The Queen Elizabeth Hospital (TQEH) is a 320-bed public tertiary teaching institution whose catchment area

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includes many lower socioeconomic areas of Adelaide, South Australia. Prevalence in this State has recently fallen below 20%; however, in the catchment area surrounding TQEH, the most recent estimates suggest a higher prevalence (24%).

At the time this study was conducted, smoking was banned in all South Australian hospitals and allowed in designated areas of hospital grounds, but it was not a requirement of hospitals to treat nicotine withdrawal during an admission or to provide cessation interventions after discharge. The dearth of hospital-based cessation services in South Australian hospitals suggests a perception that cessation is viewed as a community rather than teaching hospital issue.

Hospitalization potentially provides a ‘teachable moment’ when cessation could be encouraged through control of nicotine cravings with pharmacotherapy and support both during and after admission. Data suggest that smokers who believe that their illnesses are related to smoking are more likely to attempt cessation in response to a period of hospitalization. Furthermore, data suggest that smoking cessation leads to a reduction in healthcare utilisation, thus hospitals could potentially benefit through a reduction in readmission rates by providing cessation programmes. Hospital outpatient clinics have previously been shown to be a suitable setting for smoking cessation interventions, in scenarios where smokers were recruited from the community.

Both counselling and pharmacotherapy interventions alone have been shown to increase quit rates in comparison to an unsupported cessation attempt; however, the probability of success is greatest when the intensity of counselling is increased and/or counselling is combined with pharmacotherapies. All formulations of nicotine replacement therapy (NRT) are known to be efficacious; however, smokers who have failed using one formulation previously have a lower probability of success when using the same formulation in a subsequent attempt. It is therefore likely that given the option of more than one NRT formulation would increase quit rates.

We have previously reported the efficacy of two formulations of NRT (nicotine patch and oral inhaler) in reducing cravings experienced by inpatients at TQEH. These formulations were selected due to their suitability for use during an admission, when patients are frequently supine.

We are not aware of any studies that have examined the benefit of a post-discharge, tailored smoking cessation programme using the subjects-preferred formulation of NRT following the use of these formulations during admission for craving control.

Aims

The aims were to compare the efficacy of the nicotine patch or inhaler, as chosen by the subject, for long-term (12 months) continuous abstinence post-discharge, following the use of NRT (patch and inhaler) during hospitalization for control of nicotine cravings.

Methods

Subjects enrolled in the inpatient study were eligible for this post-discharge cessation study, which was conducted between June 2003 and December 2006. The trial was conducted in accordance with the International Code of Harmonisation and Good Clinical Practice guidelines, and approved by TQEH Ethics of Human Research Committee, with subjects provided informed consent.

The eligible population was limited to the 375 subjects who participated in the inpatient study. Briefly, inclusion into the inpatient study required subjects to be smokers hospitalized at TQEH for ≥2 days (See Jones TE and Williams J. Craving control using NRT in a teaching hospital. Intern Med J for full eligibility).

On completion of the inpatient study subjects were invited to participate in the post-discharge study which combined the subjects choice of NRT (patch or inhaler) and medium-intensity support (defined as sessions of short individual discussion). The use of either NRT formulation during this study did not necessarily follow the manufacturer’s recommended treatment regimen, but was tailored to the subject’s requirements. This involved individualizing the frequency and duration of both NRT use and outpatient visits. Subjects were reminded of the correct administration of their chosen formulation and of possible side effects. Questionnaires were administered at each visit which assessed cravings, dose and duration of NRT and non-smoking status. Both NRT formulations were provided at a subsidized cost, with a week’s NRT supply equivalent to approximately the price of a pack of 20 cigarettes.

Continuous abstinence (non-smoking from the time of enrolment) was assessed at 1, 3, 6 and 12 months. Self-reported non-smoking was corroborated by exhaled breath carbon monoxide monitoring at each visit, using a Bedfont micro-smokerlyser (Bedfont Scientific Ltd. Kent, United Kingdom). A reading of ≤6 ppm was considered consistent with non-smoking. This value was chosen because it accorded with our clinical experience, but also because it has been shown to discriminate between recent smoking and non-smoking.

Continuous baseline variables were analysed using an analysis of variance (ANOVA) between groups while frequencies were analysed using a chi-squared analysis. An
ANOVA was used to assess continuous abstinence at 1, 3, 6 and 12 months between subjects in the three treatment arms. Subjects were classified as ‘smoking’ or ‘non-smoking’, with reported abstinences treated as binary data. Subjects that were lost to follow up were included until their last confirmed visits. Subjects who were not able to attend TQEH at the 12-month visit (but completed the visit by phone) were considered abstinent if all previous self-reports of abstinence were confirmed by CO monitoring. Subjects that were known to have smoked or have returned to smoking were recorded as ‘smokers’.

Results

Of the 375 eligible subjects recruited to the inpatient study, 177 expressed interest in quitting after discharge, with 123 subjects attending at least one post-discharge visit and consequently enrolling in the study. Of these, 37 subjects chose to use the inhaler, 50 the patch, and unexpectedly, 36 subjects elected not to use either formulation of NRT and attended for support alone (Fig. 1).

Subject demographics are shown in Table 1. There were no significant differences between the subjects that chose to use the inhaler, patch or no NRT by gender, age, number of years smoked, previous quit attempts, length of hospitalization, length of participation in the inpatient study, Fagerström nicotine dependence score or reason for admission. However, subjects that chose to use the inhaler were typically heavier smokers prior to admission (P = 0.02). Following enrolment, subjects that used the inhaler attended TQEH for post-discharge visits more frequently than other subjects (P < 0.01). Overall, those using either formulation of NRT attended more outpatient visits than those that did not (P < 0.01).

Subjects were generally highly addicted to nicotine, as evidenced by their mean cigarette consumption (>30 cigarettes/day), mean duration of smoking (>35 years),

Table 1  Demographics of subjects by NRT formulation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Inhaler (n=37)</th>
<th>Patch (n=50)</th>
<th>No NRT (n=36)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>19 (51.4%)</td>
<td>27 (54.0%)</td>
<td>19 (52.8%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Mean ± SD age (years)</td>
<td>51.9 ± 14.1</td>
<td>52.0 ± 14.9</td>
<td>55.8 ± 15.3</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean ± SD (range) daily cigarette consumption</td>
<td>36 ± 18.4</td>
<td>27 ± 11.6</td>
<td>30.3 ± 12.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean (range) duration of smoking</td>
<td>36.8 ± 18.4</td>
<td>37.5 ± 14.4</td>
<td>41.1 ± 15.1</td>
<td>0.41</td>
</tr>
<tr>
<td>Number of previous quit attempts</td>
<td>1.27 ± 1.59</td>
<td>1.54 ± 1.47</td>
<td>1.44 ± 0.94</td>
<td>0.66</td>
</tr>
<tr>
<td>Admission reason</td>
<td>21 (56.8%)</td>
<td>24 (48.0%)</td>
<td>20 (55.6%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Respiratory</td>
<td>3 (8.1%)</td>
<td>8 (16.0%)</td>
<td>5 (13.9%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cardiology</td>
<td>13 (35.1%)</td>
<td>18 (36.0%)</td>
<td>11 (30.5%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Other</td>
<td>10.5 ± 8.9</td>
<td>9.3 ± 6.1</td>
<td>9.6 ± 5.7</td>
<td>0.75</td>
</tr>
<tr>
<td>Mean ± SD admission length (days)</td>
<td>7.7 ± 8.2</td>
<td>5.8 ± 4.8</td>
<td>5.8 ± 4.7</td>
<td>0.26</td>
</tr>
<tr>
<td>Mean ± SD Fagerström test for nicotine dependance</td>
<td>8.8 ± 1.6</td>
<td>9.1 ± 1.5</td>
<td>9.5 ± 0.9</td>
<td>0.12</td>
</tr>
</tbody>
</table>

NRT, nicotine replacement therapy; SD, standard deviation.
limited number of quit attempts (<2) and mean Fagerström score of nicotine dependence (9.1/10).

During the study 21 subjects were lost to follow up, with those subjects electing not to use NRT more likely to be lost to follow up than those that used either formulation of NRT (inhaler 8%, patch 14%, no NRT 28%, \( P = 0.04 \)).

A clear relationship was not established between craving during the inpatient study and choice of NRT use post-discharge, or craving during the post-discharge study and length of NRT use. There was a trend towards higher rates of continuous abstinence observed in subjects using NRT when compared to subjects that elected not to (37.9% vs 25.0%, respectively, \( P = 0.17 \)), which is similar to other cessation studies using nicotine replacement therapies.

Exhaled breath CO validation of abstinence occurred at each visit; however, at the 12-month follow-up time point less than half of those that were continuously abstinent had their abstinence confirmed by exhaled breath CO (43%, 42% and 33% for inhaler, patch and no NRT respectively). However, CO verification was performed for all abstinent subjects within a 2-month period prior to their 12-month visit.

**Nicotine exposure**

Approximate nicotine absorption from each full strength transdermal patch is 1 mg/h and from the inhaler 2 mg/cartridge.\(^{22}\) Despite being advised, they could use \( \geq 6 \) inhaler cartridges/day, mean use was only 2 cartridges per day. Hence, nicotine exposure during the study was approximately 15 mg/day with transdermal patches, which were typically worn during waking hours, but only 4 mg/day with the oral inhaler, used ad libitum. Nicotine exposure from cigarette smoking is approximately 1 mg/cigarette and hence prior to this cessation attempt, mean nicotine exposure was less than 30 mg/day.\(^{21}\)

All subjects had ceased NRT within the 12-month follow-up period.

**Adverse effects**

The most frequently reported adverse effects for subjects that used the transdermal patch were itchiness at the site of application (76%) and unusual dreams (36%). Subjects that used the nicotine inhaler reported adverse events such as bad taste on inhalation (35%) and an ‘upset stomach’ (24%).\(^{24,25}\)

All adverse effects were mild, transient and expected. No subjects withdrew as a result of toxicity.

**Discussion**

This is the first study to examine smoking cessation post-discharge following the use of NRT during an inpatient admission to control nicotine cravings.

The ability of subjects to access free NRT during admission allowed them to experience and compare the inhaler and patch formulations under the guidance of the researcher. The post-discharge study then built upon the subjects’ inpatient experiences, using a tailored NRT programme combined with medium-intensity support. The tailored programme allowed the subject to choose the formulation, dose and duration of NRT (which was provided at a subsidized cost) and the intensity of individual support. It is likely that the relationship that developed between the subject and researcher during the inpatient study would have increased enthusiasm for attending the post-discharge service and may have enhanced overall quit rates.

Almost two-thirds of the subjects that expressed an interest in quitting during their admission participated in this post-discharge study. Why the other third did not attend is not known; however, a range of factors including impaired mobility, time constraints or a return to smoking after discharge may have contributed. These patients were not followed after discharge as they did not consent to this post-discharge study.

At their first outpatient visit, most subjects chose the formulation of NRT they preferred during the inpatient study, but surprisingly almost a quarter of subjects elected not to use either formulation after discharge, attending the post-discharge study for support only. A relationship between craving during admission and choice of NRT post-discharge was not clear, which was also true of other variable (such as Fagerström score), and is likely because of confounding between variables.

The continuous abstinence rates of those electing not to use NRT were lower (although not statistically different) and a higher proportion of these subjects were lost to follow up. The most common reason given for not using either formulation was a desire to refrain from any source of nicotine. Given the lower rates of success among subjects that did not use NRT we discourage patients from this option in the clinical setting. The lower success rates may have been due to the cravings associated with nicotine withdrawal that were not mitigated because NRT was not used. Furthermore, these subjects experienced a lower level of support occasioned by their reduced need to attend outpatient visits in order to obtain ongoing NRT supplies, which may have also impacted upon their success.

Among those subjects that used NRT, the patch formulation was preferred by approximately two-thirds, which
was also the case during the inpatient study. Subjects
generally found the patch formulation easier to use and
preferred this formulation for this reason. A substantial
minority however preferred the inhaler formulation. The
inhalers ad libitum, hand-to-mouth nicotine administra-
tion is similar to that undertaken when smoking. Para-
doxically some subjects preferred this formulation for
these reasons, while others found its similarity to cigare-
tte smoking a deterrent. The inhaler was typically used
for longer than the patch formulation, which may be due
to the action of administration, which also may increase
its propensity for dependence. There was however a rela-
tively low daily nicotine exposure during the study with
this formulation, as less than the recommended number
of inhaler cartridges were used daily, which should trans-
late into fewer systemic adverse effects. Subjects were
informed to use as many inhaler cartridges as they felt
necessary and because less than the recommended number
of cartridges were used it is likely that the hand-
to-mouth action satisfied that aspect of cigarette addiction.
Because more than a third of subjects preferred this formu-
lation and had similar success rates to those that
used the patch, if it were not available it is likely that
these subjects would not have been as successful if the
programme only offered the patch formulation.

Both NRT formulations were well tolerated by subjects
and the tailored duration of use did not result in any
notable adverse events, which is not surprising because
overall exposure was less than typical manufacturer’s
directions.

The use of the subjects preferred formulation of NRT as
part of a tailored cessation intervention coupled with
medium-intensity support achieved quit rates at least as
good as cessation studies conducted in a community set-
tings using NRT.1,13–15 For a similar programme to be
introduced into another hospital using NRT available
through the PBS, the predominant cost would be the
employment of a dedicated professional.

Limitations of the study included the small sample size.
The population available for the post-discharge study was
limited to subjects recruited to the inpatient trial, and
with only a third of these subjects participating post-
discharge the sample size was too small to detect a dif-
ference between the two nicotine formulations. Another
limitation was how exhaled breath CO validation of
abstinence was conducted during this study to confirm
non-smoking at regular intervals; however, almost half of
those subjects that were abstinent at 12 months did not
perform a confirmatory CO validation of their status
within 2 weeks of this time point. Of the CO validations
that occurred, none contradicted subject’s self-reported
non-smoking status and evidence suggests that subjects
who self-report abstinence in the absence of biochemical
validation should be included in the results of the study,
particularly if validation has occurred throughout the
study.26

We would recommend a similar programme be adopted
by other hospitals, with the use of more than one formu-
lation of NRT both for inpatient craving control and post-
discharge cessation, as part of a medium-intensity tailored
intervention for patients to attempt cessation following
discharge from hospital. We believe this study to be trans-
ferable to similar hospital outpatient settings, especially
following NRT use during an admission, given the tailored
approach to NRT use and support.

Acknowledgements
The work contained herein was conducted as part of a
post-graduate degree (Jerneen Williams). All work was
undertaken at The Queen Elizabeth Hospital, South Aus-
tralia. Jerneen Williams recruited the smokers, provided
NRT, collated and analysed the data and wrote the report.
Terry Jones conceived the original idea, designed the
study and assisted writing the report. Both authors
approved the final version of the report. We wish to
thank Mr John Field, Statistician, from the University of
Adelaide, for his help with the statistical analysis and
interpretation.

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Simple clinical score is associated with mortality and length of stay of acute general medical admissions to an Australian hospital

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Key words
clinical score, acute admission, length of hospital stay, mortality, readmission rate.

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Abstract

Background: In a rural Irish hospital, a simple clinical score (SCS) determined at the time of admission enabled stratification of acute general medical admissions into five categories that were associated incrementally with patients’ immediate and 30-day mortality. The aim of this study was to examine the representative performance of this SCS in predicting the outcomes of general medical admissions to an Australian teaching hospital.

Methods: A retrospective chart review was undertaken of a representative sample from 480 admissions in 2007 to an urban university teaching hospital in Australia. The SCS was calculated and related to that patient’s outcome in terms of mortality, length of stay, nursing home placement on discharge, the occurrence of medical emergency team call and intensive care unit transfer. These data were compared, where possible, with the outcomes reported in the Irish hospital.

Results: Four hundred and seventeen complete sets of data allowed calculation of the SCS. There were significant linear correlations of the SCS (divided into quintiles) and patients’ in-hospital and 30-day mortality, their length of stay and their discharge to a nursing home. There was no association of the SCS and the patients’ readmission rate, intensive care unit transfer rate or likelihood of a medical emergency team call. The significant trends replicated those from the Irish hospital.

Conclusion: The SCS can predict significant outcomes for general medical admissions in an Australian hospital despite obvious differences to the hospital of its derivation. A wider study of Australasian hospitals and the performance of the SCS as a predictor of general medical admission outcomes is underway.

Introduction

The simple clinical score (SCS) can be predictive of mortality 30 days after admission to an acute medical unit (AMU).1 This score is determined at the time of admission and stratifies patients into five categories of risk of death within 30 days of hospital admission. The SCS has certain advantages because all of its variables can be collected at the time of admission without waiting for laboratory investigations, significant clinical expertise or labour-intensive equipment. This score was derived and validated in patients admitted to a rural hospital in Nenagh, Ireland in 2004. The SCS does not determine the need for hospitalisation, but, once the decision to hospitalise has been made, the score may facilitate the most appropriate level of care for that patient.2 The ability of this score to be representative of general medical patients elsewhere in the world, in different capacity hospitals with different sized AMUs, intensive care units (ICUs) and in an urban rather than rural location, is largely a matter of conjecture.

Acute General Medicine is a specialty that takes undifferentiated patients and it is a service that can absorb patients with single system or multi-system disease according to the expertise and staffing of the hospital concerned. In rural hospitals, the General Medicine service takes most admissions with a medical diagnosis. In urban centres, the relative size and admission policy of the General Medicine service usually adjusts to
complement the medical subspecialty services available. The primary purpose of the present study is to report the ability of the SCS to predict 30-day mortality in a cohort of patients evaluated in an acute assessment unit (AAU) of an urban tertiary referral university teaching hospital in Australia. We also determined whether SCS is associated with length of hospital stay (LOS) or even medical emergency team (MET) calls and patient transfer to ICU during the hospital admission. The final aim of this study was to compare the characteristics and the outcomes of the patient populations admitted under the General Medicine service in these two very different hospitals.

Methods

Flinders Medical Centre (FMC) is a 550-bed tertiary referral university teaching hospital that serves a regional population of about 400 000 people. All acute medical presentations to the hospital are initially assessed by the emergency department (ED). If admission to a medical unit is required, patients are admitted to the AAU or, directly to a medical specialty unit, such as coronary care, intensive care, stroke or chest pain assessment unit if the patient meets the admission criteria for that unit and the diagnosis as well as discharge planning is straightforward. The AAU is responsible for processing about 50% of the medical admissions to FMC on any given day for stabilisation and further assessment and then that unit either discharges or transfers the care of the patient to another, usually General Medical, long stay team within the hospital. There were no patients directly admitted to General Medicine long stay teams.

Data from all patients admitted to the AAU between 1 January 2007 and 31 December 2007 were entered into a computerised database. Patients above the age of 18 years were included. Patients admitted directly to ICU or to other non-General Medical specialties units from ED were excluded from this study. A total of 480 patients was selected from the first consecutive 120 patients admitted to the AAU in each of January, April, July and October in 2007. The seasonally adjusted selection of patients was designed to take into account seasonal variation of disease. Incomplete documentation, those who died within 1 h of arrival to the hospital, whose prognosis were death within 24 h and were for comfort care only were excluded from analysis. Patients who were admitted more than once during the study period were entered only once, on their first admission. The final study population comprised 417 patients with complete data. Ethical approval was granted by the hospital quality and safety governing council because the study fell under the remit of audit and safety monitoring. Fourteen parameters used to determine the initial SCS were extracted from patients’ standardised AAU admission booklets. The data were extracted by two of the authors (SR and YS) who were blinded to those patients’ outcomes. The SCS was calculated as previously reported.1 Blood pressure was measured using a mercury sphygmomanometer with the patient lying down. The body temperature was recorded by an automated tympanic thermometer (Genius 2, Accu system, Covidien, Mansfield, MA, USA). Oxygen saturation was measured electronically using GE Dinamap CareScape v100 (GE Healthcare, Freiburg, Germany). Electrocardiograms (ECG) were classified as normal or abnormal according to the interpretation of the Marquette MAC-PC computerised ECG interpretation programme. If the only abnormality was sinus tachycardia, bradycardia (50–60 beat/min), or isolated right bundle branch block, the ECG was considered normal. Altered mental status was divided into those patients with and without coma. Altered mental status without coma included confusion, agitation or obtundation. All deaths registered within South Australia from January 2007 to December 2007 were examined to identify patients who died after discharge but within 30 days of admission.

As reported previously, admissions were classified into five mortality risk categories according to their SCS: very low risk (0–3 points), low risk (4–5 points), average risk (6–7 points), high risk (8–11 points) and very high risk (>11 points).1 The different risk groups were compared in terms of age, LOS, need for MET calls, ICU management, 30-day readmission rate, in-hospital mortality, 30-day mortality and discharges to any residential facility. As in-hospital death will affect LOS, LOS was examined after adjustment for mortality.

Statistical analyses were performed using STATA 11.0 statistical software (StataCorp, College Station, TX, USA). Mean and standard deviations were calculated for continuous variables and compared using a t-test. Proportions were calculated for binary and categorical variables and compared using a χ²-test. Tests for trend across ordered groups were compared using the STATA nptrend test.

Results

Patient population and parameters

Data from patients who met the inclusion criteria and had a complete set of physiological data on admission as well as outcome data were available for 417 admissions. Demographic data of patients are summarised in Table 1. Eighty-one per cent of this Australian cohort had a score of 4 or above. The mean SCS of the entire Australian cohort was 5.9 (SD 3.1).
In this cohort, there were only 19 admissions (4.6%) who, during their stay, had a MET call and there were just eight transfers (2%) to ICU. There was no significant difference between the different risk groups in terms of attendance by the MET or transfer to ICU (Table 2).

Unplanned readmissions to FMC within 30 days of discharge occurred for 14.8% of the entire cohort. Readmission rates were not significantly different between the five groups stratified according to SCS.

**Comparison of outcomes in the two sites**

Across every SCS group category, mean LOS was shorter and patient age was younger in the Irish cohort and in each category the frequency of discharge of the patient to a residential care facility was higher at FMC. Thirty-day mortality and readmission rates were strikingly similar between the two sites across all categories. The mean age of those who died within 30 days of admission was 87.1 ± 7.1 years compared with 77.1 ± 9.6 years in the Irish cohort.

Heart failure, exacerbations of chronic obstructive pulmonary disease and pneumonia dominated both groups’ discharge diagnoses lists. Syncope (5%), urinary tract sepsis (4%) and non-cardiac chest pain (2%) completed the list of common discharge diagnoses at FMC.

At both sites, as SCS group category rose, incremental trends were seen for patient age, mean LOS, 30-day mortality rate and rate of discharge to a residential care facility. These trends were significant at the Australian site at least (\(P < 0.001\); Table 2). No particular trend in the 30-day readmission rate was observed at either FMC (\(P = 0.58\)) or in the Irish cohort.

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### Table 1 Characteristics of patients at admission

<table>
<thead>
<tr>
<th></th>
<th>FMC</th>
<th>Nenagh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>417</td>
<td>6736</td>
</tr>
<tr>
<td>Mean age ± SD, years</td>
<td>75.3 ± 15.9</td>
<td>61.9 ± 20.3</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>172 (41.2)</td>
<td>3534 (52.5)</td>
</tr>
<tr>
<td>Systolic blood pressure ± SD, mmHg</td>
<td>138.1 ± 27.7</td>
<td>136 ± 27</td>
</tr>
<tr>
<td>Pulse rate ± SD, bpm</td>
<td>83.1 ± 18.5</td>
<td>86 ± 20</td>
</tr>
<tr>
<td>Temperature ± SD, °C</td>
<td>36.4 ± 0.9</td>
<td>36.4 ± 0.8</td>
</tr>
<tr>
<td>Respiratory rate ± SD, bpm</td>
<td>20.4 ± 4.3</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>Oxygen saturation ± SD, %</td>
<td>97.2 ± 2.8</td>
<td>95.4 ± 3.9</td>
</tr>
<tr>
<td>Abnormal ECG, n (%)</td>
<td>279 (67)</td>
<td>3933 (58)</td>
</tr>
<tr>
<td>Diabetes mellitus (both types 1 and 2), n (%)</td>
<td>94 (22)</td>
<td>1066 (15.8)</td>
</tr>
<tr>
<td>Nursing home resident, n (%)</td>
<td>110 (26.4)</td>
<td>361 (5.4)</td>
</tr>
<tr>
<td>Unable to stand unaided and not a nursing home resident, n (%)</td>
<td>140 (33.6)</td>
<td>713 (10.6)</td>
</tr>
</tbody>
</table>

**Primary diagnosis at discharge**

- Heart failure: 30 (7.2%), 1563 (23.2%)
- Exacerbation of COPD: 30 (7.2%), 1021 (15.2%)
- Pneumonia: 32 (7.7%), 391 (5.8%)
- Acute coronary syndrome: 3 (0.8%), 253 (3.8%)
- Cancer: 5 (1.2%), 330 (4.9%)
- Chronic renal failure: 0 (0%), 131 (1.9%)

COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; FMC, Flinders Medical Centre.

Table 1 compares the physiological and SCS parameters on admission for the Australian and Irish hospitals. In comparison with the original Irish SCS derivation cohort, the FMC cohort was older; more patients were diabetic, were admitted from nursing homes or had mobility problems. In the Australian cohort, 41% of admissions were male patients; a lower proportion than in Irish cohort.

### Clinical outcomes for the Australian cohort

The high risk groups comprised patients with increased LOS, risk of in-hospital and 30-day mortality, and were more often discharged to a residential care facility after the episode of acute care (Tables 2,3). Twenty-seven patients (6.5%) died within 30 days of admission, of whom 17 were in-hospital deaths. Those groups with scores of 6 or higher were associated with a doubling of their LOS compared with the very low risk group.

#### Table 2 Patient characteristics and clinical outcomes by simple clinical score risk groups

<table>
<thead>
<tr>
<th></th>
<th>0–3</th>
<th>4–5</th>
<th>6–7</th>
<th>8–11</th>
<th>&gt;11</th>
<th>(P)-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCS</td>
<td>78</td>
<td>145</td>
<td>83</td>
<td>91</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Death-adjusted mean LOS ± SD, days</td>
<td>5.2 ± 7.6</td>
<td>5.8 ± 6.1</td>
<td>9.8 ± 11.1</td>
<td>8.7 ± 8.3</td>
<td>11.1 ± 8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death-adjusted LOS ≤72 h, n (%)</td>
<td>44 (56)</td>
<td>56 (39)</td>
<td>17 (21)</td>
<td>24 (29)</td>
<td>1 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MET calls, n (%)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>7 (6)</td>
<td>7 (8)</td>
<td>1 (5)</td>
<td>0.10</td>
</tr>
<tr>
<td>ICU admission, n (%)</td>
<td>0</td>
<td>4 (3)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0</td>
<td>0.70</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>0</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>8 (9)</td>
<td>5 (25)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; LOS, length of stay; MET, medical emergency team; SCS, simple clinical score.
Matching the severity of illness to the appropriate intensity of care is important for the delivery of high quality medical care. This means ensuring the right patient is in the right place at the right time. Failure to do so may give rise to a poor outcome for the patient. Consequently, several summative risk scores have been devised to enable more objective matching rather than relying on empirical judgement. This study has found that patients with an SCS that places them in the high risk category have a higher rate of in-hospital mortality, 30-day mortality and, on average, an increase in LOS. The finding of higher 30-day mortality and LOS in the high risk group is consistent with the initial derivation and validation study.

The association of lower SCS (scores of 0–3) with shorter LOS indicates that patients in the very low risk group may be considered for early discharge, perhaps through a short stay medical unit if investigations are awaited. The SCS is not a perfect judge of LOS. Among admissions with SCS of 0–3, only 56% were discharged in 72 h or less whereas out of those with an SCS >5, 23% stayed less than 72 h. A low SCS does not indicate that an admission is unnecessary or that the mortality rate is zero.

In the original cohort used in the derivation of this score, patients were admitted to a small rural hospital serving a population of 60 000 with a 36-bed AMU and a 5-bed ICU. In comparison, the FMC patients were admissions to a tertiary referral hospital serving a population of over 400 000 people with a 16-bed AAU and a 25-bed ICU. Examination of Table 3 allows some comparisons of the differing admission types to the two hospitals. The FMC ED included a separate observation unit, which possibly explains the distribution of patients according to SCS being different between Nenagh hospital and FMC. The original Irish cohort had a larger group of patients in the very low risk category while our Australian study had more in the low to high risk categories. There were older patients but also more diabetics and nursing home residents admitted to FMC although the three principal discharge diagnoses were shared at the two hospitals (comprising 22% of general medical admissions at FMC and 44% at Nenagh). The age difference might contribute to the higher mean LOS and the higher proportion being discharged to nursing homes in the FMC cohort. Importantly, the trends observed in Nenagh between SCS and mean LOS, 30-day mortality and discharges to nursing homes were present in the FMC cohort and the similarities in terms of mortality rates are striking.

Although a recent multi-centre study has found that a higher SCS was associated with an increased risk of admission to ICU, the current study did not make a similar observation. This might be related to the small number of
patients who were transferred from the FMC medical units to ICU and the unreported direct admission of patients to the FMC ICU from the ED thus bypassing the AAU. We did not thoroughly assess and exclude from the study all patients with advanced directives for comfort care only. The presence of a significant number of such advanced directives may contribute to our low rates of MET calls and of admissions to ICU. It would be sensible to discuss advanced directives with patients who were at risk of clinical deterioration and these are patients likely to have had a high SCS. The optimal timing of discussions regarding advanced directives is often unclear.

As in the Irish study, the SCS did not correlate with the 30-day unplanned readmission rate. Many other factors unrelated to the index admission were probably contributory, including chronicity of illness rather than acuteness and adequacy of community support for the patients.

The capacity of this and other scores to influence outcome is still a matter of debate and requires further research.6 The use of a modified early warning score (MEWS) has been widely reported in the medical literature and has been validated for different outcomes among acute medical patients in several hospitals in different countries.7–10 One study demonstrated no relationship between MEWS and in-hospital deaths while others reported correlations with mortality and LOS. One study has evaluated the performance of MEWS using the receiver operator characteristic. This study found the area under the curve for 30-day mortality of the MEWS to be 67% and 72% if age is included.7 On the other hand, the SCS for 30-day mortality has an area under the curve of 85%.1 No head-to-head comparison using the same set of clinical data has been done to evaluate the predictive power of the SCS for clinical outcomes in comparison with other scores, such as the MEWS or Standardised Early Warning Scoring System. Standardised Early Warning Scoring System is based on six parameters on admission and it correlates with in-hospital mortality and LOS in a cohort of medical and surgical patients.11

For a clinical predictive score to be useful in the clinical setting, it should be easy, quick and cheap to use and accurately predict a range of clinically important outcomes. The SCS fulfils these criteria. The advantage of SCS is that it utilises symptoms, signs and historical data that are likely to be available at the time a patient is admitted. It includes data on severity of illness, functional capacity and comorbidity. Functional capacity and comorbidity are not taken into consideration by most other scores. There is no specific training needed for staff to generate this score.12 Furthermore, in comparison with other scoring systems, such as the Acute Physiologic and Chronic Health Evaluation IV or the Simplified Acute Physiological Score II, time-consuming laboratory investigations are not required with the SCS.13,14 Although the SCS may be useful to stratify illness severity and subsequent care intensity, it remains to be determined whether its use will ultimately improve patient outcomes. The other issue of using an SCS is the balance between the detection of patients at risk of clinical deterioration and the additional workload and cost benefit incurred by subsequent more intensive monitoring.

There are several limitations to this study, mainly related to its design. This was a retrospective single-centre study involving chart reviews on a limited number of patients. Some data elements were incomplete because this study relied on retrospective data and it is possible that there was something systematically different between those patients for whom a complete set of physiological data was available compared with those patients for whom this information was not available. Patients <18 years, specialty medical patients, those admitted directly to ICU from ED and stroke patients were excluded from this analysis and therefore the score’s predictive ability for these outcomes cannot be extrapolated to these populations. Variance in admission policies between institutions can jeopardise applicability of this score. Furthermore, the incomplete information regarding resuscitation status and advanced treatment directives may confound our analyses of mortality and LOS.

**Conclusion**

This study supports the use of an SCS in acutely ill general medical patients at the time of admission to hospital to predict mortality, LOS and discharge destination for those requiring a residential care facility. We have confirmed that the SCS can be utilised as a risk stratification tool in a tertiary referral hospital in Australia as well as in a rural hospital in Ireland. The SCS may have relevance when deciding the management plan and timeframes for LOS. A wider prospective study of Australasian hospitals and the performance of the SCS as a predictor of general medical inpatient outcomes is underway. Such a prospective study will indicate the value of developing this score as a clinical decision tool that might influence clinician behaviour with potential impact upon patient care outcomes and healthcare costs.

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Prevalence of paraproteinaemia in older Australians

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Key words
MGUS, paraprotein, B-cell lymphoproliferative disease.

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Abstract

Background: Estimates of the prevalence of paraproteinaemia vary, from 1% in persons aged over 25 years to 10% in those aged over 80 years, although there are limited data from well-defined populations. We sought to determine the prevalence of paraproteinaemia in Australians aged 50 years and over, and to determine risks factors for its presence.

Methods: We performed a population-based, cross-sectional study using data and serum collected in the Blue Mountains Eye Study. Serum samples from 2933 patients were analysed by capillary zone electrophoresis and, where indicated, immunosubtraction, which allowed for both quantitation and isotype detection.

Results: A paraprotein was detected in 134 of the 2933 samples, giving an overall prevalence of 4.6% (95% confidence interval, 3.8–5.3%). The presence of a paraprotein was strongly age-related ($P_{\text{trend}} \leq 0.001$), with a prevalence of 2.8% in persons aged 50–59 years, rising steadily to 9.1% in those aged 80 years and over. The prevalence was significantly higher in men (5.9%) compared with women (4.0%) ($P = 0.03$).

Conclusion: We conclude that approximately one in 20 Australians aged 50 years or over harbours a paraprotein, a prevalence that appears higher than from similar cohorts in other countries.

Introduction

A paraprotein is an immunoglobulin or immunoglobulin fragment that is produced excessively by a single clone of antibody-forming cells, usually plasma cells. Also known...
as M-proteins, M-components and monoclonal proteins, there are five heavy chain isotypes (IgG, IgM, IgA, IgD and IgE), each of which may be paired with one of two light chain isotypes (kappa and lambda). The presence of a serum paraprotein has been associated with a number of conditions, most commonly monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM) and other haematological malignancies. MGUS was initially termed ‘benign monoclonal gammopathy’ in the literature in 1968, although the terminology was changed when it became apparent that the presence of a paraprotein conferred a small but increased risk of malignant transformation. MM is the most common malignant plasma cell dyscrasia, with an estimated incidence of 5.5 per 100 000 people. While there has been significant progress in our understanding of the pathogenesis and cytogenetics of MM resulting in new therapies, it conveys a poor prognosis with a median survival of between 2 and 3 years.

Thus, MGUS is recognised as a pre-malignant condition with the potential to evolve into a haematological malignancy. The ability to predict which patients are at risk of malignant transformation remains limited, although the evolving use of assays, such as the serum free light chain ratio has improved our ability to risk-stratify such groups. The prevalence of paraproteinaemia in the Australian population has not been studied. A recent, large, US study estimated the prevalence of paraproteinaemia in those aged 50 years and over to be 3.2%, and earlier studies have suggested lower rates that vary from 0.8% to 1.7%. We sought to determine the prevalence of paraproteinaemia in a defined Australian population aged 50 years and over, and to determine risk factors for its presence.

Materials and methods

Subjects and study design

We performed a cross-sectional, analytical study using data and serum samples collected during the Blue Mountains Eye Study second examination (BMES-2). The BMES is a community-based study of eye disease, vascular disease and nutrition, originally conducted from 1992 to 1994 (BMES-1), and then again in 1997 to 1999 (BMES-2 and BMES-2 Phase 2). It involved a census of a large proportion of the population, aged 50 years and older, residing in non-institutional dwellings in two adjoining postcode areas in the Blue Mountains, west of Sydney. The area selected contained a stable and homogenous population representative of New South Wales and Australia in terms of income, occupation and socioeconomic status.

Patients attended a clinic at the Blue Mountains District Anzac Memorial Hospital, during which they were consented for the study and completed a detailed demographic and medical questionnaire. Subjects then underwent physical examination, and were asked to return within 3 months to have blood taken. Routine haematological and biochemical parameters were measured, and serum samples were placed in sterile plastic aliquots, kept upright and frozen at −80°C in a locked freezer.

The BMES received ethics approval from the Western Sydney Area Health Service Human Research and Ethics Committee.

Paraprotein detection

Serum electrophoresis was performed using capillary zone electrophoresis (CZE) (Beckman Paragon CZETM 2000 system) with online ultraviolet absorbance detectors with a fixed wavelength of 214 nm (Beckman Instruments, Inc., Fullerton, CA, USA). All procedures were performed in the immunochemistry laboratory at the Institute of Clinical Pathology and Medical Research, Westmead Hospital, Sydney, Australia. Electrophoretograms were reviewed independently by two reviewers (D. F., S. B.) experienced in their interpretation. All specimens suspicious for a paraprotein underwent subsequent analysis by serum immunofixation electrophoresis by immunosubtraction (Beckman Paragon CZETM 2000 system). Paraprotein quantification was determined by multiplying the paraprotein percentage by the total protein value, determined using the Biuret method. For samples with more than one paraprotein, the sum of the concentrations was used.

Statistical analysis

Statistical analysis was undertaken using the Statistical Analysis System Version 6.12 software (SAS Institute, Cary, NC, USA). A significance level of $P = 0.05$ was applied. Student’s $t$-tests were used to compare the groups based on blood index measures. Univariate and multivariate analyses were employed to identify any correlates with the presence of paraproteinaemia. The clinical variables examined included age, sex, body mass index, smoking, hypertension, diabetes, angina, previous myocardial infarction, previous stroke, asthma, skin cancer, other cancers, hypercholesterolaemia, thyroid disease and arthritis. Laboratory variables considered included haemoglobin concentration, white cell count, platelet count, total serum protein, albumin, alanine aminotransferase and alkaline phosphatase levels. When testing for trends in age and sex, Mantel–Haenszel
Chi-square tests were employed. Logistic regression models were used for calculating age-adjusted odds ratios.

Results

Blood samples were collected from 3044 subjects, which represented 86.8% of the 3508 subjects enrolled in the BMES-2 and BMES-2 Phase 2 study. Serum samples from 2933 (96.4% of the subjects who had blood taken) were analysed for a paraprotein by CZE. The 111 samples that were not analysed were either not able to be located due to cataloguing errors, or the volumes were too small to be able to run on the CZE instrument. The number of subjects according to age and sex are presented in Table 1.

Prevalence

Immunofixation electrophoresis by immunosubtraction (IFES) was performed on 237 samples in which a paraprotein was suspected on electrophoretograms, and a paraprotein was confirmed in 134 samples, giving an overall paraprotein prevalence of 4.6% (95% CI 3.8–5.3%). Prevalence of a paraprotein was significantly associated with increasing age ($P_{\text{trend}} = 0.001$) (Fig. 1), and was significantly higher in men (5.9%) compared with women (4.0%) ($P = 0.03$). The age-related trend remained significant after controlling for sex; thus the age-adjusted odds ratio for men was 1.49 (95% CI 1.05–2.11). The prevalence in men was higher in every age group, particularly in the lowest age group (50–59), where the prevalence was 4.5%, compared with 1.6% in women (Fig. 1). The concentration of the paraprotein did not vary according to sex, age or the heavy chain isotype (data not shown).

When comparing patients with and without a paraprotein, the proportion of patients who had ever smoked was not significantly different between the two groups. Furthermore, there was no significant difference between the two groups with respect to body mass index, blood pressure, cholesterol level, self-reported medical illnesses or routine haematological and biochemical parameters, including haemoglobin concentration and serum creatinine (data not shown). Only two patients reported medical conditions known to be associated with paraproteinemia (one had been diagnosed with ‘bone marrow cancer’ and another with ‘lymphoma’).

Laboratory characteristics

Paraproteins of the IgG isotype were the most common (77%), followed by IgM (14%), IgA (7.5%), IgD (0.7%) and biclonal (0.7%) (Fig. 2). In total, 65.7% of paraproteins detected were of the kappa isotype, and 34.7% were lambda. The mean paraprotein concentration was 5.5 g/L ($\pm$SD 4.6). In all, 87% of the paraproteins were of a concentration less than 10 g/L, and only two patients (1.5%) had a concentration greater than 20 g/L (Fig. 3).

Discussion

This cross-sectional study provides an accurate estimate of the paraprotein prevalence in a defined cohort of older Australians.
Australians within a fixed geographic region. Our study demonstrated an unexpectedly high paraprotein prevalence of 4.6%, meaning that around one in 20 Australians aged 50 years and older harbours a paraprotein. Earlier studies of populations aged 50 years and older estimated the prevalence of paraproteinaemia at between 0.8–1.7%, but these studies used relatively insensitive methods of detection, including cellulose acetate electrophoresis and paper electrophoresis. Furthermore, compared with our study, most were not population based, and thus provide imprecise estimates of the prevalence of paraproteinaemia in the general population. In contrast, a recent population-based study of more than 21 000 residents aged 50 years or older in Minnesota, USA, estimated the prevalence of paraproteinaemia at 3.2% using agarose gel electrophoresis and immunofixation. In comparison to this data, our study suggests that the paraprotein prevalence in the Australian population is approximately 1.5 times higher than in North American populations.

This higher prevalence observed is only partly attributable to an older population in our study compared with the Minnesota study, because we had a higher proportion of patients aged 60–69 years (35.9% vs 28.0%) and 70–79 years (29.0% vs 21.0%). However, applying the age-related paraprotein prevalence data from the Minnesota study to our study population yields an estimated overall expected prevalence of only 3.5% (data not shown), still lower than our observed figure of 4.6% (P = 0.0027). An alternative explanation for the higher rate observed in our study may be the greater sensitivity of our CZE methodology compared with agarose gel electrophoresis. We think this is unlikely, because comparative studies have shown that the higher CZE sensitivity is mostly explained by greater detection of beta-migrating IgA paraproteins and circulating light chains, whereas our detection rate of IgA paraproteins (8%) was actually lower than in the North American cohort (11%), and neither our study nor the North American one detected circulating free light chains. We therefore conclude that our data likely represents a truly higher prevalence of paraproteinaemia in the Australian population.

The strongest risk factor for paraproteinaemia in our study was increasing age, with the prevalence of paraproteinaemia in subjects aged 80 years and over more than three times that of those aged 50–59 years. Kyle et al. reported similar data, with the prevalence in those aged 80 years and over being almost four times higher than in those aged 50–59 years. Consistent with this, several studies have also reported that paraproteins are rare in those aged under 30 years in a number of different populations.

Our finding that male sex is a risk factor for paraproteinaemia is supported by other studies of diverse patient populations, including hospitals, institutions and the general community. Saleun et al. found that paraproteins were 1.6 times more frequent in men than women, very close to the 1.5 ratio observed in our study. Kyle et al. also demonstrated that age-adjusted rates were higher in men (4.0 per 100) compared with women (2.7 per 100), and that the rate in men was roughly equal to that seen in women a decade older. This increased prevalence of paraproteinaemia in men is consistent with the observation that other plasma cell disorders also demonstrate a male predominance; the age-adjusted incidence of MM in one study was 5.2 per 100 000 in men compared with 3.6 per 100 000 in women. Explanations for the consistent observation of male predilection remain obscure.

The most common paraprotein heavy chain isotype was IgG (76.5% in this study), followed by IgM, then IgA. However, the prevalence of non-IgG paraproteins (namely IgM and IgA) was lower in our population (23.5%) than in previous studies (31% and 32.1%), a finding that is important since non-IgG paraproteinaemia confers an increased risk of malignant transformation.

Our study was limited by a lack of specific information that might have allowed us to determine the clinical significance of paraproteinaemia in these patients. However, because only two patients had paraprotein concentrations greater than 20 g/L, it is highly likely that the majority had MGUS rather than myeloma. Hospital-based studies not surprisingly show a significant rate of more sinister plasma cell disorders; for example, a review of over 1500 subjects with a paraprotein at the Mayo Clinic demonstrated a high rate of myeloma (18%) and smouldering myeloma (6%). Our data generates conflict-
ing possibilities when assessing the risk of malignant transformation from MGUS to myeloma and other malignant B-cell disorders, which is estimated to occur at a rate of approximately 0.4–1% per year.\textsuperscript{3,18} Known risk factors for malignant transformation include non-IgG paraproteinaemia, higher paraprotein concentrations and an abnormal serum free light chain ratio.\textsuperscript{19} On one hand, the higher prevalence of paraproteins in the Australian population may indicate an increased risk of malignant plasma cell dyscrasias. However, the lower prevalence of non-IgG paraproteinaemia (compared with the Minnesota study) and the low paraprotein concentrations observed in our study suggest that the risk of malignant transformation from MGUS to myeloma and other malignant B-cell disorders, which is estimated to occur at a rate of approximately 0.4–1% per year.\textsuperscript{3,18} Known risk factors for malignant transformation include non-IgG paraproteinaemia, higher paraprotein concentrations and an abnormal serum free light chain ratio.\textsuperscript{19} On one hand, the higher prevalence of paraproteins in the Australian population may indicate an increased risk of malignant plasma cell dyscrasias. However, the lower prevalence of non-IgG paraproteinaemia (compared with the Minnesota study) and the low paraprotein concentrations observed in our study suggest that the risk of malignant transformation in the Australian population may, in fact, be lower.

**Conclusion**

The present study has demonstrated a higher prevalence of paraproteinaemia in the Australian population than in other community-based studies, and has confirmed age- and sex-related influences. Whether the older Australian population is at higher or lower risk of malignant plasma cell dyscrasias is unknown and warrants prospective observation.

**Acknowledgement**

The authors acknowledge the support of Beckman-Coulter Australia Pty Ltd in providing the CZE reagents used in this study.
Assessment of chronic hepatitis B: the importance of hepatitis B virus DNA testing

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Key words
hepatitis B, HBeAg-positive, HBeAg-negative, HBV DNA, ALT.

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Abstract

Background: Chronic hepatitis B (CHB) has an estimated prevalence of 90 000 to 160 000 in Australia. Cirrhosis and hepatocellular carcinoma are important complications of CHB and appropriate evaluation of hepatitis B surface antigen (HBsAg)-positive individuals is vital to identify treatment candidates.

Methods: A review of the database of a tertiary hospital was performed and 348 HBsAg-positive individuals with baseline demographic, virological, serological and biochemical variables were identified and evaluated cross-sectionally. A small subgroup of hepatitis B e antigen (HBeAg)-negative patients with normal alanine aminotransferase (ALT) at baseline were identified and followed longitudinally.

Results: 175/348 (50%) of patients were in the HBeAg-negative, chronic hepatitis phase of disease, 22% in the HBeAg-positive immune clearance and 6% in the immune tolerant phase. HBeAg-negative patients were older and more likely to be male than HBeAg-positive patients. The correlation between hepatitis B virus (HBV) DNA and ALT levels was examined. ALT and HBV DNA levels showed no correlation in HBeAg-positive CHB and only a weak correlation in HBeAg-negative CHB. Furthermore, 35% of HBeAg-negative patients with detectable HBV DNA had a normal ALT. Conversely, 38% of HBeAg-negative patients with no detectable HBV DNA had an elevated ALT. A persistently normal ALT over 24 months was seen in five of nine HBeAg-negative patients with normal initial ALT and detectable HBV DNA.

Conclusion: Appropriate evaluation of HBeAg-negative CHB must include HBV DNA because the ALT is not a reliable guide to underlying viral replication.

Introduction

Chronic hepatitis B (CHB) is an important health problem in Australia with an estimated prevalence of 90 000–160 000.1 The majority of CHB patients in Australia are migrants who have acquired the virus in the perinatal or early childhood period by vertical or horizontal transmission in their overseas country of birth. Routine screening with hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (anti-HBs) of individuals from areas of high and intermediate prevalence rates, including South Asia, the Mediterranean and Africa, is recommended.2

An increased burden of disease, in particular from the complication of hepatocellular carcinoma (HCC) is predicted over next two decades3 and the health economic implications of CHB are significant.4 Recent data in the USA suggest that only 28% of HBsAg-positive patients receive further laboratory evaluation of their hepatitis B virus (HBV) infection.5 HBV DNA testing has been listed for a Medicare rebate since April 2008. When used alongside hepatitis B e antigen (HBeAg) status and alanine aminotransferase (ALT), HBV DNA testing allows a patient to be classified into a phase of CHB. These phases are the HBeAg-positive immune tolerant and immune clearance phases and the HBeAg-negative immune control and immune escape phases.6

HBV DNA has been shown to be a strong predictor of the risk of cirrhosis.7 Prior to the widespread accessibility of HBV DNA testing, ALT was used as a surrogate marker for hepatitis B disease activity; however, this has many limitations because not all patients with CHB have persistently elevated aminotransferases,8 notably those in the HBeAg-positive immunotolerant phase and some of those with HBeAg-negative CHB. Thus the HBV DNA is crucial in the evaluation of a patient with CHB; to classify the patient into a phase of disease, to establish a causal relationship between HBV infection and the liver disease,
as a guide to the need for therapy, and to predict the risk of complications, such as cirrhosis and HCC.

**Aims**

1. To classify patients into a phase of CHB based on HBV DNA, HBeAg status and ALT level and examine differences between the groups.
2. To evaluate the differences in proportions of patients found to be replicating by two different HBV DNA assays.
3. To examine the relationship between HBV DNA and ALT in HBeAg-positive and negative CHB both cross-sectionally and in a subgroup of patients longitudinally.

**Methods**

**Patients**

Demographic details including date of birth, sex and ethnic origin of patients seen through the St Vincent’s Hospital’s liver clinics are recorded in a Microsoft Access database. HBV serology including HBeAg and hepatitis B e antibody (anti-HBe) are recorded as well as HBV DNA levels and serum ALT levels.

For the purposes of examining patients based on the phase of disease the classification used was:

- **Immune tolerant (phase 1):** HBeAg-positive, HBV DNA detected and ALT ≤ upper limit of normal (ULN) which was defined as 35 IU/mL.
- **Immune clearance (phase 2):** HBeAg-positive, HBV DNA detected and ALT > ULN.
- **Immune control (phase 3):** HBeAg-negative, HBV DNA not detected by bDNA assay.
- **Immune escape (phase 4):** HBeAg-negative and HBV DNA detectable by bDNA assay.

**Hepatitis B virus serological and DNA testing**

HBsAg is measured using a commercially available immunoassay (Abbott Laboratories, North Chicago, IL, USA) and HBeAg and HBeAb by an immunoassay produced by BioMerieux Clinical Diagnostics (Marcy l’Etoile, France). Since April 2004 HBV DNA levels have been measured by the Bayer Versant HBV DNA 3.0 assay (bDNA signal amplification probe method; Bayer Healthcare, Tarrytown, NY, USA). The dynamic range is 357 to 17,543,900 IU/mL. Patients who were above or below the dynamic range of the assay were assigned the upper and lower limit as their HBV DNA value respectively. One international unit per millilitre is equivalent to 5.6 copies/mL. Between May 2000 and April 2004, HBV DNA levels were performed using a capture hybridisation assay (Digene Hybrid Capture, Digene Diagnostics Inc., Beltsville, MD, USA) with a lower limit of detection of 0.5 pg/mL (approximately 25,000 IU/mL), and rates of HBV detectability on a separate cohort of patients tested with the Digene assay were compared to rates using the Bayer Versant assay. All tests pertaining to HBV DNA were performed at the Victorian Infectious Diseases Reference Laboratory.

**Statistical analysis**

Statistical analysis was performed with the statistical package SPSS (version 17.0, SPSS Inc., Chicago, IL, USA). The corrected χ²-test or two-sided Fisher’s exact test was used to compare categorical data, while the Student’s t-test or one-way ANOVA was used for group comparisons of parametric quantitative data and the Mann–Whitney or Kruskal–Wallis test for similar comparisons of non-parametric data. Results were presented as mean or median whenever appropriate. In all cases tests of significance were two-tailed with a level at <0.05.

**Results**

**Patient characteristics**

In total, 348 patients with a complete baseline dataset of HBV DNA, HBeAg status, ALT and demographic features were available for analysis. HBV DNA was performed on the Bayer Versant HBV DNA assay in these patients. They were examined for differences in their characteristics based on the phase of disease (Table 1) as outlined in Methods. The patient age differed significantly between the four groups (P < 0.001); HBeAg-positive immune tolerant (mean age 32) and immune clearance (mean age 35) groups were significantly younger than the HBeAg-negative immune control and immune escape groups (mean ages 42 and 45 respectively). Post-hoc testing showed that the two HBeAg-positive groups did not differ significantly in age from each other, nor did the two HBeAg-negative groups. Gender make-up of the four phase groups also differed (P = 0.019) with the immune tolerant group having the lowest proportion of men (40%) and the immune escape having the highest proportion at 68%.

The ethnic make-up of the total group was Asian 75%, non-Mediterranean White people 7%, Mediterranean 8%, African 3% and other ethnicities 7%. The ethnic make-up of the phase groups differed significantly (P = 0.001) with fewer Asians in the immune control groups (55%) compared to the other groups and proportionally more Africans in this group, although the number of Africans overall was small.
All patients with detectable HBV DNA by the Bayer Versant assay (n = 271/348) were examined for the distribution of their HBV DNA in HBeAg-positive (n = 96) and negative (n = 175) groups (Table 2). In the HBeAg-positive replicating group the majority of patients (72%) had an HBV DNA of >10^7 IU/mL and only 11% of patients had an HBV DNA of <10^5 IU/mL. In the HBeAg-negative replicating group, the majority (61%) of patients had an HBV DNA of <10^5 IU/mL.

The distribution of baseline ALT was also examined in the group of 348 patients (Table 3). The proportion of HBeAg-positive replicating patients who had a normal (≤35 IU/mL) baseline ALT was approximately 20%. In the HBeAg-negative replicating group, 35% of patients who had a detectable HBV DNA had a concomitant ALT that was in the normal range. The degree of elevation of ALT was modest overall with only 34% and 18% of the HBeAg-positive and HBeAg-negative replicator groups respectively, having an ALT of >3 times the ULN.

### Table 1 Patient characteristics by phase of disease (n = 348)

<table>
<thead>
<tr>
<th></th>
<th>Immune tolerant</th>
<th>Immune clearance</th>
<th>Immune control</th>
<th>Immune escape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers (%)</td>
<td>20 (6)</td>
<td>77 (22)</td>
<td>76 (22)</td>
<td>175 (50)</td>
</tr>
<tr>
<td>Average age, years (SD)</td>
<td>32 (11.65)</td>
<td>35 (11.51)</td>
<td>42 (14.20)</td>
<td>45 (12.83)</td>
</tr>
<tr>
<td>&lt;30 years, number (%)</td>
<td>12 (60)</td>
<td>32 (42)</td>
<td>17 (22)</td>
<td>27 (15)</td>
</tr>
<tr>
<td>Male, number (%)</td>
<td>8 (40)</td>
<td>40 (52)</td>
<td>47 (62)</td>
<td>119 (68)</td>
</tr>
<tr>
<td>Asian, number (%)</td>
<td>15 (75)</td>
<td>58 (75)</td>
<td>42 (55)</td>
<td>145 (83)</td>
</tr>
<tr>
<td>Non-Mediterranean White people, number (%)</td>
<td>3 (15)</td>
<td>10 (13)</td>
<td>7 (9)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Mediterranean, number (%)</td>
<td>0</td>
<td>5 (7)</td>
<td>11 (15)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>African, number (%)</td>
<td>0</td>
<td>1 (1)</td>
<td>6 (8)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Other ethnicity, number (%)</td>
<td>2 (10)</td>
<td>3 (4)</td>
<td>10 (13)</td>
<td>10 (5.5)</td>
</tr>
<tr>
<td>HBV DNA, median (range) (IU/mL)</td>
<td>17 857 140</td>
<td>17 857 140</td>
<td>357 (&lt;357)</td>
<td>39 174</td>
</tr>
<tr>
<td>ALT, median (range) (IU/mL)</td>
<td>31 (14–35)</td>
<td>92 (36–1997)</td>
<td>28 (9–653)</td>
<td>48 (11–2511)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; HBV, hepatitis B virus.

### Table 2 Distribution of baseline HBV DNA in patients with detectable HBV DNA by Bayer Versant assay (n = 271)

<table>
<thead>
<tr>
<th>Baseline HBV DNA (IU/mL)</th>
<th>HBeAg-positive replicators (HBV DNA &gt;357 IU/mL) (n = 96)</th>
<th>HBeAg-negative replicators (HBV DNA &gt;357 IU/mL) (n = 175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>357 to &lt;1000</td>
<td>1 (13)</td>
<td>20 (11.5%)</td>
</tr>
<tr>
<td>1000–9999</td>
<td>3 (3%)</td>
<td>44 (25%)</td>
</tr>
<tr>
<td>10 000–99 999</td>
<td>7 (7.5%)</td>
<td>42 (24%)</td>
</tr>
<tr>
<td>100 000–999 999</td>
<td>10 (10.5%)</td>
<td>25 (14%)</td>
</tr>
<tr>
<td>1 mill–9.99 mill</td>
<td>6 (6%)</td>
<td>20 (11.5%)</td>
</tr>
<tr>
<td>≥10 million</td>
<td>69 (72%)</td>
<td>24 (14%)</td>
</tr>
<tr>
<td>Total</td>
<td>96 (100%)</td>
<td>175 (100%)</td>
</tr>
</tbody>
</table>

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

### Table 3 Distribution of baseline ALT in patients tested with Bayer Versant assay

<table>
<thead>
<tr>
<th>Baseline ALT level (IU/mL)</th>
<th>HBeAg-positive replicators (DNA &gt;357 IU/mL) (n = 96)</th>
<th>HBeAg-negative replicators (DNA &gt;357 IU/mL) (n = 175)</th>
<th>HBV DNA undetectable (bDNA assay) (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT ≤ 35 (&lt;ULN)</td>
<td>19 (19.8%)</td>
<td>61 (34.9%)</td>
<td>48 (62.3%)</td>
</tr>
<tr>
<td>ALT 36–52 (1 to &lt;1.5 × ULN)</td>
<td>15 (15.6%)</td>
<td>34 (19.4%)</td>
<td>11 (14.3%)</td>
</tr>
<tr>
<td>ALT 53–70 (1.5 to &lt;2 × ULN)</td>
<td>11 (11.4%)</td>
<td>32 (18.3%)</td>
<td>8 (10.4%)</td>
</tr>
<tr>
<td>ALT 71–105 (2 to 3 × ULN)</td>
<td>18 (18.8%)</td>
<td>16 (9.1%)</td>
<td>5 (6.5%)</td>
</tr>
<tr>
<td>ALT &gt; 105 (&gt;3 × ULN)</td>
<td>33 (34.4%)</td>
<td>32 (18.3%)</td>
<td>5 (6.5%)</td>
</tr>
<tr>
<td>Grand total</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ULN, upper limit of normal.
In total, 77/348 patients tested with the Bayer Versant assay had HBV DNA < 35 IU/mL. All except one of these patients were HBeAg-negative. Thirty-eight per cent of these patients with undetectable HBV DNA had an abnormal ALT (> 35 IU/mL), including 13% with an ALT 2–3 × ULN suggesting secondary liver pathology.

**Correlation between baseline HBV DNA and ALT**

Correlations between ALT and HBV DNA performed on the Bayer Versant cohort showed a small positive relationship between ALT and HBV DNA in the HBeAg-negative replicating group (Pearson correlation coefficient = 0.240, \( P = 0.01 \)), but no relationship between them in HBeAg-positive replicating patients (\( P = 0.976 \)).

**Comparison of HBV DNA detectability rates between Bayer Versant and Digene DNA assays**

The overall rate of HBV DNA detectability in the main cohort of patients tested with the Bayer Versant HBV DNA assay was 78% (271/348). A further 235 patients had been seen in clinics and had had HBV DNA performed prior to April 2004 on the Digene II assay, and in this group the proportion of patients with detectable HBV DNA was 48% (113/235).

**Serial HBV DNA and ALT in HBeAg-negative replicators with normal baseline ALT**

Sixty-one of the 175 HBeAg-negative replicating patients had a normal baseline ALT (≤35), and in this subgroup there were nine patients (four women, five men) who had had serial ALT levels performed at least 6 monthly over a 24-month period. An intermittent low level rise in ALT to over the normal range was noted in four patients on six out of a total of 16 tests. In the other five patients, the follow-up ALTs remained persistently normal.

The median baseline HBV DNA of these nine patients was 7989 IU/mL (range 883 IU/mL to 902,312 IU/mL). Three patients had a baseline HBV DNA of <2000 IU/mL and the other six were ≥2000 IU/mL. Serial HBV DNA levels had also been performed at time points corresponding to the 6 monthly ALT levels in seven of these patients (Table 4), and in all tests follow-up DNA levels showed ongoing replication.

**Discussion**

Our study of a large Australian cohort of CHB patients reveals three things which we feel are pertinent to the initial evaluation of CHB. Firstly, CHB should ideally be conceived of as having four phases of disease\(^7\) and we outline in an Australian adult cohort some of the demographic, virological and serological differences in patients in these phases. Secondly, the serum ALT and HBV DNA do not correlate strongly with each other. Thus HBV DNA testing to establish the presence of viral replication is important, particularly in HBeAg-negative CHB where fluctuating or even persistently normal ALT levels can be seen in patients who have detectable serum HBV DNA. Thirdly, the sensitivity of HBV DNA assays has improved in recent years, and many patients previously thought to be non-viraemic may actually be shown to have detectable HBV DNA in their serum and require further assessment.

CHB can seem a complex condition due to changes in testing, varying nomenclature of the natural history phases and the evolution in the treatments available. Further evaluation of the HBsAg-positive patient should be performed and we believe initial assessment should include HBeAg, HBV DNA and ALT in order that patients

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**Table 4 Longitudinal ALT and hepatitis B virus DNA levels in hepatitis B e antigen-negative replicating patients with normal initial ALT**

<table>
<thead>
<tr>
<th>Patient</th>
<th>ALT 0 m</th>
<th>ALT 6 m</th>
<th>ALT 12 m</th>
<th>ALT 18 m</th>
<th>ALT 24 m</th>
<th>DNA 0 m</th>
<th>DNA 6 m</th>
<th>DNA 12 m</th>
<th>DNA 18 m</th>
<th>DNA 24 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>29</td>
<td>35</td>
<td>22</td>
<td>3</td>
<td>28</td>
<td>1,799.286</td>
<td>1,643.393</td>
<td>923.3929</td>
<td>387.8571</td>
<td>412.1429</td>
</tr>
<tr>
<td>Patient 2</td>
<td>22</td>
<td>23</td>
<td>24</td>
<td>3</td>
<td>27</td>
<td>9,230.714</td>
<td>503.9286</td>
<td>6,155.536</td>
<td>2,213.75</td>
<td>600.7143</td>
</tr>
<tr>
<td>Patient 3</td>
<td>25</td>
<td>27</td>
<td>24</td>
<td>22</td>
<td>33</td>
<td>1,255.179</td>
<td>2,104.286</td>
<td>1,535.536</td>
<td>711.4286</td>
<td>1,089.286</td>
</tr>
</tbody>
</table>

**Persistently normal ALT**

<table>
<thead>
<tr>
<th>Patient</th>
<th>ALT 0 m</th>
<th>ALT 6 m</th>
<th>ALT 12 m</th>
<th>ALT 18 m</th>
<th>ALT 24 m</th>
<th>DNA 0 m</th>
<th>DNA 6 m</th>
<th>DNA 12 m</th>
<th>DNA 18 m</th>
<th>DNA 24 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 4</td>
<td>27</td>
<td>64</td>
<td>31</td>
<td>24</td>
<td>28</td>
<td>4,644.821</td>
<td>2,558.036</td>
<td>9,954.821</td>
<td>4,019.643</td>
<td>17,046.96</td>
</tr>
<tr>
<td>Patient 5</td>
<td>29</td>
<td>18</td>
<td>15</td>
<td>39</td>
<td>18</td>
<td>7,989.286</td>
<td>1,451.429</td>
<td>375.7143</td>
<td>23,757.05</td>
<td>22,114.82</td>
</tr>
<tr>
<td>Patient 6</td>
<td>29</td>
<td>46</td>
<td>14</td>
<td>38</td>
<td>45</td>
<td>54,422.32</td>
<td>140.263.4</td>
<td>36.395</td>
<td>8,279.107</td>
<td>79,364.64</td>
</tr>
<tr>
<td>Patient 7</td>
<td>34</td>
<td>31</td>
<td>36</td>
<td>32</td>
<td>33</td>
<td>37,105.18</td>
<td>17,462.86</td>
<td>2,661.964</td>
<td>36,062.14</td>
<td>45,208.39</td>
</tr>
</tbody>
</table>

**Intermittently normal ALT**

<table>
<thead>
<tr>
<th>Patient</th>
<th>ALT 0 m</th>
<th>ALT 6 m</th>
<th>ALT 12 m</th>
<th>ALT 18 m</th>
<th>ALT 24 m</th>
<th>DNA 0 m</th>
<th>DNA 6 m</th>
<th>DNA 12 m</th>
<th>DNA 18 m</th>
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<tbody>
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<td>31</td>
<td>24</td>
<td>28</td>
<td>28</td>
<td>4,644.821</td>
<td>2,558.036</td>
<td>9,954.821</td>
<td>4,019.643</td>
<td>17,046.96</td>
</tr>
<tr>
<td>Patient 5</td>
<td>29</td>
<td>18</td>
<td>15</td>
<td>39</td>
<td>18</td>
<td>7,989.286</td>
<td>1,451.429</td>
<td>375.7143</td>
<td>23,757.05</td>
<td>22,114.82</td>
</tr>
<tr>
<td>Patient 6</td>
<td>29</td>
<td>46</td>
<td>14</td>
<td>38</td>
<td>45</td>
<td>54,422.32</td>
<td>140.263.4</td>
<td>36.395</td>
<td>8,279.107</td>
<td>79,364.64</td>
</tr>
<tr>
<td>Patient 7</td>
<td>34</td>
<td>31</td>
<td>36</td>
<td>32</td>
<td>33</td>
<td>37,105.18</td>
<td>17,462.86</td>
<td>2,661.964</td>
<td>36,062.14</td>
<td>45,208.39</td>
</tr>
</tbody>
</table>

**Bold represents abnormal ALT values (i.e. ALT > 35).** ALT, alanine aminotransferase.

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may be classified into a phase of disease. Our data highlights some of the ways in which these phases of disease differ. Firstly, the HBeAg-positive patients are younger than HBsAg-negative patients and they have higher HBV DNA levels. HBeAg seroconversion is usually followed by a period of immune control with very low levels of virus. Although ongoing viral replication and chronic HBsAg-negative hepatitis B (the immune escape phase) may develop close to the phase of HBeAg loss, it usually occurs as a relapse some years after a period of quiescence, and this is reflected in the finding that our patients in the immune escape phase are significantly older than the HBeAg-positive patients. Male gender is associated with a higher risk of hepatitis relapse in HBeAg-negative patients, and in our cohort the proportion of men is highest in the immune escape group at 68%. The immune escape phase comprises half of our cohort which underlines the increasing problem that HBsAg-negative chronic hepatitis is becoming in many parts of the world.

The ethnic make-up of the cohort of patients at our centre has changed over the past 5 years when compared with a report in 2005. There has been an increase in the number of Asians overall and fewer patients of Mediterranean and non-Mediterranean White origin. This is likely to reflect patterns of migration to Australia. In the Australian literature, other reports of HBsAg-positive patients have included cohorts from prison settings and injecting drug user groups. In these groups adult-acquired hepatitis B is more likely to be prevalent than in our cohort of predominantly perinatally acquired disease. A report of HBsAg-positive patients screened at the endoscopy unit of a tertiary hospital showed that 70% of the 45 currently infected patients were born in the Asia-Pacific region. HBeAg was not tested in these patients, and therefore their phase of disease was not known. Another report of pregnant women referred to Liverpool Hospital’s liver clinics showed that the majority of those were of South-East Asian background and 29% were HBeAg-positive. Patients were not strictly classified into a phase of disease but were placed into groups of low (<10^5 copies/mL), high and very high viral loads.

The relationship between ALT and HBV DNA levels is different in HBeAg-positive and negative disease. HBeAg-positive patients with rare exceptions are all replicating and a normal ALT signifies immune tolerance. In HBeAg-negative patients, however, we show that on a single evaluation an elevated ALT cannot be equated with elevated HBV DNA, because 35% of patients with detectable virus have an ALT below the ULN. The converse finding that 38% of patients with undetectable virus have an abnormal ALT once again underscores the importance of measuring HBV DNA so that other possible causes of liver disease (e.g. non-alcoholic steatohepatitis) may not be mistakenly attributed to hepatitis B. We also show that in HBsAg-negative patients ALT levels which are either persistently or intermittently normal over a 2-year period are often associated with ongoing low level viral replication. Thus, as has been shown by others, we confirm that there is a correlation between HBV DNA levels and ALT in HBsAg-negative patients, but it is weak.

Increasingly sensitive HBV DNA assays reveal that active replication is ongoing in the majority of patients with CHB. Patients deemed to be an ‘inactive carrier’ of hepatitis B (without active viral replication) on the basis of an older HBV DNA assay should be retested with a more sensitive assay and should be monitored yearly to detect transition to the immune escape phase of disease.

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL) study identified an HBV DNA level of \( \geq 10^6 \) copies/mL (1.78 \times 10^3 IU/mL) as portending an increased risk of HCC, and in both our HBsAg-positive and negative replicating patients the vast majority are above this threshold. There has been debate about the HBV DNA threshold which should be used to define inactive disease (phase 3, the immune control phase) with recommendations being reduced over the past few years from 100 000 copies/mL (17 857 IU/mL) to 2000 IU/mL. Current US guidelines use an HBV DNA level of 2000 IU/mL to distinguish between HBsAg-negative patients with chronic HBsAg-negative hepatitis (immune escape) versus those in the ‘inactive HBsAg carrier’ (immune control) phase. However, this definition of ‘inactive HBsAg carrier’ also includes the criteria of persistently normal ALT/AST levels and a liver biopsy showing the absence of significant hepatitis. Significant proportions (approximately 60%) of patients with HBsAg-negative chronic hepatitis and HBV DNA <2000 IU/mL have been shown to have histological indications for treatment. Furthermore, a small number of patients with chronic HBsAg-negative hepatitis B have been shown to have fluctuations in viral loads below 2000 IU/mL periodically. Strict definitions of the phase groups usually involve serial ALT monitoring to establish a persistently normal or elevated state and liver histology findings. It is important to note that our definitions do not include these criteria and that the HBV DNA thresholds used differ from international guidelines. They served however as an easily applied clinical tool for this cross-sectional study.

The decision to treat hepatitis B is an individual one which needs to incorporate several factors including the risk of development of cirrhosis and HCC, HBV DNA and ALT levels, the degree of histological fibrosis and inflammation and patient factors, such as age and likelihood of compliance. Although usually not candidates for
treatment, patients in the HBeAg-positive immune tolerant and HBeAg-negative immune control phases still require regular monitoring.

Conclusion

We describe a uniquely Australian experience of CHB in a large diverse group of patients with detailed demographic, biochemical and virological characterisation. The ALT is not always a good guide to a patient’s HBV DNA level so should not be relied on exclusively as a surrogate marker of viral replication. In order that CHB patients access and benefit from advances, clinicians must take the steps of screening at-risk populations and performing an appropriate initial evaluation of them which should include HBV DNA level.

Acknowledgements

The authors thank Mr James Williams for assistance with statistical analysis.

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Clinically important detection of infection as an ‘incidental’ finding during cancer staging using FDG-PET/CT

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Key words
FDG-PET/CT, cancer staging, infection.

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Abstract

Background: FDG-PET/CT is widely used in the management of a variety of malignancies with excellent overall accuracy, despite the potential for false positive results related to infection and inflammation.

Aim: As cancer patients can develop clinically inapparent infections, we evaluated the prevalence and nature of incidental findings reported to be suggestive of infections that had been identified during clinical cancer staging with FDG-PET/CT.

Methods: The study involved a retrospective analysis of 60 patients managed primarily at our facility from a total of 121 cases identified as having possible infection on clinical reporting of more than 4500 cancer staging investigations performed during the calendar year of 2008.

Results: Occult infections were uncommon overall (1%), but most often because of pneumonia (31.6%), upper respiratory tract infections (21.1%) or wound infections (15.8%). Abnormal scans contributed to patients’ management in 52.7% of cases. Two out of 13 patients whose scan abnormalities were not investigated further had worsening changes on repeated scan and one of these patients had clinical deterioration.

Conclusions: In patients with FDG-PET/CT scans suggestive of infection and in whom a final diagnosis could be reached, the positive predictive value for FDG-PET/CT scans was 89% suggesting that abnormal scans indicative of infection should be investigated further in this population.

Introduction

Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) is widely used in the diagnosis, staging and management of a variety of malignancies.1 This imaging method identifies areas with a high rate of glycolysis in which FDG accumulates. Increased glucose metabolism, however, is not specific to malignant cells. Inflammatory and infectious processes are frequently noted to have increased glucose metabolism and false positive results attributable to infection have been described during evaluation of patients with malignancies.2 These observations have resulted in an interest in investigating the potential use of FDG-PET imaging in a range of infectious and inflammatory conditions.

Patients with malignancy can develop infections as a consequence of either surgical interventions or a compromised immune system following chemotherapy. These may be difficult to diagnose, particularly as they are often asymptomatic. They may also be difficult to treat because of the underlying immunocompromised state, which can predispose to a range of opportunistic organisms. Incidental abnormalities are not uncommon on PET/CT. A recent study from our institution found that 12% of patients had incidental FDG-PET/CT abnormalities that were thought to be independent of the primary disease process being evaluated.3 Of the evaluable sites, 33% were suspected to be a second primary malignancy and 67% were considered more likely to represent a benign process. However, this study did not report how many of the benign processes were due to infections.

No previous study has evaluated incidental findings on FDG-PET/CT scanning attributed to infections or the outcomes associated with these findings. The objectives of this study were therefore: (i) to describe the frequency of incidental findings of increased FDG uptake reported on routine clinical PET/CT that were suggestive of

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infection in a study population of patients with underlying malignant conditions and (ii) to assess the effect and clinical outcomes of these incidental findings on the management of these patients.

Methods

Setting

This study was conducted at the Peter MacCallum Cancer Centre (PMCC), a tertiary referral centre for the management of a broad range of malignant conditions, including haematological, head and neck, lung, breast, gastrointestinal, genito-urinary, gynaecological, skin, bone and soft tissue tumours.

Eligible patients and study design

Patients who had FDG-PET/CT performed for staging of malignancy between 1 January 2008 and 31 December 2008 and who had incidental findings suggestive of infection were included in the study. Incidental findings suggesting infection were identified using the PMCC PET Centre database and the following search terms contained within the dictated report field: ‘infection’, ‘abscess’, ‘collection’, ‘fever’, ‘febrile’, ‘pyrexia’ ‘sepsis’, ‘fungal’, ‘colitis’, ‘pneumonia’, ‘pneumonitis’ ‘osteomyelitis’, ‘cellulitis’, ‘endocarditis’, ‘lymphadenitis’ and ‘inflammation’. FDG-PET/CT reports of all eligible patients were reviewed. Patients were excluded from the study if they were less than 18 years of age, the definitive management had occurred at a healthcare facility other than PMCC or no infections were identified from the conclusion of the scans reports. Medical records of studied patients were reviewed by a single researcher. Data obtained for each patient included age, sex, nature of underlying of malignancy, current chemotherapy and/or radiotherapy, signs and symptoms (if present) before the imaging, confirmatory pathology results, management plan following the imaging result and the contribution of FDG-PET/CT to subsequent patient management.

Imaging protocol

All PET/CT studies were acquired on a PET/CT scanner (Discovery ST or Discovery LS, GE Medical Systems, Milwaukee, WI, USA). Patients were fasted for a minimum of 4 h before scanning and generally in excess of 6 h. Blood glucose levels were less than 10 mmol/L at the time of FDG administration. A dose of 285–370 MBq was administered intravenously through a cannula. A non-contrast CT scan was acquired in helical mode at 140 kVp, 80 mAs and reconstructed at a slice thickness of 3.27 mm. The FDG-PET scan encompassed the same axial extent as the CT scan, representing four- to six-bed positions depending on the size of the patient. Each bed position had an acquisition time of 5 min and was acquired in 2-D or 3-D mode depending on the patient’s weight. The images were reconstructed using iterative reconstruction using the order-subset estimate maximisation algorithm.

Definitions

The likelihood of infection based on the FDG-PET/CT report was classified as equivocal if the uptake was beyond normal physiological activity, but uncertainty existed regarding the aetiology of this, or positive if the uptake was beyond normal physiological activity and suggestive of an infective focus. Scan results were based only on the clinical report issued at the time of initial investigation and not reinterpreted in light of subsequent findings. In addition to the study investigator, a panel of three other infectious diseases physicians was consulted in a blinded fashion where uncertainty existed regarding the significance of a scan.

The FDG-PET/CT scan was considered contributory to the patient’s management when it resulted in any of the following:

1. Investigations (invasive or non-invasive) were ordered by the treating clinician to confirm or exclude the presence of an infection.
2. Initiation or modification of therapy, such as commencing antimicrobials or removal of infection site (device, surgical debridement).

The FDG-PET/CT scan was considered non-contributory to the patient’s management if:

1. Abnormalities on FDG-PET/CT were not investigated further by the treating clinician.
2. The patient already had a known infection, the presence of which was confirmed by FDG-PET/CT scan.
3. The patient was already on treatment for an infection at the time of the scan and no modification to therapy made as a result of the scan findings.

Abnormal FDG-PET/CT scans were considered true positive results when abnormal FDG uptake was localised to the organ or tissue where infection was subsequently found by additional diagnostic techniques or compatible with clinical findings. Abnormal results were regarded as false positive when the detected abnormality was considered to be unrelated to infection. A final diagnosis was based on positive blood or tissue culture, biopsy or surgery. When this was not performed or was negative, a probable diagnosis was made based on clinical features and follow-up serology, diagnostic PCR of blood or tissue specimens or conventional radiological studies. Current chemotherapy/radiotherapy referred
to chemotherapy or radiotherapy instituted within 1 month before FDG-PET/CT scan.

**Statistical analysis**

Proportional outcomes were calculated for positive and equivocal scans to determine true positive and false positive results for infection.

**Results**

**Study population**

A total of 242 scans was initially identified using the defined search terms from all scans performed in 2008 (=4500) (Fig. 1). Of these, 121 scans were excluded as the scan reports had the defined search terms, but no infections were actually identified in the scan report. Sixty-one scans were excluded as these patients were managed at external healthcare facilities. The remaining 60 scans (in 57 patients) fulfilled the study requirements and were included in the study. The median age of patients was 56 years (range 19–78) and 37 patients (64.9%) were male. The most frequent underlying malignant condition was haematological malignancy (47.4%), followed by head and neck (24.6%) and gastrointestinal tract (8.8%) malignancies. Ten patients were receiving chemotherapy and one patient was undergoing radiotherapy at the time of scan. Eleven out of 27 patients (40.7%) with haematological malignancy had undergone a bone marrow transplant (eight autologous and three allogenic). Table 1 summarises characteristics of the study population. Tables 2 and 3 summarise findings for positive and equivocal scans.
positive FDG-PET/CT scans

Of the 60 abnormal FDG-PET/CT scans, 47 (78.3%) were reported as being highly suggestive of infection. A final diagnosis was made in 37 cases. Scan results were classified as true positive in 89.2% and false positive in 10.8% of positive PET/CT scans in which a final diagnosis was possible (Fig. 1). In other patients a final diagnosis was not possible as scan abnormalities were not investigated further by the treating clinician. These patients were excluded from the calculation of the positive predictive value. The positive predictive value of FDG-PET/CT scans was 89%. The most common diagnoses associated with a positive FDG-PET/CT scan were pneumonia (31.6%), followed by upper respiratory tract infections (21.1%) and wound infections (15.8%). Of note, PET/CT scan was able to identify two clinically inapparent wound infections and one unknown ischiorectal abscess (Fig. 2).

Table 1: Patients undergoing PET scanning for staging of malignancy (n = 57)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>37 (64.9)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>56</td>
</tr>
</tbody>
</table>

Underlying malignancy

| Haematological | 27 |
| Lung           | 1 |
| Head and neck  | 14 |
| Gastrointestinal | 5 |
| Gynaecological | 4 |
| Bone and soft tissue | 3 |
| Skin           | 2 |

Current therapy

| Chemotherapy | 10 |
| Radiotherapy | 1 |

Previous stem cell transplant | 11 |

Symptomatic at time of scan

| Pneumonia | 27 (47.4) |
| URTI      | 8 |
| Wound infection | 4 |
| Fever     | 2 |
| Abdominal abscess | 3 |

PET, positron emission tomography; URTI, upper respiratory tract infection.

Table 2: Final diagnoses in patients with positive PET scans for infection

<table>
<thead>
<tr>
<th>Diagnosis†</th>
<th>n</th>
<th>Contributory</th>
<th>True positive</th>
<th>False positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12</td>
<td>5</td>
<td>12</td>
<td>—</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Empyema</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>URTI</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected lymphocele</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Others

| Malignancy | 2 | 2 | — | 2 |
| BOOP       | 1 | 1 | — | 1 |
| Post influenza vaccination | 1 |
| Bladder reconstruction | 1 |

No diagnosis‡ | 10 | 0 |

Sites

| Lung       | 7 |
| Sacrum     | 1 |
| Maxilla    | 1 |
| Posterior molar | 1 |
| Tooth      | 1 |

†Individual patients may have had >1 diagnosis. ‡Abnormal scans findings were ignored by the treating physician. BOOP, bronchiolitis obliterans organising pneumonia; URTI, upper respiratory tract infection.

Table 3: Final diagnoses in patients with equivocal PET scan

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Contributory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>5</td>
<td>2†</td>
</tr>
<tr>
<td>No pathology identified</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

†Both patients had repeated PET scans to monitor the abnormalities in the lung fields. In one patient, abnormalities resolved without a known diagnosis. In another patient, abnormalities persisted with a new avid lesion, but no final diagnosis was possible as the lesion was deemed too small to biopsy. In this respect, PET scans were judged to be contributory to patients' management. PET, positron emission tomography.

Incidental infections during FDG-PET/CT
FDG-PET/CT scans were false positive in four patients. One patient was diagnosed to have bronchiolitis obliterans organizing pneumonia (BOOP), an inflammatory process without an infectious aetiology, by lung biopsy. Extensive investigations did not show an infectious source. Another patient with metastatic cervical cancer had intense FDG uptake in the anterior abdominal wall. This was reported as possible post-surgical infection, but most likely represented normal wound healing on follow-up. The third patient had previous reconstructive bladder surgery in which avid FDG uptake in urine mimicked a right tubo-ovarian abscess. The fourth patient had increased FDG uptake in the sigmoid colon suggestive of a diverticular abscess, which was later found to be a hyperplastic polyp.

Nine of the 10 patients in whom the scan abnormalities were not investigated further remained well on follow-up (four had resolution of abnormalities and one had persistent changes on repeat scanning). The anatomical sites involved in these patients were lungs (six), maxilla (one), sacrum (one) and a posterior molar tooth (one). One patient with mantle cell lymphoma in remission had new FDG avid lung opacities and became symptomatic 4 months later. A repeat FDG-PET/CT scan showed extensive metabolically active opacities in both lungs, and lung biopsy showed BOOP (Fig. 3).

**Equivocal FDG-PET/CT scans**

Thirteen scans were reported as being suspicious but equivocal for infection. Two patients with equivocal scans had no infectious or malignant diagnosis. In one patient with mediastinal B cell lymphoma, focal avid FDG uptake in skin and subcutaneous tissue in the occipital region was noted, which was found on biopsy to be connective tissue with focal granuloma. Another patient with metastatic melanoma had a focal moderately avid FDG uptake in the right axilla, which on biopsy did not show evidence of infection or malignancy. Five equivocal scans subsequently were found to be malignant disease in an atypical location, including a splenic metastasis from lung cancer and extranodal disease site in relapsed lymphoma. One patient with diffuse large cell lymphoma in remission was diagnosed with pneumonia based on clinical features. A repeat scan 2 months later showed resolution of previous
abnormal uptake in the left lower lobe. No diagnosis was made in five patients with equivocal scans.

Further management

Overall, FDG-PET/CT scan was contributory to patients’ management in 52.7% of cases. In total, nine patients were investigated with additional microbiological tests, 11 patients had invasive procedures performed and nine patients had further radiological testing following the results of the abnormal FDG-PET/CT scans. Only two patients had microbiologically confirmed infections – picornavirus (pneumonitis) and methicillin sensitive Staphylococcus aureus (wound infection). Eight patients commenced directed antimicrobial therapy and four other patients had changes made to their antimicrobial therapy following the scan results.

Discussion

In recent years, FDG-PET/CT has been shown to be useful in the assessment of patients with chronic osteomyelitis, infected lower-limb prosthesis, fever of unknown origin, AIDS and vascular graft infection.4–6 Although FDG uptake in infectious or inflammatory lesions was initially thought to be a disadvantage in the evaluation of patients with malignancy, two studies suggest that FDG-PET may be useful for diagnosis and management of infections in immunocompromised patients.7,8 Benign conditions that have been shown to increase FDG uptake included infection, inflammation without infection (e.g. sarcoidosis), arterial thrombosis, inflammatory arthritis and regional lymph node hyperactivity following immunisation.

Our study showed that in a patient population with malignant conditions, incidental findings that are suggestive of infection on FDG-PET/CT scans are uncommon (≤1%). The most frequent site of infection was the respiratory tract.9,10 For the 37 scans where a final diagnosis was reached, the positive predictive value was 89%. Bleeker-Rovers et al. evaluated the clinical value of FDG PET in 55 patients suspected of focal infection or inflammation and reported a sensitivity of 100%, specificity 89%, positive predictive value of 95% and negative predictive value of 100%.11 In this study, 58% of episodes were infection, 5% neoplasm, 7% non-infectious inflammatory causes and 18% had no final diagnosis. It should be noted that our population is different as we are looking at incidental findings of infection whereas their study was in those with suspected infection or inflammation.
Positive FDG-PET/CT scans suggestive of infection contributed to patients’ management in approximately 40% of cases. More than half of the patients in the pneumonia group already had a working diagnosis at the time of scanning. Equivocal FDG-PET/CT scans contributed to the management in approximately 70% of patients. As equivocal scans were mainly due to the inability to differentiate infection from tumour recurrence, these resulted in patients undergoing further investigations (invasive and non-invasive) as well as being administered chemotherapy.

In the current study, where an abnormal FDG-PET/CT scan was not investigated further by the treating clinician, the majority of abnormalities were in the lung fields. Two out of 13 patients had worsening changes on repeated scans. One patient who had an allogeneic bone marrow transplant performed for relapsed mantle cell lymphoma was diagnosed with BOOP on lung biopsy. Several reports have associated BOOP with haematological malignancies, especially in the setting of lymphoma treated with rituximab therapy. BOOP can present with solitary or multiple pulmonary nodules and although an unusual benign cause of hypermetabolism on FDG PET/CT, it should be considered in the differential diagnosis. Another patient with nasopharyngeal carcinoma had a new avid lesion in the left apical pulmonary zone, but this was deemed too small to biopsy. While uncommon, incidental findings on FDG-PET/CT scanning may indicate significant pathology in some patients. Our group has previously reported the merit of FDG-PET/CT scanning for diagnosis of occult tuberculosis.

It should be noted that some of the sites of uptake misinterpreted as being suspicious for infection turned out to represent important pathological conditions. These included unusual sites of metastatic disease, a pre-malignant lesion and inflammatory lung disease. These results complement our earlier study demonstrating that experienced reporting clinicians can quite reliably differentiate between the various potential causes of augmented tissue uptake of FDG, including second malignancies and benign granulomatous diseases. They further support the importance of investigating those abnormalities considered highly suspicious of an alternative pathology to that being actively investigated by the scan referral.

In determining the degree to which study findings are relevant to other centres and patient populations, it is important to understand the nature of the study population. Almost half of our study population consisted of patients with haematological malignancy, the majority of these being lymphoma. Abnormal FDG uptake has previously been reported in patients with lymphoma undergoing surveillance PET scanning which has not been due to disease relapse. One study showed that 23.1% of PET scans showing abnormal FDG uptake were diagnosed as non-tumoral radiotracer uptake. Another small case series found that two out of seven patients with persisting focal increased in FDG activity early in the follow-up period were diagnosed to have aspergillosis or sarcoidosis. Five out of six patients with equivocal scan results in our study were thought to have infection or tumour recurrence.

Limitations of the current study include the fact that we evaluated patients with positive and equivocal findings suggestive of infection on routine clinical reporting of FDG-PET/CT scan performed for a range of clinical indications, including primary staging, therapeutic monitoring and post-treatment surveillance. The identification of potential sites of infection was based on the clinical report issued at the time of scanning, which was potentially influenced by a combination of clinical information available at this time and the experience of the reporting specialist in recognising atypical patterns of FDG uptake relative to that expected for the malignancy being evaluated. However, none of the patients had confirmed infection before scan. Further, we did not attempt to capture the proportion of patients with a negative staging FDG-PET/CT scan in whom infection may have subsequently been diagnosed. The search terms used to identify potential study participants may not have been comprehensive and we may have inadvertently overlooked some scans suggestive of infection. For example, we did not include the term ‘inflammatory’ when searching for eligible study participants as many non-infective disorders can produce an inflammatory response. In support of this approach, however, we did reviewed 100 FDG-PET/CT scan reports using only the search term ‘inflammatory’ and did not identify any additional infections as a result. Also, being a retrospective study, accuracy or completeness of data could not be confirmed. Furthermore, a limited sample size was studied at a single centre and findings may not be directly generalised to all patients with malignancy.

**Conclusion**

When FDG-PET/CT scanning is performed for staging of malignancy, findings suggestive of infection are uncommon. When present, the most frequent site for abnormalities is the respiratory tract. Our findings demonstrate that in patients with a PET/CT scan consistent with infection, the positive predictive value for FDG-PET/CT scans is 89%, indicating the beneficial role of this method in making a diagnosis and that abnormal scans suggestive of infection should be investigated further in this population.
References


Indigenous beliefs about biomedical and bush medicine treatment efficacy for indigenous cancer patients: a review of the literature

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Key words
Indigenous, cancer, treatment, bush medicine.

Abstract
Background: Australia’s Indigenous people suffer from higher cancer mortality than non-Indigenous Australians, a discrepancy partly caused by differences in beliefs about treatment efficacy between Indigenous patients and their non-Indigenous healthcare providers. This paper critically reviews the literature associated with Indigenous beliefs about cancer treatment, both ‘bush medicine’ and biomedical, in order to provide recommendations to healthcare providers about accommodating Indigenous beliefs when treating cancer.

Methods: A search was undertaken of peer-reviewed journal papers using electronic databases and citation snowballing. Papers were selected for inclusion based upon relevance to themes that addressed the research questions.

Results: Literature suggests that Indigenous beliefs about treatment efficacy for cancer involve five themes: (i) concerns about the toxicity of treatment; (ii) disconnect with the physician; (iii) fears about absence from home during treatment; (iv) different beliefs about disease aetiology; (v) biomedical cancer treatments failing to address holistic health.

Conclusions: Although some information is known about Indigenous Australian healing beliefs and practices associated with cancer treatment, few studies have addressed ways in which Indigenous and biomedical approaches to cancer treatment might be integrated. Some recent work has examined the role of belief in cancer treatment, specifically bush medicine, but more research is required.

Introduction
Indigenous Australians suffer from higher cancer morbidity and mortality than non-Indigenous Australians. They are less likely than non-Indigenous people to use preventive and screening services, and, when diagnosed, to receive treatments such as surgery, chemotherapy and radiotherapy. There are many reasons for this discrepancy, including socioeconomic and educational factors, language barriers, and lack of healthcare provider familiarity with cultural practices and transportation issues.
guiding healthcare providers’ consideration of beliefs about treatment in developing cancer treatment plans for Indigenous Australians. Furthermore, the review seeks to identify gaps in knowledge and areas for future research. Characterisation of explanatory models and belief systems and application of such knowledge to medical practice are essential to reducing morbidity and mortality among Indigenous people with cancer.

Methods – search strategy and approach

This review draws upon the existing literature to present a summary of what is known about Indigenous views of bush medicine and biomedical treatments for cancer, and to provide recommendations for healthcare providers about accommodating both treatment types with the goal of reducing cancer mortality among Indigenous Australians.

We undertook a search of the literature for material relevant to the following research questions:

- What is known about Indigenous Australians’ views of biomedical cancer treatment?
- What is known about Indigenous Australians’ views of bush medicine treatments for cancer?
- What success, if any, has there been in combining these two approaches to treat cancer in Indigenous Australian patients?
- What recommendations might be presented to Australian healthcare providers to facilitate their integration of both treatment methods, with the goal of improving outcomes and decreasing morbidity and mortality among Indigenous Australian cancer patients?

The search process was similar to a systematic review in methodically utilising electronic databases, and it also incorporated the critical interpretive synthesis approach in that themes emerged as the literature was searched. This dual method was more appropriate given the relative paucity of literature relevant to the topic at the time of writing.

Peer reviewed journal papers were selected following a search of electronic databases including Proquest, Science Direct, Google Scholar, PubMed, Medline, Academic Search Premier (EBSCO), PsychINFO, Informit and ISI Web of Knowledge, and citation snowballing was undertaken. Key search terms used included combinations of the following: Indigenous, Aboriginal, cancer, belief, bush medicine, treatment. Publications were considered for inclusion if they addressed at least one of the research questions mentioned earlier. Papers that did not refer to Indigenous or Aboriginal or Torres Strait Islander people of Australia were excluded.

Results

Available literature revealed five themes related to Indigenous people’s beliefs about treatments and treatment efficacy for cancer:

1. Concerns about the toxicity, side-effects and potential disfigurement of treatment.
2. A feeling of disconnect with the physician.
3. Fears about distance from home and family when treatment requires relocation to a hospital far from home.
4. Beliefs about disease aetiology that differ from those presented by the Western biomedical model.
5. Failure of biomedical treatments to address holistic health, in contrast to bush medicine treatments that do address holistic health.

Concerns about the toxicity, side-effects and potential disfigurement from treatment

The outcomes of many qualitative studies reveal Indigenous concerns about the toxicity, side-effects, and potential disfigurement of cancer treatment, and these beliefs underpin to some extent quantitative hospital admission data showing that Indigenous people are less likely to receive aggressive cancer therapies. Condon et al. completed a retrospective cohort study of 1197 Indigenous and non-Indigenous people in the Northern Territory diagnosed with colon, rectum, lung and breast cancer, as well as with non-Hodgkin lymphoma, between 1991 and 2000. Surgery was recommended for 70% of non-Indigenous patients and 61% of Indigenous patients; chemotherapy for 34 and 35%, and radiotherapy for 34 and 36% of non-Indigenous and Indigenous patients respectively. Of the patients for whom each procedure was recommended, for non-Indigenous and Indigenous patients, respectively, 99% and 90% chose surgery, 93 and 87% chose chemotherapy, and 94 and 84% chose radiotherapy. Finally, of the patients who chose the procedures, for non-Indigenous and Indigenous patients, respectively, 99 and 100% completed surgery, 83 and 68% completed chemotherapy, and 96 and 88% completed radiotherapy. This demonstrates a difference in treatment for Indigenous people, in providers’ treatment recommendations, and in patients’ consent to and completion of treatment.

Qualitative studies have attempted to characterise the reasons for these discrepancies. Prior indicates that interviews, focus groups, and community observation in a remote community in Queensland revealed ‘a prevailing belief among Indigenous women that cancer was a “deadly disease” and that treatment was mostly futile’. Moreover, women ‘dreaded the prospect of cancer
A feeling of disconnect with the physician

Patient-physician relationships can be prone to miscommunication regardless of the patient’s cultural background, and such miscommunication is especially
Fears about distance from home and family when treatment requires relocation to a hospital far from home

Although the concern of Indigenous patients that treatment for cancer requires travel and being distant from home and family is not directly related to views of treatment efficacy, such views remain important reasons for foregoing biomedical treatment, and therefore merit discussion here.

Cancer treatment usually occurs at larger medical centres that may be hundreds of kilometres away from where a patient lives, in an environment that is culturally distant from home. Cancer diagnosis and treatment are stressful times, and the stress is worsened by the lack of a social support network when the patient is in hospital for treatment, and by considerations of logistics and costs. Moreover, travelling to hospital and remaining there for treatment means that patients cannot fulfil community social obligations, prompting some patients to decline any hospital-based treatment so they can remain at home. Many patients taking their own leave from home and family. Additionally, cancer itself can be isolating, as some Indigenous patients and their families believe that cancer is contagious and will shun contact with the affected person: the feeling of emotional distance and isolation from one’s community, which might follow a cancer diagnosis, can be compounded by the physical distance imposed by having to receive treatment at hospitals away from home and family.

Beliefs about disease aetiology that differ from those presented by the Western biomedical model

Among some Indigenous people there is a perception that cancer is a ‘white man’s disease’, brought to the continent by Europeans, and that it therefore requires ‘white man’s medicine’ and is especially toxic to Indigenous people. This perception of cancer as a European malady links it to other diseases brought to the continent by the first European settlers, such as gonorrhoea and syphilis – diseases that have a social stigma and induce feelings of shame in those who contract them. Moreover, cancer itself can be considered to have been brought on by sorcery as a form of payback, and Indigenous patients with cancer can experience shame in the face of a cancer diagnosis.

These perceptions of cancer aetiology affect Indigenous peoples’ perceptions of how cancer should be treated. While living in a Warlpiri community, Saethre investigated perceptions of disease and treatment, focusing on the types of treatment sought for particular illnesses. Although the patient stories provided do not include the experiences of cancer, the data are useful in that they show a tendency to seek Western medications such as paracetamol and antibiotics when they are available. Bush medicine was used but could often be difficult to obtain. Urban Indigenous respondents have also indicated that though they might like to use bush medicine, they cannot owing to an inability to procure it in the urban environment. This suggests that although Western medicines might be considered useful for illnesses perceived to be ‘white man’s diseases’, traditional healers are still sought: this is particularly the case if the reason for the disease is believed to be a form of payback. Some believe that cancer affects only Indigenous people, and one respondent in Saethre’s study indicated that a disease that affects only Indigenous people needed to be cured by a traditional healer: ‘Those doctors, they don’t understand Indigenous sickness. They do X-rays but they still can’t see that bone inside’.

The literature reveals different and sometimes conflicting views about the effects of cancer on Indigenous patients, though a common theme is the view that cancer did not exist prior to the arrival of European settlers, and that its status as a disease brought by Europeans affects how it should be treated by healers, both traditional and biomedical. Regardless, it is clear that colonial history has shaped perceptions of disease aetiology and treatment efficacy, both biomedical and Indigenous, for specific diseases in Indigenous patients.

Failure of biomedical treatments to address holistic health, in contrast to bush medicine treatments that do address holistic health

As discussed in the work of Boulton-Lewis, which describes beliefs of Indigenous health sciences students, health is defined as ‘wellbeing’, affected by lifestyle choices and relationships, and ‘involves balanced holistic dimensions, including physical, mental, spiritual and in some cases social and environmental aspects’. Illness was perceived as ‘imbalance involving holistic dimensions including physical, spiritual, social and environmental’. Some students responded that illness could be induced by interaction with evil or unhappy spirits. In contrast, the Western perception of illness, particularly cancer, is one of ‘biomedical reductionism’. Miscommunication about the process of cancer treatment and unwillingness or inability to adhere to treatment programmes can often be traced back to these two very different views of health, illness, and treatment.

Some Indigenous cancer patients consider biomedical treatment inadequate, especially because (as described
earlier) side-effects make them feel worse than they did prior to treatment. Bush medicine is perceived as addressing holistic health, ‘often signifying a re-connection to land, ancestral and spiritual roots that enhanced the person’s overall wellbeing’.\textsuperscript{6} As one respondent said about bush medicine: ‘There is something in it . . . that is good for your insides, just as a cleanser. Makes all your body organs healthy and strong, it gets rid of all your internal stress’.\textsuperscript{6} The view of bush medicine as a stress reliever fits with a view of cancer as stress-related, an effect of the upheavals and social changes associated with European colonisation.\textsuperscript{7} Bush medicine is believed to relieve stress and to act as a cancer therapy that simultaneously prevents, treats and palliates (for terminal patients).\textsuperscript{7}

In some cases, Indigenous patients seek Western medical care and the skills of a traditional healer, or understand the scientific aetiology of a disease in the context of traditional Indigenous belief systems.\textsuperscript{18} This allows for the combination of viewpoints, treatments and perspectives but often occurs in an uncoordinated way, with inadequate treatment for Indigenous patients and frustration for healthcare providers. A more effective and efficient way to treat Indigenous patients is to recognise at the outset the importance of holistic healing and to incorporate it into the treatment programme. This is discussed in further detail below.

**Success in combining treatment approaches?**

Literature detailing methods for combining biomedical and traditional healers or biomedical and bush medicine treatment is nearly non-existent. There is evidence that Indigenous cancer patients and survivors, as well as the family members of individuals with cancer, are willing to use both treatment approaches.\textsuperscript{6,7}

Saethre provides a first-hand anthropological account of two Indigenous people in a Warlpiri community who sought both biomedical and bush medical treatments for their illnesses.\textsuperscript{16} Saethre makes the distinction between physical illnesses and spiritual illnesses, the former of which can be treated with Western medicines or bush medicines, the latter of which, sometimes caused by sorcery, require the assistance of an ngangkari healer. Both approaches may be pursued concurrently when an illness – such as cancer – is presented to a Western physician while also believed to be caused by sorcery.\textsuperscript{6,10,22}

Saethre discusses the practice of ‘two way’ medicine in which ‘illness management continues to occur in the clinic, but patients . . . have the choice of consulting nurses, Indigenous Health Workers, or Indigenous healers and being prescribed pharmaceuticals or bush medicines’. Through describing the medical histories of two community members, Saethre illustrates how Indigenous people adapt the two systems to suit their needs, such as using biomedical drugs (antibiotics and paracetamol) concurrently with ngangkari consultation, or attributing severe illnesses treated in Western hospitals to spiritual causes. Ultimately, Saethre reports how the ‘two way’ system fails to recognise that this overlap occurs and argues that ‘while local conceptions of health do influence how illness is conceived and treated, they should not be automatically reduced to a single or rigid Indigenous system that is contrasted with biomedicine’.\textsuperscript{18} Since many Indigenous people are willing to seek biomedical treatment, an approach that seeks to separate ‘bush medicine’ and ‘biomedicine’ with regard to patient care is likely to be ineffective for many Indigenous people.\textsuperscript{3,6,17,19,20} Rather, effective treatment needs to integrate both approaches, and to recognise that Indigenous patients can and do combine their perceptions of and treatments for illnesses, including cancer.

**Conclusion**

The available research regarding Indigenous Australians’ beliefs about treatment efficacy for cancer reveals that concerns about biomedical treatment side-effects, long-distance travel to hospitals, cultural distance between patient and provider, differences in belief about disease aetiology, and the inadequacies of biomedical treatment with regard to holistic healing influence Indigenous cancer patients’ willingness to undertake and to complete biomedical therapy for cancer. The literature suggests that Indigenous cancer patients generally view biomedical treatment as effective in treating cancer, a ‘white man’s disease’ for which ‘white man’s medicine’ can be effective.\textsuperscript{3,10} However, it is often difficult to identify the extent to which Indigenous patients are truly ‘informed’ about biomedical cancer treatment, its side-effects, and its efficacy, as evidenced by well-described problems with communication between health providers and Indigenous patients,\textsuperscript{3,14,22} the actions of patients who begin treatment and then cease because of side-effects and toxicity, as well as by the perception among some that treatment is tantamount to a cure.\textsuperscript{12}

Few data have been collected about beliefs in efficacy of bush medicine when used specifically for cancer, though the work of Shahid suggests that belief in efficacy is important.\textsuperscript{7} Only limited conclusions can be drawn about the use of bush medicine for cancer, as little research has been completed in this area. Indigenous patients are also generally not forthcoming in sharing information about bush medicine, possibly fearing that their non-Indigenous providers will discourage them
from taking it or otherwise induce feelings of shame.\textsuperscript{6,7} Moreover, research suggests that patients might be concerned that sharing information about bush medicine will reduce its efficacy.\textsuperscript{6,7} It appears even more difficult to explore the perspectives of traditional healers, given their concerns of being custodians of traditional knowledge that could be exploited by non-Indigenous people.\textsuperscript{6,7}

This review of beliefs about treatment efficacy reveals that more research is needed regarding Indigenous expectations about side-effects and treatment toxicity and the difficulties associated with patient-physician communication. More research in these areas might contribute to Indigenous patients being encouraged to participate in cancer screening where the consequences of finding an abnormality must be a consideration. Reducing the fear and mystery associated with treatment means that if cancer were discovered, patients may be more willing to complete a full treatment programme. A thorough understanding of beliefs and anxieties about treatment would allow healthcare workers to address these concerns early, facilitating the promotion of participation in screening programmes. Australia could also learn from other developed countries such as Canada, New Zealand and the United States in their Indigenous-led approaches that have been adopted in order to improve treatment engagement and outcomes.\textsuperscript{24–27}

Indigenous Australians are diverse and heterogeneous, so treatment needs to be personalised to individual beliefs and concerns. However, health providers showing that they care enough to know about the beliefs of Indigenous people that fall outside of the standard Western model may also help Indigenous patients to feel that they are receiving sincere, culturally sensitive care. The feeling of ‘being treated as a number’ and the absence of patient-physician relationship are recurring themes in research exploring Indigenous peoples’ views of healthcare services.\textsuperscript{9} Identification of the broad range of thinking in relation to healing, and specific beliefs about bush medicine – how it works, when it is used and what makes it appealing – could promote among healthcare providers greater willingness to use a more holistic healing model when treating Indigenous patients. If beliefs about and utilisation of bush medicine for cancer were more fully characterised, treatment plans that combine both biomedical and bush medicine treatments could be developed, potentially leading to better psychosocial outcomes as well as increased treatment adherence and patient satisfaction, and decreased morbidity and mortality. Moreover, as complementary medicine usage is so common in the general community, changes in approach – catalysed by the need to improve Indigenous cancer outcomes – are likely to have broader applicability in the multicultural societies of our modern world.

### Guidelines for healthcare providers

The following are some underlying guiding principles for hospital Cancer Centres and those involved in cancer care for Indigenous patients, provided from the literature discussed, in order to promote more culturally safe and effective care for Indigenous cancer patients.

- Indigenous involvement in the design and process of care for Indigenous cancer patients is critical. Indigenous cancer patients often describe feelings of isolation and cultural alienation, and the presence of another Indigenous person, who has survived treatment, provides comfort and hope and facilitates patient-physician communication. The presence of Indigenous health workers or Indigenous hospital liaison officers, of the same gender as the patient and who have survived cancer themselves, was especially helpful during the process of diagnosis and treatment.\textsuperscript{8,11} An Indigenous health worker can play multiple roles in providing care within the tertiary hospital environment and in forging better linkages with primary and community-based care.\textsuperscript{28–30} While design of cancer treatment facilities is important, it has been argued that managing effective treatment for Indigenous people within the current medical system requires culturally sensitive person-to-person contact, support for Indigenous family structures and a respect for the importance of place and community to Indigenous patients.\textsuperscript{31}

- Healthcare providers should ensure, as much as possible, that cancer patients are truly informed prior to commencing treatment. Informed consent consists of five elements: competence, disclosure, understanding, voluntariness and consent.\textsuperscript{32} Attention to how communication occurs and how information is given and received is critical to understanding. The presence of an Indigenous health professional or patient advocate will help facilitate obtaining informed consent consistent with the definition earlier.

- Thought should be given to practical aspects of cancer treatment, such as the difficulties of separation from family, community and land; transportation to and from the treatment site and associated expenses; and ability to take time from work, whether domestic (childcare) or occupational. Healthcare providers should take these factors into account when developing treatment plans to promote greater treatment adherence and overall patient wellbeing. The Indigenous Women’s Cancer Support Group described by Finn and colleagues shows the potential of Indigenous-led support approaches.\textsuperscript{33}

- Healthcare providers should make an effort to elicit explanatory models for cancer and to learn about the
beliefs by which the Indigenous patient understands the world. If cancer is perceived as payback, and the patient believes that the use of bush medicine or Indigenous healing techniques is necessary, physicians should work to accommodate these beliefs and also to foster open communication to ensure that treatment plans attend to the holistic health needs of their patients.

References


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Mortality and its predominant causes in a large cohort of patients with biopsy-determined inflammatory myositis

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Key words
polymyositis, dermatomyositis, inclusion body myositis, mortality, Bohan and Peter criteria, standardised mortality ratio.

Abstract

Background: There is a paucity of literature on the patterns and predictors of mortality in idiopathic inflammatory myopathies (IIM).

Aims: To determine the patterns and predictors of mortality in a South Australian cohort of patients with biopsy-proven IIM.

Methods: The living/deceased status (and for deceased patients the causes of death) of patients with histologically determined IIM was determined from the Births, Deaths and Marriages Registry. Standardised mortality ratios (SMR) were generated compared with the age/gender matched South Australian population. The effect of presence/absence of the components of the Bohan and Peter criteria on risk ratios (RR) for mortality was determined. The effect of comorbidities and autoantibodies on mortality was investigated.

Results: The SMR for mortality in IIM was 1.75 and was significantly increased in all disease subgroups, being highest in patients with dermatomyositis (2.40). Dominant causes of death were cardiovascular disease (31%), infections (22%) and malignancy (11%). Risk factors for death were age at time of biopsy (hazard ratio 1.05), ischaemic heart disease (RR 2.97, \( P < 0.0001 \)), proximal weakness at diagnosis (RR 1.8, \( P = 0.03 \)), definite diagnosis of IIM per the Bohan and Peter criteria (RR 2.14, \( P < 0.0001 \)), and the absence of autoantibodies (RR 1.9, \( P < 0.001 \)).

Conclusions: Patients with IIM are at 75% increased risk for mortality, and cardiovascular diseases account for the commonest causes of death. This study suggests a thorough cardiovascular evaluation of these patients is indicated, and raises the possibility that targeted interventions such as the use of aspirin or statins may improve outcomes in IIM.

Introduction

The idiopathic inflammatory myopathies (IIM) are a group of systemic autoimmune diseases with dominant manifestations on skeletal muscle. The three best recognised disease subsets are polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM).1 As for many autoimmune diseases, both genetic2 and environmental3 factors are considered important, and recently there has been considerable interest in the role of myositis-specific and myositis-associated autoantibodies (MSA and MAA) in pathogenesis.4
The classification criteria for IIM developed by Bohan and Peter in 1975 include the presence of symmetrical weakness, increased serum creatine kinase (CK), myopathic changes on electromyography (EMG) and a supportive muscle biopsy. According to these criteria, myositis is said to be definite, probable or possible if four, three or two criteria are present respectively, and the diagnosis of DM requires additionally the characteristic cutaneous features. Some of the major concerns with the use of these criteria are first and foremost the fact that they were established prior to the recognition of IBM as a distinct entity and thus do not distinguish IBM from PM. Furthermore, potential for misclassification of disease subtype is recognised to occur. Hence for the present muscle biopsy is considered the definitive diagnostic test and aids not only in diagnosis but also in accurate classification of disease.

Although survival of patients with IIM has improved since the widespread use of corticosteroids and immunosuppressive medications, patients with IIM continue to have increased mortality, with a reported 5-year survival rate of 60%. Accurate assessment of prognosis in IIM is hindered by the relative rarity of these conditions and by the lack of adequate follow-up of a homogeneous population of patients defined by the same classification criteria. The vast majority of studies have included patients based on the Bohan and Peter criteria and such studies have been criticised for the heterogeneity of selected patients.

The rationale for determining mortality and the causes of this chronic disease extends beyond a description of its epidemiology. An understanding of prognostic factors and the ability to delineate which patients are at risk for premature mortality will enable directed approaches and improve patient management.

The aim of the present study was to estimate mortality rates in patients diagnosed with IIM compared to those of the general population, and to examine the association of existing comorbidities and the presence of autoantibodies on the risk of death in a large homogeneous population of patients in South Australia (SA) with biopsy-proven IIM.

Materials and methods

We performed a retrospective cohort study using data from the South Australian Myositis Database (SAMD), a statewide register in which are recorded the details of patients who have a histologically confirmed diagnosis of inflammatory myositis subsequent to 1980. Information recorded includes demographic details, living/deceased status and comorbidities existing at the time of database entry. Also recorded were the presence/absence of MSA and MAA in a large number of patients. The presence or absence of individual components of the Bohan and Peter criteria had been recorded, as well as whether patients fulfilled definite, probable or possible diagnoses according to these criteria. The dates of muscle biopsy and where applicable, the date of death were recorded. The establishment of this database has been facilitated by all diagnostic adult muscle biopsies performed in SA being reported in a central diagnostic Neuropathology Laboratory, in the Institute of Medical and Veterinary Science. Histological diagnoses are made according to the criteria described by Hohlfeld, and biopsies are subjected to peer-review. The database has been approved by the Research Ethics Committees of all teaching hospitals in SA.

Data from the SAMD was combined with that from the Births Deaths and Marriages Registry, South Australia (BDMR), to determine current living status (alive or deceased), and for deceased patients the dates and causes of death. The date on which the BDMR was searched (2 October 2009) was used as the censoring date for the study. Patients were followed up from their date of muscle biopsy (and diagnosis) until their date of death, or 2 October 2009 for living patients.

The causes of death were categorised into myositis, cardiovascular (myocardial infarction, cardiac arrest, congestive cardiac failure, ischaemic heart disease (IHD), arrhythmia, acute coronary occlusion and cardiogenic shock), respiratory (respiratory failure, adult respiratory distress syndrome and apnoea), infections and malignancy. Patients whose listed cause of death did not fit into one of these five categories were assigned the category ‘other’.

Statistical analysis

Standardised mortality ratios (SMR) were determined for each of the subgroups of IIM, the comparator being the standard South Australian population stratified by sex and 5-year age groups. The increased risk of death for existing comorbidities, including IHD, diabetes mellitus and hypertension (HT), was assessed in univariate analysis using risk ratios (RR). RR for death by univariate analysis were also determined for the individual components of the Bohan and Peter criteria, as well as whether patients satisfied definite, probable or possible diagnoses according to these criteria. Kaplan–Meier curves were constructed for each IIM subgroup and survival between groups was compared using the log rank test. Cox regression was used to compare hazard rates between groups after adjustment for age and gender. SMR were determined for each of the myositis subgroups according to the presence or absence of MSA or MAA.
Results

Four patients were excluded from analysis due to missing date of birth. Of the remaining 370 patients on the SAMD, 118 were ascertained as deceased according to the BDMR. An additional six were known to be deceased because the date of death was not given. The overall median follow-up time for the remaining 364 IIM patients was 4.78 years, 5.51 years for DM (390 patient-years), 6.23 years for PM (1577 patient-years) and 5.51 years for IBM (390 patient-years).

The number of deaths per year per 100 persons was 4.6 for IIM, and 3.8, 7.0 and 4.0 for PM, IBM and DM respectively. The SMR for IIM was 1.75 and was significantly increased compared to the general population in all subgroups, being highest in patients with DM (Table 1).

The Kaplan–Meier survival estimates following muscle biopsy are shown in Figure 1. The overall estimated median survival time post-muscle biopsy for IIM was 13.7 years (95% CI 11.7–21.7) for 2598 patient-years of follow-up. Patients with PM, IBM and DM were followed up for a total of 1541, 601 and 325 patient-years, and the estimated 50% median survival times were 19.3 (12.8–25.2), 9.7 (8.4–12.0) and 28.7 (11.1) years for each of the groups. Thus there was considerable variation in median survival time among the subgroups of IIM, and a log rank test for equality of survivor function confirmed that patients with IBM had lower survival compared with PM ($P = 0.0024$) and DM ($P = 0.06$). There was no difference in survival between patients with PM or DM ($P = 0.85$). Although the SMR was highest in patients with DM, the median survival time post-biopsy was also the highest for patients with DM (28.7 years), most likely explained by the younger age of these patients. Age-adjusted Kaplan–Meier survival curves (Fig. 1b) showed a trend that patients with PM have the lowest survival. In age and sex-adjusted Cox regression the hazard ratios (HR) for death were 1.2 and 1.18 for IBM and DM respectively. The HR for age at time of biopsy was 1.05 (1.04–1.07), indicating a 5% increase risk of death with every year increase in age at the time of muscle biopsy. No influence of gender was seen.

Causes of death

Cardiovascular diseases were by far the commonest cause of death. Of the 118 deceased patients 36 died from cardiovascular causes (30.5%), 26 from infections (22.0%), 16 from respiratory causes (13.6%), 13 from malignancy (11%), and for five patients myositis was

<table>
<thead>
<tr>
<th></th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>SMR</th>
<th>95% CI</th>
<th>P-value for SMR versus 1.0</th>
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<td>18.3</td>
<td>2.13</td>
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<td>&lt;0.001</td>
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<td>3.8</td>
<td>2.40</td>
<td>1.10–4.55</td>
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<td>3.4</td>
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<td>0.07–2.10</td>
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</table>

Table 1 Standardised mortality ratio (SMR) and 95% confidence intervals (CI) for patients with idiopathic inflammatory myopathies (IIM) and for the three disease subgroups (dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM))
listed as the primary cause of death (4.2%). A further 22 patients (18.6%) died from other non-classified causes (this included cerebrovascular accidents for seven patients and pulmonary embolism in two). Of the 36 patients who died from cardiovascular causes, 16 had acute myocardial infarction. Among the 26 patients with infection as the primary cause of death, 19 had pneumonia, one had a lung abscess, five had septic shock and one had urinary sepsis.

Effect of coexisting comorbidities on risk of death

We next determined the RR for death conferred by the presence of IHD, HT and diabetes mellitus in patients with IIM (Table 2). Patients with IIM who had IHD had a significantly increased RR for death (2.97, 1.65–5.28) compared with patients who did not have IHD. Although we have shown that IIM is associated with a high prevalence of HT and diabetes mellitus, the present study showed HT did not increase the risk for death in IIM. There was however a trend towards an increased risk of death in patients with diabetes mellitus (RR = 1.63, P = 0.11) which did not reach statistical significance. Together this suggests that IHD and diabetes mellitus are more strongly associated with the risk of death than HT in IIM.

Effect of components of the Bohan and Peter diagnostic criteria on risk of death

Patients with inflammatory myositis may present with a combination of elevation of serum levels of CK, proximal weakness, myopathic triad on EMG, and it is noteworthy that all features are not necessarily present. The presence of proximal weakness at the time of presentation conferred a significantly increased risk for death, and elevation of CK levels was associated with a (non-significant) reduction in mortality (Table 3). Patients who satisfied ‘definite’ Bohan and Peter criteria had a significantly increased risk for death compared with patients with either ‘probable’ or ‘possible’ diagnoses (RR 2.14).

Effect of autoantibodies on SMR

We next investigated the effect of autoantibodies (MSA or MAA) on SMR in IIM. Patients with IIM who had autoantibodies had a substantially reduced SMR compared to those without autoantibodies (0.618, 0.13–1.81), and the effect was strongest in patients with PM (Table 4). Autoantibodies in patients with IBM did not have a protective effect. Among patients without autoantibodies, the SMR was increased in all three subgroups of IIM, and the subgroup with DM had the highest SMR.

Effect of autoantibodies on presence of existing comorbidities

We sought to determine whether the absence of autoantibodies is associated with an increased risk for IHD or diabetes or whether it is an independent risk factor for death in IIM. Among antibody-positive patients, IHD was present in 6/34 (17.6%) compared with 19/83 (22.9%) without antibodies; RR = 0.79 (0.37–1.69, P = 0.53). Diabetes was present in 8/34 (23.5%) of patients with autoantibodies and 23/87 (26.4%) patients without antibodies; RR = 0.89 (0.45–1.76, P = 0.74). HT was present in 20/37 (54.1%) with antibodies and 52/88 (59.1%) without antibodies; RR = 0.87 (0.50–1.49, P = 0.60). Although a significant difference in risk for IHD, diabetes and HT conferred by the presence of autoantibodies is difficult to detect because of our small numbers, it appears that the absence of autoantibodies does not significantly increase the risk for these comorbidities and therefore may be an independent risk factor for death.

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### Table 2. Risk ratio for death for patients with existing ischaemic heart disease (IHD), hypertension or diabetes mellitus at the time of database registration compared to patients without each of these comorbidities

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<th>Deceased/total without comorbidity</th>
<th>Risk ratio for death</th>
<th>95% CI</th>
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<td>17/132</td>
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<td>28/127</td>
<td>13/77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
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<td>Yes</td>
<td>40</td>
<td>14</td>
<td>14/54</td>
<td>21/132</td>
<td>1.63</td>
<td>0.90–2.96</td>
<td>0.11</td>
</tr>
<tr>
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<td>111</td>
<td>21</td>
<td>14/54</td>
<td>21/132</td>
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Discussion

In this study we have examined the mortality and causes of death associated with a large population of patients with biopsy-proven IIM. We found our population has a 75% increased mortality compared with the general population. The predominant risk factors for death in IIM we identified were age at time of biopsy (HR 1.05), presence of IHD (approximate threefold increased risk), proximal weakness at the time of diagnosis, definite diagnosis of IIM per the Bohan and Peter criteria, and the absence of autoantibodies.

The 75% increased mortality was seen in all disease subgroups and was the highest in patients with DM (Table 1). The SMR of 1.75 is considerably lower than that (2.92) observed in a Finnish study of PM/DM patients diagnosed between 1969 and 1985.15 Importantly, this discrepancy may reflect the fact that the present study included patients with IBM, whilst the other did not, but may also reflect improved management approaches over time. The excess mortality seen in IIM is comparable to that reported in rheumatoid arthritis (RA), in which the SMR is between 1.5 and 1.6,16,17 and ankylosing spondylitis, in which the SMR has ranged

| Risk ratio for death for patients with versus those without increased creatine kinase (CK) levels, proximal weakness, myopathic triad on electromyography (EMG), and for patients who satisfy definite, probable and possible Bohan and Peter (BP) criteria |
|------------------------------|---------|---------|-----------------|-----------------|--------|
| Alive | Deceased | Deceased/total with variable | Deceased/total without variable | Risk ratio for death | 95% CI  

<table>
<thead>
<tr>
<th><strong>Increased CK</strong></th>
<th>Alive</th>
<th>Deceased</th>
<th>Deceased/total with variable</th>
<th>Deceased/total without variable</th>
<th>Risk ratio for death</th>
<th>95% CI</th>
<th>P-value for ratio versus 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>143</td>
<td>64</td>
<td>64/207</td>
<td>20/51</td>
<td>0.79</td>
<td>0.53–1.17</td>
<td>0.26</td>
</tr>
<tr>
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<td>31</td>
<td>20</td>
<td>78/212</td>
<td>10/48</td>
<td>1.77</td>
<td>0.99–3.15</td>
<td>0.03</td>
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</table>

**Proximal weakness**

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<th>Alive</th>
<th>Deceased</th>
<th>Deceased/total with variable</th>
<th>Deceased/total without variable</th>
<th>Risk ratio for death</th>
<th>95% CI</th>
<th>P-value for ratio versus 1.0</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>134</td>
<td>78</td>
<td>47/89</td>
<td>1.24</td>
<td>0.80–1.94</td>
<td>0.31</td>
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<tr>
<td>No</td>
<td>38</td>
<td>10</td>
<td>14/33</td>
<td>1.77</td>
<td>0.99–3.15</td>
<td>0.03</td>
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</table>

**EMG triad**

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<th>Deceased/total with variable</th>
<th>Deceased/total without variable</th>
<th>Risk ratio for death</th>
<th>95% CI</th>
<th>P-value for ratio versus 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>42</td>
<td>47</td>
<td>43/163</td>
<td>2.14</td>
<td>1.53–2.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
<td>14</td>
<td>14/33</td>
<td>1.24</td>
<td>0.80–1.94</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**BP: definite**

<table>
<thead>
<tr>
<th>Alive</th>
<th>Deceased</th>
<th>Deceased/total with variable</th>
<th>Deceased/total without variable</th>
<th>Risk ratio for death</th>
<th>95% CI</th>
<th>P-value for ratio versus 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>37</td>
<td>43</td>
<td>43/163</td>
<td>2.14</td>
<td>1.53–2.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>122</td>
<td>41</td>
<td>41/163</td>
<td>2.14</td>
<td>1.53–2.98</td>
<td>&lt;0.0001</td>
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**BP: probable**

<table>
<thead>
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<th>Deceased</th>
<th>Deceased/total with variable</th>
<th>Deceased/total without variable</th>
<th>Risk ratio for death</th>
<th>95% CI</th>
<th>P-value for ratio versus 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>70</td>
<td>20</td>
<td>20/90</td>
<td>0.53</td>
<td>0.35–0.81</td>
<td>0.0019</td>
</tr>
<tr>
<td>No</td>
<td>89</td>
<td>64</td>
<td>64/153</td>
<td>0.53</td>
<td>0.35–0.81</td>
<td>0.0019</td>
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</tbody>
</table>

**BP: possible**

<table>
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<th>Deceased</th>
<th>Deceased/total with variable</th>
<th>Deceased/total without variable</th>
<th>Risk ratio for death</th>
<th>95% CI</th>
<th>P-value for ratio versus 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>40</td>
<td>13</td>
<td>13/53</td>
<td>0.66</td>
<td>0.40–1.09</td>
<td>0.08</td>
</tr>
<tr>
<td>No</td>
<td>119</td>
<td>71</td>
<td>71/190</td>
<td>0.66</td>
<td>0.40–1.09</td>
<td>0.08</td>
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</tbody>
</table>

Table 4: The standardised mortality ratios (SMR) and associated 95% confidence intervals (CI) for patients with polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM) with myositis-specific or myositis-associated antibodies (autoantibody-positive) compared with those idiopathic inflammatory myopathy patients without such autoantibodies (autoantibody-negative).

<table>
<thead>
<tr>
<th>Autoantibody-positive</th>
<th>Observed deceased</th>
<th>Expected deceased</th>
<th>SMR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>11</td>
<td>2.2</td>
<td>0.46</td>
<td>0.01–2.55</td>
<td></td>
</tr>
<tr>
<td>IBM</td>
<td>2</td>
<td>1.9</td>
<td>1.08</td>
<td>0.13–3.89</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>0</td>
<td>0.8</td>
<td>0.00</td>
<td>0.00–4.65</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0.0</td>
<td>0.00</td>
<td>0.00–274.22</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>4.9</td>
<td>0.62</td>
<td>0.13–1.81</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Autoantibody-negative</th>
<th>Observed deceased</th>
<th>Expected deceased</th>
<th>SMR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>41</td>
<td>24.8</td>
<td>1.65</td>
<td>1.19–2.24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IBM</td>
<td>37</td>
<td>16.5</td>
<td>2.25</td>
<td>1.58–3.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>9</td>
<td>3.0</td>
<td>3.04</td>
<td>1.39–5.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>3.4</td>
<td>0.58</td>
<td>0.07–2.10</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>47.7</td>
<td>1.87</td>
<td>1.50–2.30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
from 1.33–1.8,18–20 but overall somewhat lower than the SMR of 2.4 reported in an international systemic lupus erythematosus (SLE) cohort.21 In systemic sclerosis the SMR has been documented to be 1.5 (diffuse subset 2.92, overlap disease 2.4 and limited subset 1.3),22 with diffuse scleroderma having the highest SMR of the connective tissue disorders. The reported death rate in IIM has ranged from 22% in a French cohort of PM/DM followed for a median 4 years,23 to 26% in a Spanish population or PM/DM.24 Our higher death rate of 33.5% after 57 months of median follow-up is more comparable to the 33% death rate reported in a New Zealand population-based study of patients with 76 months median follow-up time, and this is likely to reflect the inclusion of patients with IBM in both these study populations.25 This discrepancy again reiterates the problems in comparing non-uniform patient populations.

Previous studies have shown that the strongest predictive factor for mortality in IIM is age at disease onset.15,21,24,26–28 Our observed HR for death (1.05) is similar to the 1.04 HR observed in a cross-sectional study of 107 patients with DM/PM based on the Bohan and Peter (BP) criteria.24

In terms of the muscular disease, patients who satisfied definite Bohan and Peter criteria had a higher risk of death compared with those with probable or possible diagnoses (Table 3). We further report that the presence of proximal weakness was also predictive for death. Data are conflicting as to whether CK levels have prognostic value in IIM. Lack of CK elevation in DM has been correlated with a poor prognosis29,30 and higher CK levels have been associated with greater increments in muscle power in PM/DM.31 However, CK levels were shown not to influence survival in a large Finnish study of 176 patients with DM and PM,15 and also in the French group of 77 DM/PM patients.23 In the present study, we observed a trend that patients with elevation of CK had a reduced mortality risk (RR for death = 0.80) (Table 3) which did not reach statistical significance.

Almost one-third of our patients with IIM died from cardiovascular diseases, and indeed cardiovascular problems have been ranked as the highest cause of mortality in IIM by several studies, the proportions of deaths attributed to cardiovascular causes ranging from 14.7% to 55%,15,27,32,33 This variation is largely accounted for by the selection criteria used. Notably the studies with the lower incidence of IHD had selected only patients with PM and DM,15 whilst in those including IBM, the incidence of IHD was in the order of 50–55%,27,32 The link between accelerated atherosclerosis and the systemic autoimmune rheumatic diseases RA and SLE is well established;54 however, the vascular risk profile of IIM patients seems underestimated. We have recently reported a previously unrecognised high prevalence of HT (62%) and diabetes mellitus (29%) in our cohort of patients with IIM (14), although in the present study, neither were found to be predictors of death. We had also observed that IHD was a commonly associated comorbidity in patients with IIM. In a Spanish cohort of 107 patients with DM/PM, left ventricular dysfunction conferred a strong risk for death, with a HR = 5.2 (95% CI 2.4–11.1, P < 0.0001).24

We observed a significantly higher death rate from infection (22%) compared with the 2–2.5% rate of infection reported in two studies of PM/DM diagnosed by the BP criteria.15,24 However, notably infectious complications have been reported to occur in up to 30% of patients27,33,36 and opportunistic infections in 11% of patients with PM and DM.35 Part of the problem in comparing these studies is not only the selection criteria, lack of inclusion of IBM with the BP criteria, but also the possible differences in classification of cause of death. For instance, pneumonia was classified as an infection in our study, but was classified as a respiratory cause of death in the French cohort of PM/DM,23 and as an extension of the musculoskeletal disease itself in the study by Airo et al.15 Indeed on closer analysis of their data, pneumonia was the main cause of death in 23/107 (21%) of the patients with PM and 5/42 (12%) of DM in the study of Airo et al. which is very similar to the proportions observed herein, and aspiration pneumonia resulting in death occurred in 55% of patients with PM/DM in the French study.23 Marie et al. also found that aspiration pneumonia occurred most frequently during the first 2 months after diagnosis of the IIM, and was frequently related to oesophageal motor involvement and compromised ventilatory capacity. Together these studies and ours suggest that infectious complications particularly pneumonia confer a significant risk for death in patients with IIM, and hence should be diagnosed and treated promptly.

Previous studies which have included patients with cancer-associated myositis have consistently reported malignancy as the commonest cause of death,10,21,27,28,37 accounting for up to 47% of deaths.21 The study by Airo et al. in which patients with cancer-associated myositis were not included showed a similar death rate from cancer (16%) as that observed in the present study (11%).

Autoantibody testing in IIM has clinical value as individual autoantibody specificities are associated with distinct clinical features.18,19 Autoantibody testing also helps predict the risk of malignancy as patients without MSA or MAA are at increased risk of cancer.40 We have shown for the first time that autoantibodies are protective for mortality in IIM, and of note this was an independent protective factor as autoantibodies were not observed with
differential frequency in patients with IHD, diabetes or HT.

Many studies on mortality in myositis have selected patients from a single centre with inherent potential for selection bias towards differential severity of disease, and preference towards specific management strategies. Our study, however, included all patients diagnosed within SA, managed at both public and private hospitals and also included non-hospitalised patients. We acknowledge that in this study, the BDMR will not ascertain the living/deceased status of patients who were diagnosed by muscle biopsy with IIM in SA and subsequently moved interstate; however, it is likely this number is modest. Further there are some concerns with using the cause of death as that listed on the death certificate, which is more likely to list acute events as the cause of death rather than a sustained chronic rheumatic illness. Such limitations acknowledged, we have in this study confirmed the excess mortality associated with IIM and show for the first time that the presence of autoantibodies is protective from mortality. Our demonstration that IHD confers a significant increased RR for death in IIM enables the identification of patients at greatest risk, and raises the possibilities that targeted interventions such as the use of statins and aspirin may improve survival in patients with IIM.

Acknowledgement

The authors are grateful to Dr Sally Cox (Flinders Medical Centre, Adelaide) for her assistance in establishing the SAMD.

References

23 Marie J, Nachulla E, Hatron PY, Hellot MF, Levesque H, Devulder B et al. Polymyositis and dermatomyositis: short term and longterm outcome, and
Recreational drug use in type 1 diabetes: an invisible accomplice to poor glycaemic control?

P. Lee, J. R. Greenfield, K. Gilbert and L. V. Campbell

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Key words
type 1 diabetes, substance abuse, cocaine, ketoacidosis.

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Email: p.lee@garvan.org.au

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Abstract

Recreational drug use during ‘rave’ parties is increasingly popular, but the impact of recreational drug use in type 1 diabetes (TID) is not known. We determined the self-reported pattern and effects of recreational/illicit drug use in Australians with TID people by inviting people with TID to participate in an anonymous online/paper survey of drug use, through national radio broadcast and online/hospital advertising. Of the people with TID who responded to our survey, more than three quarters reported having used recreational/illicit drug, but few people had informed health professionals about drug use. Drug use was associated with worse glycaemic control and higher risk of diabetic ketoacidosis. Medical awareness of common, currently underreported, drug use in young people with TID is essential. It offers the possibility of helping such patients improve related suboptimal metabolic control.
Recreational use of illicit drug is an important health issue globally.1–3 Approximately 10% of the general population has problems related to drug use, and young adulthood is the peak time for developing such a problem.4,5 In the USA, 18- to 25-year-olds are three times more likely to have an alcohol or substance use disorder than younger or older people (21% vs 9% and 7% respectively).6 In the 2004 National Drug Strategy Household Survey in Australia, the prevalence of recreational drug use exceeded 30% among young adults.7

Recreational drug use causes significant physical and psychological complications, especially in people with comorbidities. Management of type 1 diabetes (T1D) in young adults who use drugs is difficult partly because of paucity of data on the pattern and impact of drug use among young people with T1D. We and others have described life-threatening diabetic ketoacidosis (DKA) in the setting of recreational drug use in T1D.8–11 It is possible that recreational drug use contributes relatively commonly to poor metabolic control in young people without being identified. This study examines recreational drug use among young people with T1D in Australia from an anonymous survey. The aim was to investigate the self-reported pattern and impact of recreational drug use in Australians with T1D.

Two collection modes were used in the survey: web-based and paper questionnaires. People with T1D in Australia were recruited through radio broadcast, hospital advertising, and a consumer network newsletter and online community. Respondents were asked 10 questions encompassing demographic details and pattern of drug use. A general invitation was extended to all people with T1D, regardless of whether they used or did not use drugs. The Human Research Ethics Committee, St Vincent's Hospital approved the studies.

The data were analysed with the use of SPSS Statistics version 17 (SPSS, Chicago, IL, USA). Results are expressed as mean ± SD. Differences in continuous variables were analysed by the unpaired t-test. Differences between categorical variables were assessed using the chi-square test. Odds ratio and confidence intervals were determined by multinominal logistic regression. \( P < 0.05 \) was considered statistically significant.

As the survey was broadcasted nationally, total response rate of the survey could not be determined. Of a total number of 504 respondents in the survey (331 female, age 31 ± 1 years), 388 (77%) had used drugs at least once and 237 (47%) had used drugs within the last year. Regarding tobacco and alcohol consumption, 28% were smokers and 48% consumed more than 20g of alcohol per day on a regular basis. Table 1 summarises the pattern of drug use among the respondents. Among those who used drugs, 24% reported daily use and 68% were poly-drug users (≥3 drugs). The six most common drugs were cannabis (88%), ‘Ecstasy’ (63%), ‘Speed’ (51%), cocaine (40%), ‘Ice’ (19%) and ketamine (15%).

In contrast to tobacco smoking, which was most prevalent among 25- to 29-year-olds (37%), recreational drug use was the most common among persons less than 20 years old (80%) and least common between 25 and 29 years (72%). The most common mode of drug use was smoking (37%), followed by ingestion (32%) and snorting (27%). Five per cent injected intravenously. ‘Speed’ and ‘Ice’ constituted two thirds of intravenous drug use.

Drug users were similar in age and gender to non-users (Table 2). Drug users were significantly more likely to smoke tobacco, but less likely to consume excess alcohol regularly. Fewer drug users (73%) remembered their last

| Table 1 Pattern of drug use amongst respondents in the survey. Numbers represent percentage of total number of respondents (n = 504) |
|---|---|---|---|---|---|
| Drugs | Drugs ever used† | Drugs recently used‡ | Daily use | Weekend use | ‘Party’ use |
| Methylenedioxymethamphetamine (Ecstasy) | 64 | 19 | 1 | 8 | 48 |
| Methamphetamine (Speed) | 52 | 11 | 2 | 7 | 35 |
| Dextromethamphetamine (Ice) | 16 | 1 | 1 | 4 | 8 |
| Ketamine | 10 | 1 | 0 | 1 | 8 |
| Methyleneoxymethamphetamine ('Love pill') | 1 | 0 | 0 | 1 | 1 |
| Heroin | 7 | 0 | 0 | 0 | 4 |
| Methcathinone ('Cat') | 1 | 0 | 0 | 0 | 0 |
| Methyleneoxymethamphetamine ('Eve') | 1 | 0 | 0 | 0 | 0 |
| Phencyclidine | 1 | 0 | 0 | 0 | 1 |
| Cannabis | 88 | 14 | 19 | 22 | 1 |
| Cocaine | 40 | 7 | 1 | 5 | 1 |
| Any illicit drug | 77 | 47 | 24 | 48 | 100 |

†Drugs ever used in the past. ‡Drug use within the last 12 months.
HbA1c compared with non-users (96%, \( P = 0.02 \)). HbA1c was higher among drug users than non-users (8.4 ± 2.1 vs 7.6 ± 1.6%, \( P = 0.03 \)). Two thirds of drug users had informed their partners and/or friends about their drug use, while less than a quarter had informed family. Seven per cent had informed health professionals, and 23% of drug users had told no one about drug use.

Factors associated with poor glycaemic control (HbA1c ≥ 9%) were evaluated by examining the association of glycaemic control with age, sex, duration of diabetes, smoking history and drug use. In univariate analyses (Table 3), poor glycaemic control was associated with younger age, tobacco smoking and drug use. All three factors remained significant in multivariate analyses, with drug use the strongest variable. The likelihood of having poor glycaemic control was tripled among drug users compared with non-users (Table 3). Fourteen ex-drug users reported changes in their HbA1c. Drug cessation was associated with a reported 29% reduction in HbA1c.

Among the 200 respondents who answered this question, close to one third reported not checking blood glucose levels when using drugs. An increase in blood glucose during drug use was reported by 17% of patients, while a decrease in 13%.

More than two thirds of respondents reported not altering their insulin dose during drug use, while almost 20% omitted insulin before drug use. A minority either increased (5%) or decreased the dose (4%). Twenty-two respondents (all Ecstasy users) claimed the need to increase their insulin dose by 100–150% (all taking insulin glargine) to reduce hyperglycaemia.

Little is known about the pattern of drug use among young people with T1D by their treating doctors. Through an anonymous national survey, the current study reports that drug use is common among respondents. Most importantly, a significant association exists between drug use, and both underreporting and poor glycaemic control.

### Table 2 Comparison of characteristics between drug users and non-users

<table>
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<tr>
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<th>Drug users</th>
<th>Non-drug users</th>
<th>( P )-value</th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>388</td>
<td>116</td>
<td>—</td>
</tr>
<tr>
<td>Mean age</td>
<td>30 (2)</td>
<td>32 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>% of female</td>
<td>79%</td>
<td>63%</td>
<td>NS</td>
</tr>
<tr>
<td>% of respondents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never been hospitalised with DKA</td>
<td>78%</td>
<td>84%</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospitalised once</td>
<td>15%</td>
<td>12%</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalised more than once</td>
<td>7%</td>
<td>4%</td>
<td>NS</td>
</tr>
<tr>
<td>Knew their last HbA1c</td>
<td>76%</td>
<td>96%</td>
<td>0.02</td>
</tr>
<tr>
<td>Last HbA1c</td>
<td>8.4 (2.1)</td>
<td>7.6 (1.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>% tobacco smokers</td>
<td>34%</td>
<td>9%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>% regular drinkers†</td>
<td>47%</td>
<td>53%</td>
<td>NS</td>
</tr>
</tbody>
</table>

†Consumes more than 20 g of alcohol per day. NS, not significant; DKA, diabetic ketoacidosis.

### Table 3 Factors associated with poor glycaemic control (HbA1c ≥ 9%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>( P )-value</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>( P )-value</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female versus male</td>
<td>0.7 (0.4–1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;31 versus ≥31 years</td>
<td>2.3 (1.2–4.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 versus ≥10 years</td>
<td>1.6 (0.9–2.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker versus non-smoker</td>
<td>2.1 (1.1–3.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Drug use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Users versus non-users</td>
<td>4.1 (1.6–10)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CI, confidence interval; NS, not significant.
All respondents reported drug use during parties, many on weekends (Table 1). The risk of hyperglycaemia, ketosis and acidosis in T1D is magnified in the setting of ‘rave’ parties. Insulin non-compliance is common during a ‘rave’, and more than 20% of respondents reported omission or reduction of insulin before drug use, which may explain the high rate of DKA, especially with concurrent stimulant use. Stimulants increase release of catecholamines and cortisol, hormones that enhance gluconeogenesis, glycogenolysis and lipolysis, thus fuelling hyperglycaemia and the formation of ketones.

Based on self-reported HbA1c, drug users in the current study had significantly worse glycaemic control than non-users, with reported improvement following cessation. In this group, drug use was the strongest factor associated with poor glycaemic control, independent of age, gender, duration of diabetes and tobacco smoking. Although the evaluation was based on self-reported HbA1c, the findings must be interpreted with caution. However, significantly fewer drug users knew of their last HbA1c levels. Drug use may coexist with other high-risk behaviours, and drug-taking may indicate poor social support, chaotic lifestyle and maladjustment to a chronic illness. This is consistent with the reported high mortality from acute diabetes-related events associated with drug abuse.

It is uncertain how diabetes should be managed during drug use, particularly whether insulin dosage requires adjustment. Variable effects on glycaemia were reported in the current study. Although stimulants classically lead to catecholamine excess, resulting in hyperglycaemia by inhibition of insulin secretion, hyperglucagonaemia, and enhancement of gluconeogenesis and glycogenolysis, increased insulin dosage needs to be balanced against potential hypoglycaemia from missed meals, increased activity and other drug or alcohol effects. Adjustment of insulin dosage should be individualised based on type, dose and pattern of drug use, and previous glucose monitoring. Information from continuous glucose monitoring devices during ‘rave’ parties may further the understanding of glycaemic excursions with drug use in real-life circumstances. In the meantime, such causes of poor glycaemic control remain covert.

Our survey is the largest published report of recreational drug use in T1D. Only four other studies have examined the pattern of drug use in young people with T1D, predominantly using structured questionnaires with target populations of 80–193 subjects from diabetes camps or tertiary clinics. Our study extended invitation nationally to all young people with T1D, capturing over 500 respondents, in contrast to previous cross-sectional studies involving subjects from a limited clinical setting.

The current study does not include all young people with T1D, and the response rate is unknown. Therefore, the true prevalence of drug use in T1D cannot be ascertained. Regardless of the true prevalence, given its adverse effects on glycaemia, drug use is associated with clinically significant deterioration in diabetes control. Given only 7% of positive respondents to the survey had informed their health professionals about drug use, a similar screening questionnaire may be incorporated into routine care in diabetes clinics. A similar screening questionnaire may be incorporated into routine care in diabetes clinics. It may reduce the anxiety arising from direct disclosure during a consultation and encourage self-reporting, similar to that observed in the current study.

Our survey indicated that drug use is currently under-reported and poorly managed even in modern multidisciplinary diabetes centres. It appears a significant, but currently hidden, contributor to poor glycaemic control and adverse health outcomes in young adults with T1D. With heightened awareness and increased acceptance that poly-drug use occurs, medical personnel should be able to elicit a drug history from patients in a non-judgmental way. Adjustments in therapy could reduce the accompanying metabolic risks.

Acknowledgements

The authors thank Dr Charles Verge (Sydney Children’s Hospital), Professor Peter Colman (Royal Melbourne Hospital), Ms Wendy Bryant (St Vincent’s Hospital, Sydney), Ms Penny Moris (St Vincent’s Hospital, Sydney), Ms Melissa Armstrong (St Vincent’s Hospital, Sydney), and all physicians, diabetes educators and nurses in helping with the recruitment of participants. We especially thank the Type 1 Diabetes Network and ABC Radio in advertising our survey. Last but not least, we thank all the participants for completing the survey.

References

New HIV diagnosis after occupational exposure screening: the importance of reporting needlestick injuries

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Key words
HIV, needlestick, occupational exposure.

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Human immunodeficiency virus (HIV) infection is most often diagnosed as part of the investigation of a suspicious clinical illness or as part of a regular testing programme in a patient either with known risk factors such as men-who-have-sex-with-men, injecting drug users or in settings where testing is routine, such as antenatal screening, for immigration or insurance purposes.

We describe three cases of new diagnosis of HIV infection in a 5-year period between 2003 and 2008 as a direct result of testing following occupational exposures (NSIs) in a low-prevalence setting. In each case the finding was unexpected. Our series provides a reminder of the importance of prompt reporting of NSIs by healthcare workers, access to rapid HIV testing and post-exposure prophylaxis with antiretrovirals to prevent transmission.
post-exposure prophylaxis (PEP) with antiretrovirals to prevent transmission.

Case 1: A 40-year-old man presented with a short history of neurological symptoms. A computed tomography brain revealed a left frontoparietal mass lesion, and he underwent a burr hole and biopsy of the lesion.

During the procedure, a HCW sustained a NSI during which there was a penetrating injury through glove and skin by a piece of blood-exposed equipment. The occupational exposure protocol was initiated, and an urgent HIV antibody test by enzyme-linked immunosorbent assay on the source patient was positive. HIV infection was later confirmed by western blot, cluster of differentiation antigen 4 (CD4) count was 63 cells/μL (normal range 389–1569) and HIV viral load (VL) was >100,000 copies/mL (demonstrating potential high infectivity). The brain biopsy demonstrated diffuse large cell lymphoma, and the patient commenced radiotherapy and antiretroviral therapy. The HCW commenced antiretrovirals 12 h after the NSI and had negative follow-up HIV antibody tests.

Case 2: A 41-year-old man was admitted to intensive care with an undiagnosed illness characterised by fevers, hypothermia, coagulopathy and acute renal failure. During the admission a NSI with a hollow-bone needle through a glove occurred during a procedure. A HIV antibody test on the source was positive, CD4 count was 4 cells/μL and HIV VL was 212,000 copies/mL. Commencement of PEP was delayed for 84 h for multiple reasons, including delays in the HCW reporting the injury and in the laboratory reporting the positive test. The HCW’s treatment course was complicated by multiple drug reactions, but subsequent HIV antibody tests were negative.

Case 3: A staff member was cleaning a recently occupied room at a rehabilitation facility. A NSI with a used insulin syringe was sustained, and the last occupant of the room was located and tested for blood-borne viruses. The male patient, who had been admitted to the facility with a diagnosis of dementia, had a positive HIV antibody test. His CD4 count was 149 cells/μL and HIV VL was >100,000 copies/mL. The staff member was commenced on PEP 4 h after the NSI. The patient subsequently died, and the staff member’s follow-up HIV antibody tests were negative.

We report three cases of HIV infection diagnosed on screening for blood-borne viruses following occupational exposures from patients with HIV infection which had not been previously recognised.

Unfortunately, occupational exposures continue to be a common occurrence in HCWs. In Adelaide hospital, rates of NSIs among medical staff were 10.4 NSIs/100 full-time equivalents (FTEs), higher than nursing or paramedical staff. An English survey of senior surgeons reported a very high rate of 29.1 NSIs/2-year period, a higher rate than junior surgeons. Overall, recent rates of NSI in HCW have been reported at 3.01/100 FTEs with rates dropping following the introduction of safety devices. Recent Victorian surveillance data also demonstrate a decrease in percutaneous occupational exposures from 0.52/1000 occupied bed days (OBDs) in 2005 to 0.38 per 1000 OBDs in 2008.

NSI are often unreported, especially in the surgical setting. Rates of non-reporting of 14–24% were found in a Brisbane study. Over 50% of NSIs went unreported in surveys from the UK and in US surgical residents. Factors contributing to lack of reporting include lack of time, a perceived low risk of transmission at the time of the injury and the perceived lack of involvement of a high-risk patient. Surgeons’ perceptions of the risks of transmission from a positive source patient may also influence their willingness to report NSIs. Surgeons incorrectly underestimated the seroconversion rates after NSI for HIV and hepatitis B and C. In Australia there is a low HIV infection prevalence of 92 per 100,000 in 2009 compared with the USA where prevalence is 275/100,000. However, as evidenced by our cases, despite lower prevalence, there is still a risk that patients may have a previously undiagnosed HIV infection.

The risk of transmission of HIV after an occupational exposure varies according to the type of exposure. There is increased risk of transmission with the injury occurring with a hollow-bone needle, visible blood on the needle, a deep injury, the absence of gloves and a high VL of the source patient. The average risk is estimated to be 0.3% without PEP. The risk of transmission of hepatitis B virus infection without intervention is 22–31% for a hepatitis B surface antigen positive and hepatitis B e antigen positive source patient. Hepatitis C transmission risk is estimated to be 1.8% (range 0–7%) depending on VL.

Under-reporting risks non-diagnosis and delaying or not commencing effective PEP regimens. In a HCW who is non-immune, hepatitis B immunoglobulin and vaccination reduce hepatitis B transmission by 75%,12–15 PEP for HIV has been shown to be effective in animal studies. Human studies are very limited, but there is evidence that zidovudine PEP is associated with a reduced HIV seroconversion rate. Although there is no effective antiviral prophylaxis to prevent hepatitis C infection, HCWs can be offered with follow-up serology and/or alanine aminotransferase measurements to detect seroconversion or acute viral hepatitis.

At least one of these three cases of new HIV infection, diagnosed at the time of testing post NSI, would have
been unlikely to ever have been tested otherwise. The positive tests had important implications for the patient and their contacts. They reinforce the idea that even in a setting where HIV is unexpected, HCWs cannot risk becoming complacent about NSIs and their reporting and that standard precautions should be followed. Action should be taken by the HCW in consulting with the staff health service or equivalent prior to the availability of test results for blood-borne viruses from the needlestick donors. All HCWs should be encouraged to access counselling, timely testing and effective PEP according to local guidelines.18,19

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Lymphoma, thymoma and the wooden man: stiff-person syndrome post-thymoma excision and non-Hodgkin lymphoma remission

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Key words
stiff-person syndrome, GAD antibody, lymphoma, thymoma, immunopathology.

Abstract
Stiff-person syndrome (SPS) is an uncommon yet under-diagnosed, neuromuscular disorder characterised by progressive muscle rigidity with superimposed painful muscle spasms triggered by tactile, auditory or emotional stimulation. We describe the world's first case report of typical SPS in a patient with previously excised thymoma and treated non-Hodgkin lymphoma. This is of relevance because of the increasingly elucidated autoimmune aetiology of SPS.

A 66-year-old man presented with a 2-week history of progressive spastic paraparesis and increasing falls. His mobility was severely impaired by inability to bend his knees and hips due to stiffness. He consulted a neurologist 4 months prior for one episode of diplopia and vertigo, and frequent noise-triggered, intermittent right facial twitching and jaw trismus causing tongue lacerations, for which clonazepam 0.25 mg bd was prescribed. He had been systemically well. There was no sensory, bladder or bowel disturbance. He denied back pain, recent weight loss, night sweats or recent contaminated wounds.

His past medical history was significant for a lymphocytic thymoma excision with radiotherapy 5 years ago. He has also been in remission from a stage II non-Hodgkin lymphoma affecting his left groin and lower limb post-chemotherapy and radiotherapy 19 years ago. His other co-morbidities include benign thyroid follicular adenoma, obstructive sleep apnoea, impaired glucose tolerance, hypertension, prostatic hyperplasia and zoster ophthalmicus.

On examination he had bilateral 4/5 hip flexion weakness and profound muscle stiffness restricting movement of all lower limb joints. He had global, brisk lower limb reflexes and bilateral extensor Babinski’s without objective sensory deficits. Cranial nerve and upper limb examinations were normal. His spirometry was normal.

Urgent non-contrast magnetic resonance images of the brain and whole spine were unremarkable. Repeat magnetic resonance imaging of the whole spine with gadolinium 3 days later was also normal. His contrast CT chest/abdomen and pelvis was unremarkable, with no residual thymic tissue, thyroid megaly or lymphadenopathy demonstrated.

His creatinine kinase was mildly elevated initially at 257 U/L (reference range <200 U/L), falling to 135 U/L the next day without intervention. Otherwise extensive blood testing, including inflammatory and tumour markers, autoimmune screen, thyroid function tests, immunofixation, coeliac and syphilis serologies, were unremarkable. His acetylcholine receptor and antimuscle-specific kinase antibodies, HTLV I and II, thyroid globulin and thyroid peroxidase antibodies were also negative.

During his hospital admission, he developed intermittent lower limb myoclonus triggered by loud noise. He also sustained minor tongue lacerations from nocturnal jaw spasms. His mobility remained poor, with difficulty ambulating even using the forearm-support frame. Stiff-person syndrome (SPS) was suspected and he was commenced on baclofen 10 mg t.d.s. with some improvement in his spasticity, and reduction in facial and lower limb myoclonus.

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The diagnosis of SPS was further supported by a subsequent serum anti-glutamic acid decarboxylase antibody (GAD ab) > 2000 units/mL (reference range <10 units/mL). Lumbar puncture was also performed, demonstrating an elevated protein of 0.82 g/L (reference range 0.15–0.45 g/L). His cerebrospinal fluid (CSF) immunoglobulin G (IgG) was 0.06 g/L, with a normal IgG/albumin ratio of 0.12 (reference range <0.25), and normal CSF oligoclonal bands and glucose.

He was trialled with 4 days of 1 g methylprednisolone without effect. He was then given intravenous immunoglobulin (IVIG) 0.4 g/kg/day for 5 days (total 51 g/day). Clonazepam and baclofen were slowly up-titrated to 0.5 mg t.d.s. and 15 mg t.d.s., respectively, over 2 weeks. His spasticity was significantly reduced and his mobility improved to a four-wheel walker without assistance. He was transferred to a rehabilitation hospital, and discharged home 2 months later.

He suffered a mild relapse of leg spasticity 3 weeks post-discharge, but responded well to prednisone 50 mg daily and repeat IVIG infusion. He remains able to mobilise using a single point stick, with only mild right leg stiffness and no further facial spasms. Azathioprine was slowly introduced to 100 mg daily, and his prednisone was weaned to 25 mg alternate days, with continued monthly IVIG infusions.

SPS is an uncommon yet under-diagnosed autoimmune neuromuscular disorder, first described in 1956 by Moersch and Woltman. It is characterised by truncal and proximal limb muscle rigidity and superimposed episodic spasms, often associated with other autoimmune diseases, malignancies and anxiety disorders.

The episodic spasms of SPS begin with abrupt, painful, bilateral jerks of various muscle groups, which are followed by a sustained tonic activity that resolves over seconds to minutes. These myoclonic jerks are typically precipitated by unexpected auditory, tactile or emotional stimuli.

SPS may be under-recognised because muscle stiffness, spasms and cramps are common, and anxiety and emotional components may be dismissed as primary psychiatric illness. Therefore the diagnosis of SPS requires awareness and high index of suspicion. Differential diagnosis of SPS includes tetanus, fibromyalgia, dystonias, various myopathies and less commonly, myotonia and neuromyotonia, which affect distal more than proximal muscles, and have distinguishing characteristic EMG findings. Startle myoclonus and the characteristic EMG findings are helpful in distinguishing SPS from other differentials. High serum and/or CSF GAD antibodies further support the diagnosis.

The autoimmune aetiology of SPS was established in 1990 by the detection of grossly elevated GAD ab in the serum and CSF of SPS patients. Blood and CSF GAD ab are present in 60–90% of classic SPS patients. GAD ab block the conversion of glutamate to the major inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Marked intrathecal antibody response in SPS is hypothesised to block the action of the GAD-65 isoform that regulates short-term demands for GABA in the spinal grey matter interneurons and intra-cortical inhibitory neurones without structural damage. This causes defective descending inhibitory spinal modulation, resulting in the unique syndrome of chronic tetany and spasmodic reflex myoclonus from enhanced spinal interneurone excitability.

GAD ab are also found in other diseases, including type 1 diabetes mellitus (T1DM). However, as demonstrated in our patient, SPS patients have at least 50 times higher than baseline serum GAD ab titres (7–215 micrograms/mL) than in T1DM (10 times the baseline; 200–1760 ng/mL), and appear to recognise different epitopes. GAD ab level monitoring is not clinically useful in SPS.

Three major subsets of SPS are recognised: autoimmune, paraneoplastic and idiopathic. The commonest autoimmune variants are associated with pernicious anaemia (5%), thyroid disease (10%) and T1DM (30–60%). The paraneoplastic variant occurs in 5% of SPS and should be suspected with prominent upper limb and neck spasticity, especially when unilateral. Amphiphysin and gephyrin antibodies are more commonly found, with or without GAD ab.

Other clinically distinct SPS-plus syndromes include stiff-limb syndrome, jerking stiff-person syndrome and progressive encephalomyelitis with rigidity and myoclonus.

Reflecting the intrathecal de novo synthesis of antibodies, the CSF in SPS is usually abnormal, as in our patient. Oligoclonal IgG bands are detected in 60% of cases, whereas the cell count, total protein and IgG levels are less frequently elevated. EMG shows a background of physiological continuous motor activity with a unique, stereotyped recruitment order of muscles along the axial neuroaxis during spasmodic reflex myoclonus.
The two main goals of treatment are to enhance GABA neurotransmission and immunomodulation. Long-acting benzodiazepines (diazepam and clonazepam) and baclofen diminish the severity of spasms and stiffness, and are the mainstay of treatment. Diazepam dose ranges from 5 to 100 mg/day in divided doses every 3–6 hours, and baclofen up to 40–60 mg per day in twice or three times daily doses. Intrathecal baclofen through an implanted pump is effective, but at the risk of serious complications, including acute withdrawal reactions, autonomic crisis and death. Botulinum toxin injection, dantrolene and antiepileptic drugs are occasionally used.

Immunomodulation is required for SPS patients with suboptimal responses to diazepam or baclofen. As our case demonstrates, oral or intravenous corticosteroids up to 60 mg/day may be effective in some patients. However, IVIG at 2 g/kg given over 3 to 5 days is the preferred immunotherapy. A randomised controlled trial with cross-over design demonstrated efficacy of IVIG in 16 SPS patients with GAD abs. Improvement may last between 1 and 4 months, and maintenance infusions are required. Plasmapheresis may be effective in up to 40% of patients as reported in case studies, but has variable response rates. Rituximab is promising as a direct antibody depleting immunotherapy that results in transient reductions in intra-thecal GAD antibody levels with significant clinical improvements in some case studies.

To our knowledge, only four cases of thymoma-associated SPS are reported in the literature, often of the lymphocytic type B1 or B2 and associated with concurrent myasthenia gravis. GAD abs were positive in two of the four patients, and most SPS symptoms resolved following thymectomy. Rare SPS cases with Hodgkin lymphoma and one case of diffuse large B cell lymphoma of the pituitary have also been described. However, the combination of non-Hodgkin lymphoma, thymoma and SPS have not been described to date. This unusual case of classic SPS is consistent with the increasingly elucidated antibody pathogenesis of SPS, and highlights this under-diagnosed and unique disorder that should be considered in unusual presentations of myelopathy, back or limb spasms, and/or anxiety/phobia disorders.

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Polypharmacy – we make it worse! A cross-sectional study from an acute admissions unit

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Abstract

Although polypharmacy is a major problem in the elderly, very few data have been published from Australasia. We retrospectively audited 68% of elderly patients admitted acutely to our medical unit (n = 424, mean age 80.3 ± 8 years) during a 30-day period (September, 2008). We found that long-term medications increased during hospital stay from 6.6 ± 4 to 7.7 ± 4 (P < 0.001). Adverse drug reactions were responsible for 24 admissions (5.7%). Polypharmacy is made worse by acute admission to hospital.

Polypharmacy is usually defined as an inappropriate number of different medications for the patient, and for most elderly patients, the number is five or more.1,2 To some extent, the absolute number of medications is arbitrary and useful only for research or audit purposes. However, elderly patients taking five or more medications are at increased risk of inappropriate prescribing and adverse drug reactions (ADRs).1,3 Polypharmacy in the elderly is the result of several interlinked factors, including multi-system disease, specialist treatment by multiple providers, rigid application of guidelines based on data from younger patients and pharmaceutical company influence.4

As our population ages, the incidence of polypharmacy (and its complications) is likely to increase. Those aged over 65 years old make up 15% of the population of the United States but account for 25% of drug expenditure.3 New Zealand government statistics show that the over 65-year-old age group is projected to increase from its current level (12.3% of the population) to 20% by 2031.5 Apart from increasing drug expenditure, this is likely to increase the number of patients admitted with ADRs. Overseas, it has been demonstrated in America and Europe that ADRs are a significant cause of mortality and morbidity in the elderly, accounting for up to 11% of hospital admissions.7,8 A recent review in Internal Medicine Journal highlighted that there is very little published data from Australian or New Zealand hospitals.2

Our acute medical assessment unit (AMAU) in Christchurch Hospital serves a population of 475 000 and contains 25 beds. Average length of stay is 4.7 days. In the geriatric age group (>65 years old), we admit up to 800 patients per month. For this study, we undertook a retrospective analysis of all admissions to AMAU for the month of September 2008. In this sample, we wanted to assess: (i) the degree of polypharmacy on admission, (ii) the effect of admission on polypharmacy and (iii) how often polypharmacy contributed to admission.

A pro forma was designed to collect information on medications prescribed for elderly patients (Appendix I). It included patient demographic details, presenting symptoms, number of long-term medications on admission and discharge, final diagnosis and ADR. Presenting symptoms were grouped into seven broad categories: dyspnoea (respiratory illness and heart failure), falls (seizure/arrhythmia/syncope), weakness (stroke and musculoskeletal conditions), infection (urinary tract, chest, septicaemia and cellulitis), chest pain, metabolic disease (diabetes mellitus, and renal failure) and...
hospital stay was 1.1 compared to other age groups. The mean increase in medications during admission was greater than the other two groups (P = 0.024). Younger age group (65–75 years) were on less medications compared to the other two groups (P = 0.001). This pattern occurred in all age groups. The mean increase in medications during hospital stay was 1.1 ± 1.0. On admission, patients in the younger age group (65–75 years) were on less medications than the other two groups (P = 0.063), but on discharge, there was no difference between groups (P = 0.63) (Table 1).

Of the 424 admissions, there were 24 ADRs directly responsible for admissions (5.7% of analysed admissions). Of these, four occurred in the 65–75-year-old group; 14 in the 76–85-year-old group and six in the >85-year-old group. There was no difference in the frequency of ADRs between age groups (P = 0.45). Surprisingly, ADRs were not more frequent in those patients taking more medications on admission (P = 0.97). ADRs included (relative frequencies in brackets): hypoglycaemia 3 (13%), falls 3 (13%), acute confusion 3 (13%), hypotension 3 (13%) arrhythmia 3 (13%), miscellaneous 9 (35%) (Table 2).

We have demonstrated that acute admission to our hospital resulted in more long-term medications being prescribed to our elderly patients. Thus, polypharmacy, if defined simply as a mean of five or more different medications per patient, was present on admission and made worse by hospital stay in all the elderly subgroups we studied. ADRs accounted for at least 5.7% of these admissions.

These results are disappointing but consistent with what other hospital-based studies have shown in western countries. The retrospective nature of this study may have predisposed to an underestimation of the number of medications on admission (but not on discharge) and therefore possibly exaggerated the effect of hospitalisation. Our medication counts came from doctors’ records, and sometimes, this information may be misleading. For example, some patients have had their medications renewed by practitioners’ letters, junior doctors’ admission notes and the inpatient drug charts; the number of discharge medications from the electronic medical discharge summary. Long-term PRN medications (e.g. analgesics inhalers, hypnotics) were included, but short course medications, such as antibiotics were discounted. Non-prescription medications, skin ointments, eye drops and nose drops were omitted. For further analysis, patients were arbitrarily divided up into three subgroups according to: (i) age and (ii) number of medications prescribed on admission.

An ADR was determined to be the reason for admission if it was diagnosed by the admitting physician and specifically listed as a diagnosis in the medical discharge summary. Statistical comparisons were undertaken using standard two-tailed t-tests and Pearson chi-square analyses.

During September 2008, 851 patients were admitted to AMAU of which 626 were over 65 years old. The study is based on data obtained from 424 patient records we retrieved from this group (68%) and were analysed according to the pro forma. Readmissions were not included. Patients’ presenting symptoms were distributed among the following categories: dyspnoea 51 (12%), falls 78 (18%), weakness 55 (13%), infection 119 (28%), chest pain 38 (9%), metabolic disease 18 (4%), miscellaneous 9 (2%).

The mean age was 80.3 ± 8 years (57% female). The patients were divided according to age into three categories: 65–75 years, 105 patients (25%); 76–85 years, 196 patients (46%); >85 years, 123 patients (29%).

For the whole group, the average number of medications on admission was 6.6 ± 4. On discharge, this had increased to 7.7 ± 4 (P < 0.001). This pattern occurred in all age groups. The mean increase in medications during hospital stay was 1.1 ± 1. On admission, patients in the younger age group (65–75 years) were on less medications than the other two groups (P = 0.024), but on discharge, there was no difference between groups (P = 0.63) (Table 1).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of patients (% of total)</th>
<th>Admission</th>
<th>Discharge</th>
<th>Increase</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>65–75</td>
<td>105 (25)</td>
<td>5.8 ± 3</td>
<td>7.4 ± 4</td>
<td>+1.6 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>76–85</td>
<td>196 (47)</td>
<td>6.8 ± 4</td>
<td>7.8 ± 4</td>
<td>+1.0 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;85</td>
<td>123 (28)</td>
<td>6.9 ± 3</td>
<td>7.6 ± 3</td>
<td>+0.7 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>424†</td>
<td>6.6 ± 4</td>
<td>7.7 ± 4</td>
<td>+1.1 ± 1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†Refers to total number of patients.

Table 1 Mean numbers of regular and long-term PRN medications (± standard deviation) taken on admission and discharge grouped according to age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients (% of total)</th>
<th>Number of ADRs</th>
<th>ADR frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65–75</td>
<td>105 (25)</td>
<td>4</td>
<td>3.8</td>
</tr>
<tr>
<td>76–85</td>
<td>196 (46)</td>
<td>14</td>
<td>7.1</td>
</tr>
<tr>
<td>&gt;85</td>
<td>123 (29)</td>
<td>6</td>
<td>4.9</td>
</tr>
<tr>
<td>Total</td>
<td>424†</td>
<td>24</td>
<td>5.7†</td>
</tr>
</tbody>
</table>

†Refers to mean ADR frequency across all age groups.

Table 2 Adverse drug reaction (ADR) frequency according to age and number of medications on admission

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multiple prescriptions from different sources and may be unable to remember which is current. The most common discrepancies are ‘covert additions’ to the patient’s drug list rather than ‘deletions’. However it has been shown that these additions are short-term or non-prescription drugs (e.g. benzodiazepines, NSAIDS, paracetamol) and so would not have been included in our count anyway. Therefore, not including these medication discrepancies is unlikely to have falsely lowered the long-term medication count on admission. Unfortunately, we did not record what new long-term medications were started, and we suspect this is the main mechanism for the increase during hospital stay. We have to accept that sometimes, for example in patients with multi-system disease, appropriate treatment requires medications to be increased. Despite these caveats, the main result of this study remains valid: hospital admission was associated with a mean increase in the number of long-term medications for the whole group. There are several other contributing factors for this finding. Our consultant physicians are a mixture of geriatricians, sub-specialists and generalists, and we suspect that there is variation in hospital practice with regard to addressing polypharmacy in the elderly. Junior doctors are very reluctant to stop medications without senior approval; similarly, sub-specialists do not like to stop medications that other specialists have started. When the patient leaves the hospital, the general practitioner is even less likely to stop medications for similar reasons. In our medical wards, drug rationalisation is not routinely undertaken, even at discharge, mainly because we have insufficient numbers of ward pharmacists, and junior doctors are too busy.

We suspect that our result for ADR frequency (5.7% of all admissions) is conservative because this was based on individual consultants’ diagnoses and the junior doctors’ discharge summaries, the accuracy of which may be variable. For a variety of reasons, both senior and junior doctors sometimes fail to list polypharmacy and ADRs as diagnoses that may account for why our ADR frequency was lower than what other studies have found. ADR frequency is variable between studies, depending on method of data capture, but generally increases with the age of the patients studied. Despite these concerns, we suggest that the patient numbers in this study (and their broad range of presenting symptoms), should allow the results to be compared with other similar units. Furthermore, data collection was representative of our elderly patients in that it was undertaken on consecutive admissions to a single ward by one doctor (TB), who achieved a satisfactory inclusion rate (68%) limited only by the availability of patient notes.

The significance of polypharmacy can be measured in terms of economic waste, but the main cost relates to that of human suffering directly from ADR-related morbidity and mortality. There are several approaches to this problem in the hospital setting. These include: pharmacist intervention on the ward, better communication between prescribers, education of doctors by geriatricians with regard to appropriate withdrawal of medication, and improvement of the delivery of prescriptions between hospitals and community pharmacists. Some medications have to be withdrawn slowly (antidepressants, sedatives, proton pump inhibitors), which requires a team approach across the primary-secondary care interface.

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### Appendix I

**Polypharmacy pro forma**

1. MALE/FEMALE
2. AGE
3. PRESENTING COMPLAINT
4. NUMBER OF MEDICATIONS AT ADMISSION
5. ADMISSION RELATED TO MEDICATION PROBLEMS?
6. FINAL DIAGNOSIS
7. NUMBER OF MEDICATIONS AT DISCHARGE
Hypothesis. The importance of a histological diagnosis when diagnosing and treating advanced cancer. Famous patient recovery may not have been from metastatic disease

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Key words advanced and metastatic cancer, osteogenic sarcoma, accurate histological diagnosis, tuberculosis, choosing appropriate treatment.

Abstract

Over the past 33 years, mystery has surrounded the diagnosis and treatment of a very influential Australian patient. In the long gap between amputation of his leg for osteogenic sarcoma and successful treatment for widespread tuberculosis, he was told he had advanced and incurable metastatic sarcoma. Details of his recovery and the treatments used have been extensively described. An alternative hypothesis is advanced to explain his recovery. This hypothesis is advanced for two reasons. The first is to underline the modern recognition of the need to consider diagnostic investigations, including biopsy, before assigning the diagnosis of advanced cancer to any patient. This principle is especially vital in cases where two diseases can present in the same way. The second is that there a risk that if diseases are incorrectly labelled, incorrect treatments may be given. This can lead to misleading interpretations being made about non-traditional treatments providing ‘cures’, which can influence the decision-making of patients seeking answers and even lead them away from potentially curative traditional treatments.

As treatments for cancer become more sophisticated and more narrowly targeted, there is a changing paradigm in the management of advanced malignancy. This is that new lesions that develop in patients with a prior cancer diagnosis should be considered for biopsy before the diagnosis of recurrent or metastatic disease is accepted. There are several reasons: firstly, the need to differentiate non-malignant conditions that can mimic cancer; secondly, the awareness that patients who have had one cancer are often at increased risk of a second (different) cancer; and thirdly, the need to determine concordance of tumour markers between primary and secondary cancers, given their therapeutic implications.

That current practice is changing is relevant to the intriguing anecdote of one of Australia’s highest profile and most influential cancer survival stories. The well-known history, details of which have been made public by the patient himself and by his chroniclers, involves a man who was originally diagnosed with osteogenic sarcoma in late 1974 at age 24, and treated by full right leg amputation shortly thereafter. Subsequently a series of events developed that were considered to have been caused by metastatic disease. At one time he was given a 2-week prognosis, but nonetheless he went on to survive ‘against the odds’, using a multitude of treatments. The recent publication of a 30-year follow up and a subsequent challenge to that publication’s accuracy add to the mystery.

Two contrasting hypotheses have up to now been advanced to explain the patient’s recovery. The first is that he was cured of very advanced, metastatic osteogenic sarcoma by a variety of traditional and non-traditional treatments. Some of the non-traditional treatments have been published and followed by many Australian patients with cancer over the past 30 years in the hope of achieving a similar outcome. The second is that the patient recovered from both advanced
metastatic cancer and disseminated mycobacterial infection, either tuberculosis (TB) or BCG’osis. The proponents of this theory are divided on whether the disseminated mycobacterial infection occurred contemporaneously with the advanced cancer or after the advanced cancer had gone into remission.

However, the latest chronology of events, if correct, raises the possibility of a third hypothesis. This is that the patient, having been cured of localised high-grade osteogenic sarcoma of the leg by surgery in 1975, then developed advanced TB alone without metastatic cancer. The possibility of inaccuracy in the patient’s diagnosis has been alluded to previously. Under this hypothesis, which we believe to be the most likely of the three, the patient’s illness may have been wrongly labelled as advanced metastatic cancer for 3 years before TB was diagnosed and successfully treated in 1978–1979.

The ability of disseminated TB to mimic advanced cancer is well documented. The publicly available medical facts that support the third hypothesis are summarised in the timeline in Figure 1 and are as follows:

1 The patient had full right leg amputation in January 1975 for a histologically proven osteogenic sarcoma. Comment: this surgical procedure was carried out with the aim of cure.
2 In November 1975, the patient consulted his original surgeon because of new pelvic symptoms. He had X-rays and was found to have a large right pelvic mass that was presumed to be caused by metastatic cancer, but was not biopsied. Chest X-rays (CXRs) revealed enlarged mediastinal nodes. He was given a prognosis of 3–6 months. Comment: it is noteworthy that lymphadenopathy is a rare manifestation of metastatic osteosarcoma; typically the first presentation of metastatic osteosarcoma is with pulmonary secondaries (90%). The other common site of first metastasis is bone. In the largest published series, ‘regional’ metastases occurred in only 5 of 501 metastatic relapses. On the other hand, these developments are quite consistent with the onset of disseminated TB.
3 By February 1976, the patient had also developed severe drenching sweats nightly, dramatic weight loss and severe left leg pain interpreted as sciatic pain. X-rays confirmed masses in his right ilium, sacrum and L5 vertebrae. These areas were treated with three intensive sessions of radiation therapy in February 1976. CXR in early March 1976 showed a large left hilar mass with peripheral opacification in the left lung. Comment: this constellation of symptoms and signs is more typical of a severe systemic infective process such as disseminated TB than metastatic disease, with the lesions in the right ilium, sacrum and L5 vertebra being consistent with large tuberculomas.
4 In March 1976, IVP confirmed right hydronephrosis. Comment: renal TB is the second most common extra-pulmonary manifestation of TB, second only to lymphadenitis, and is often associated with hydronephrosis. We can find no record in the literature of hydronephrosis as a complication of osteosarcoma.
5 At this time in February 1976, ‘Three new cancerous lumps were beginning to grow on the patient’s breastbone.’ and by September–October 1976, the patient had developed cough and haemoptysis. Large palpable masses were now present around the sternum and anterior ribs and a mass was again seen in the hilum of the left lung on CXR with inflammatory changes in the left lower lobe. Comment: haemoptysis and the described CXR changes are profoundly atypical for metastatic osteogenic sarcoma (which characteristically involves lung parenchyma and not the hila) and are more typical of infection, such as a hilar tuberculoma with secondary bacterial or tubercular pneumonia in the left lower lobe. The left hilar and central and right chest wall masses were not biopsied before the patient received 3 months of intensive multidrug chemotherapy for what was presumed to be metastatic cancer. Although his oncologist felt that the lumps stopped growing on chemotherapy, these masses are consistent with tuberculomas, possibly in direct continuity with tuberculous mediastinitis. Tuberculous mediastinal lymphadenitis is a frequent manifestation of primary pulmonary TB. Extraneous extension may occur into adjacent structures, such as the bronchus and chest wall and may form fistulae. One relevant case report describes a tuberculous sternal mass misdiagnosed as malignant disease.
6 In mid-1977, the patient began coughing up blood and sputum containing what were interpreted as spicules of bone. At the same time, the chest wall lumps started to recede. Comment: these ‘spicules’ were not examined histologically and are consistent with inspissated pus from a left hilar tuberculosis that has formed a fistulous connection to the left main bronchus. Equally likely, given the appearance of these ‘spicules’, is broncholithiasis, the presence of calcified or ossified material within the lumen of the tracheobronchial tree. This can be a rare consequence of calcific TB eroding into the bronchus. The subsequent resolution of the palpable chest wall masses is consistent with discharge and resolution of a large multilobular tuberculoma, probably through a bronchial fistula. As stated in the conclusions of two major manuscripts, TB may involve the lungs, airways, vessels, mediastinum, pleura, chest wall or any combination of these structures.
January 1975
Right full-leg amputation for mid-femur osteogenic sarcoma.

X-rays reveal enlarged left hilar and/or mediastinal nodes and right pelvic mass.

No significant improvement and chemotherapy ceases.

CXR shows left hilar mass and scattered peripheral inflammatory changes in left lung. Lumps on anterior chest wall enlarge. Commences intensive multi-agent chemotherapy.

Develops severe left sciatic pain, drenching night sweats, severe weight loss and right hydronephrosis. Radiation therapy given to lower lumbar spine and right pelvic mass. Three small lumps appear on anterior chest wall.

Develops cough.

CXR shows left hilar mass and scattered peripheral inflammatory changes in left lung. Lumps on anterior chest wall enlarge. Commences intensive multi-agent chemotherapy.

Lumps on chest wall enlarge whilst in Philippines. Weight drops to 41kg.

CXR shows persistence of large left hilar lung mass and peripheral changes in left lung.

Chest wall lumps begin to regress.

CXR shows persistence of large left hilar lung mass and peripheral changes in left lung.

Chest wall lumps continue to resolve but severe cough and night sweats persist.

Chest wall lumps disappear. Cough increased. Profuse night sweats persist.

CXR shows evidence of previous tuberculosis and ongoing bronchiectasis, with a left hilar mass compressing the left upper lobe bronchus by 50%. Pelvis X-ray shows large osteoblastic masses in right ilium, sacrum and LS, unchanged from 1978.

Continued recurrent chest infections and bronchiectasis lead to left pleuropneumonectomy. Mature cancellous bone noted in the resected lung.

Lumps on chest wall enlarge whilst in Philippines. Weight drops to 41kg.

Develops sciatic pain, drenching night sweats, severe weight loss and right hydronephrosis. Radiation therapy given to lumbar spine and enlarged inguinal node.

Develops multiple joint pains which are diagnosed as hypertrophic pulmonary osteoarthropathy. TB diagnosed and patient commences multidrug therapy for 12 months. Fully recovers and returns to full-time work in 3 months.

Develops severe left sciatic pain, drenching night sweats, severe weight loss and right hydronephrosis. Radiation therapy given to lower lumbar spine and right pelvic mass. Three small lumps appear on anterior chest wall.

CXR shows left hilar mass and scattered peripheral inflammatory changes in left lung. Lumps on anterior chest wall enlarge. Commences intensive multi-agent chemotherapy.

No improvement and chemotherapy ceases.

CXR shows persistence of large left hilar lung mass and peripheral changes in left lung.

Chest wall lumps continue to resolve but severe cough and night sweats persist.

Chest wall lumps disappear.

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Continued recurrent chest infections and bronchiectasis lead to left pleuropneumonectomy. Mature cancellous bone noted in the resected lung.
7 By March 1978, the palpable chest wall lumps had disappeared, but the pelvic and left hilar lung masses remained unchanged and the patient had redeveloped intermittent, severe low back pain. X-rays at this time confirmed a large calcified right pelvic mass and a now very destructive process in the L5 vertebra.7 Also, an incessant cough and drenching night sweats persisted.7 Comment: all these developments were consistent with progressive and widespread TB.

8 In June 1978, the patient had developed widespread joint aches and swelling. He saw a new oncologist in Adelaide, where he was then living, who did X-rays and told the patient that ‘all the metastases with bone in them had more or less disappeared’. However, he also informed the patient that he had TB and that he felt that, upon review of all his X-rays, it had been present and undiagnosed for at least 2 years. He also diagnosed the severe widespread joint aches and swelling as hypertrophic pulmonary osteoarthropathy. The patient commenced a 12 months course of treatment for TB and quickly re-attained full health.3,7 Comment: it is clear from this chronology that at least some of the patient’s disease manifestations which previously had been attributed to metastatic cancer were in fact due to TB. Intriguingly, hypertrophic pulmonary osteoarthropathy has been described as a rare manifestation of both pulmonary TB20 and of pulmonary parenchymal metastases from osteogenic sarcoma.29 However, this patient had no radiologic pulmonary parenchymal masses consistent with metastatic osteosarcoma.

A recent review looks specifically at the prognosis, case-fatality rate and duration of untreated HIV-negative TB in patients who have been incorrectly diagnosed. The duration of TB from onset to cure or death is approximately 3 years and appears to be similar in smear-positive or smear-negative TB. The 10-year case-fatality rate is 70% for untreated smear-positive TB and 20% for untreated smear-negative, culture-positive TB.30 We do not have details of the smear or culture status of the patient described in this report. The surgical findings at the time of left pleuropneumonectomy in 2004 of widespread adhesions, bronchiectasis and tuberculous cavitation and scarring7 are very supportive of the hypothesis mentioned earlier.29 The histological findings of mature cancellous bone and foci of coarse sclerotic and heavily calcified bone in the centrally located mass, 35 × 30 cm, surrounding the bifurcation of the left main bronchus are quite consistent with the sequelae of resolved benign inflammatory conditions, such as tuberculomas that have also involved the pleura substantially.

This third possible hypothesis is advanced for two reasons. The first is to underline the modern recognition of the need to consider diagnostic investigations, including biopsy, before assigning the diagnosis of advanced cancer to any patient. This principle is especially vital in cases where two diseases can present in the same way. As Cantwell et al.,11 state, in reporting another case of a patient with both osteogenic sarcoma and TB, ‘a high index of suspicion is urged to diagnose atypical cases’, particularly where it may help avoid the use of potentially cytotoxic chemotherapy in the presence of undiagnosed active TB. Secondly there is a risk that if diseases are incorrectly labelled, incorrect treatments may be given. This can lead to misleading interpretations being made about non-traditional treatments providing ‘cures’, which can influence the decision-making of patients seeking answers and even lead them away from potentially curative traditional treatments.

In presenting this hypothesis, we emphasise that we are not in any way criticising the patient’s medical attendants who unquestionably acted fully in accordance with the standards of the time. Indeed, the need to consider obtaining histological confirmation of presumed metastatic disease is only now becoming part of standard oncological practice. We note that one of the leading textbooks of oncology states in its latest edition in relation to possible cancer recurrence: ‘Whenever possible, tissue acquisition for diagnostic confirmation . . . should be considered.’31

Whatever the correct diagnosis, we acknowledge the courage and determination of the patient that allowed him to recover from a prolonged and very debilitating illness. We especially note the psychological resilience that enabled him to overcome the dire prognosis he was given that fortunately turned out to be inaccurate.

Nonetheless, there is an aphorism, attributed to the late Carl Sagan, that exceptional claims require exceptional evidence. We contend that unequivocal evidence that the patient was cured of widespread metastases is lacking, and that the unusual treatments that were employed in this case cannot be held out as an example of a path to be followed by other patients with metastatic cancer.

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Personal Viewpoint

References


A 72-year-old man presented with 1 week of increasing shortness of breath, right shoulder pain and non-productive cough on a background of metastatic cholangiocarcinoma. His chest X-ray showed an extensive right-sided pleural effusion. To alleviate his symptoms, 1800 mL was drained with an intercostal catheter. The straw-coloured fluid contained adenocarcinoma cells on cytology, protein 32 g/L and lactate dehydrogenase 1240 IU/L.

Computed tomography (CT) of the chest post-drainage demonstrated right hydropneumothorax. Daily chest X-rays (Fig. 1) over a week revealed no improvement in lung expansion despite increases in suction applied through the intercostal catheter. A diagnosis of trapped lung was reached due to failure of lung reexpansion and visceral pleural thickening on CT (Fig. 2). The patient was discharged and asked to return if he became symptomatic for further pleural drainage, with consideration of pleural catheter insertion.

Trapped lung in the setting of a malignant pleural effusion indicates short expected survival, directing treatment towards symptom relief, with minimal hospitalisation. Surgical decortication is the definitive treatment, but is reserved for symptomatic patients in whom other causes of dyspnoea have been excluded and who are considered appropriate candidates for surgery.

References
A fluffy chest radiograph

A 35-year-old man with chronic renal failure was referred with nodular opacities predominantly in the upper and midzones bilaterally on a chest radiograph (CXR, Fig. 1). He had a failing renal transplant and was on immunosuppressives, with haemodialysis being initiated. An urgent bronchoscopy organised to look for opportunistic infections was normal, and bronchial washings were negative for acid-fast bacilli and other opportunistic organisms. A computed tomography (CT) scan of the chest (Fig. 2) showed widespread pulmonary, vascular and soft tissue calcification. His serum calcium was raised at 3.0 g/dL, consistent with the diagnosis of metastatic pulmonary calcification. His dialysis was optimised and serum calcium corrected. He remains well on follow up.

Pulmonary calcification occurs in a variety of systemic and pulmonary disorders. It is termed metastatic when in structurally normal lungs and dystrophic in previously injured lungs. Metastatic pulmonary calcification is a recognised complication of chronic renal insufficiency, commonly seen in untreated renal failure, failed transplantation and during haemodialysis. Although not manifested clinically, around three quarters of patients with chronic renal failure have pulmonary calcification on autopsy. Small nodules that are usually not calcified are the most common finding on a CXR. The appearances

Figure 1 Plain chest radiograph demonstrating bilateral nodular infiltrates which are predominantly seen in the upper zones.

Figure 2 Non-contrast computed tomography images, mediastinal windows. Extensive pulmonary and soft tissue calcification is demonstrated in panels a and b (arrows, thin). These are of the same density as bone suggestive of calcification. Thick arrows annotate tracheal calcification in panel a and pulmonary vascular calcification in panel b.
may simulate other findings, such as pulmonary oedema, haemorrhage or infections. CT scan demonstrates pulmonary nodules, where calcification is often obvious, and vascular and soft tissue calcification. Investigations that may be helpful if the diagnosis is in doubt are bone scan and a tissue biopsy. This condition does not need any specific treatment.

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LETTERS TO THE EDITOR

Clinical-scientific notes

Silver linings: a case study

A 65-year-old woman presented with community-acquired pneumonia. She was noted to have bluish discolouration of her face especially in the perioral, periorbital and forehead regions. The lunulae of her fingernails, but not her toenails, were noted to be similarly discoloured. She had noticed these changes for several months.

The patient had no medical illnesses of note and her only medications were garlic, fish oil, glucosamine and calcium carbonate supplements. She had been ingesting her own preparation of colloidal silver over a 2-year period to ‘strengthen her immune system’. Her husband had also engaged in this practice and had also developed similar nail changes.

Laboratory testing revealed a normal methaemoglobin concentration and normal copper/ceruloplasmin concentrations. Iron studies were consistent with an inflammatory illness. The serum silver was elevated at 0.16 (0.05 μmol/L).

The differential diagnosis considered included cyanosis, drug effects, for example from amiodarone or antimalarial medications, haemochromatosis, Wilson’s disease, methaemoglobinemia and heavy metal exposure. A punch biopsy of the patient’s facial skin reported conspicuous deposition of minute black to brown extracellular granules in the dermis. Deposition was around...

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Figure 1 Comparison of patient and author lunulae.
adnexal structures especially eccrine ducts. These findings were considered consistent with colloidal silver ingestion.

Silver was extensively used in the pre-antibiotic era as a germicidal agent to treat infections, such as syphilis and gonorrhoea, as well as non-infectious diseases, such as nervous disorders and epilepsy. Current medical uses include impregnated wound dressings and topical antibacterial cream for burns (silver sulfadiazine). It is also used on invasive devices, such as prosthetic joints and heart valves for its germicidal properties.

Soluble silver complexes with proteins and binds to sulfhydryl, amino, carboxyl, phosphate and imidazole groups. Light catalyses the reduction to metallic silver, which is deposited in connective tissue around vascular tissue and glands of the papillary layer of the dermis, as noted in this patient (Fig. 1). Silver can accumulate in the skin, liver, kidneys, corneas, gingiva, mucous membrane, nails and spleen. Argyria (skin and nail discoloration) and argyrosis (conjunctival and corneal pigmentation) are the most common signs of chronic silver toxicity.

Despite having no biological role in humans, colloidal silver is promoted by some in the alternative medicine arena as a cure-all for multiple diseases. The Therapeutic Goods Administration has not approved any colloidal silver product for use as a therapeutic good in Australia stating that there is 'little evidence to support therapeutic claims made for colloidal silver products'. Despite this there are three real concerns:

1. Inadequate research into efficacy and toxicity.
2. Patients choosing these products are less likely to seek appropriate medical review leading to delayed and/or missed diagnoses.
3. Potential psychological distress related to permanent skin discolouration.

These concerns underline the necessity of remaining vigilant and in dialogue with our patients regarding their health beliefs and the therapeutic modalities they may choose.

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References


Multimodal treatment of post-tissue plasminogen activator-related intracerebral haemorrhage

A 62-year-old man received tissue plasminogen activator (tPA) post-central retinal artery occlusion as part of an ethics approved study.1 Except for right sided monocular vision loss, he had no other neurological deficits and had a normal pre-tPA computed tomography brain scan. Within 10 minutes of thrombolysis the patient developed dysphasia and a right hemiplegia. He had progressive impairment of consciousness, dropping his Glasgow Coma Scale to 5 and required intubation. A computed tomography scan showed a left posterior parietal intraparenchymal haemorrhage of 5 × 3.3 cm with 10.8 mm of midline shift, and uncal herniation (Fig. 1A–C).

Four units of fresh frozen plasma, two units of platelets followed by prothrombinex, factor VII and vitamin K were given to reverse the effects of tPA. He underwent a left decompressive haemianietomy, with haematoma evacuation (Fig. 1D–F) and cerebral cooling (maintained at 34.0°C) for 48 hours postoperatively followed by slow re-warming. He underwent a period of rehabilitation and made a steady recovery. By day 39 postoperation he had a National Institutes of Health stroke score of 7 with mild

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right sided deficits and a mild expressive dysphasia, was ambulant with x1 assist and walker, and had 4/5 power of the right upper and lower limbs. Three months later the patient was ambulating independently with no motor deficits.

A parenchymal haematoma post-tPA administration is the most dreaded complication of thrombolytic therapy with an approximate risk of 2–3% in stroke, 0.5% in myocardial infarction and central retinal artery occlusion. Despite the use of tPA for both myocardial and ischaemic stroke reperfusion for approximately three decades, the evidence base for treating such an event is scarce. Anecdotally many centres, including our own, attempt to reverse the effects of tPA with coagulation factors and platelet transfusions, often with minimal success and a high case fatality of up to 70%.1

The pathophysiology of a tPA-related haemorrhage is complex and involves vascular reperfusion injury and altered blood-brain permeability. In addition, the blood clot itself causes oedema, and subsequent haemoglobin break down products induces neuronal toxicity through free radical generation.4 Thus effective therapy needs to address these issues.

In our case, the effects of tPA were reversed using factor VII,5 prothrombinex, fresh frozen plasma and platelets, the immediate effects of the oedema dealt with through a decompressive haemicanecrectomy6 and cerebral cooling7 while the toxic effects of the haematoma limited following haematoma removal.6 While each component therapy has been evaluated in isolation, with a randomised controlled trial demonstrating that factor VII reduces the absolute haematoma growth by 8%,8 in our case combining them together resulted in a good outcome. This case report suggests that tPA-related intracerebral haemorrhage could be treated with a multimodal approach combining medical therapy with clot

Figure 1 Axial computed tomography brain demonstrating post-(tissue plasminogen activator) tPA-related intracerebral haemorrhage extending from the left superior parietal lobe (A) as far inferiorly as the parietal – temporal lobe junction (B) with significant midline shift and uncal herniation (C). Post-hemicraniection and clot evacuation (D,E): there is improvement in midline shift and oedema with resolution of uncal herniation (F).
evacuation and provides impetus to conduct further clinical trials using this approach.

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Mental health history and disruptive behaviours in the medical setting

The relationship between mental disorders and violence is a controversial one. Although the literature reveals a strong association,1 some writers have cautioned that most violent people are not suffering from a mental disorder.2 Accordingly, the Institute of Medicine concluded that the contribution of people with mental disorders to overall rates of violence is small.1 A potentially important variable, however, is the type of violence or aggression under consideration. In this study, we examined relationships between past mental healthcare utilisation, a measure of general psychiatric status and aggressive behaviours in a specific scenario – disruptive behaviours in the medical setting.

Participants were males and females, aged 18 years or older, being seen for non-emergent medical care at an internal medicine outpatient clinic staffed predominantly by residents. We excluded individuals with compromising medical, intellectual, cognitive or psychiatric symptoms that would preclude the ability to successfully complete a survey.

During clinic hours, one of the authors (S. F.) solicited patients in the lobby of the outpatient clinic, assessed exclusion criteria and invited candidates to complete a survey. We initially asked participants about demographic information and then explored four types of mental healthcare utilisation, with yes/no response options (i.e. ‘Have you ever been seen by a psychiatrist?’; ‘Have you ever been hospitalised in a psychiatric hospital?’; ‘Have you ever been in counselling?’ and ‘Have you ever been on medication for your nerves?’). Finally, we asked participants about 17 disruptive behaviours related to the medical setting. With yes/no response options, participants were asked, ‘In dealing with medical personnel (office staff, assistants, nurses, doctors), either in an inpatient or outpatient medical (non-psychiatric) setting, have you…’, with items such as ‘Yelled or screamed at medical personnel’, ‘Cussed at medical personnel’, ‘Verbally threatened medical personnel’, and ‘Threatened to hit or strike medical personnel’. The author-developed Disruptive Behaviours Survey is located at http://www.MindingtheMind.com/disruptivebehaviors.pdf. This project was approved by an institutional review board and completion of the survey was indicated as implied consent.

At the outset, 441 individuals were approached; 401 agreed to participate (90.9%). Of these, 395 completed study measures, 64.6% female and 35.4% male, ranging in age from 18 to 92 years (M = 53.45, standard deviation = 16.20). Most were white/Caucasian (89.4%), and all but 7.6% had at least graduated high school.
Substantial minorities of respondents had ever seen a psychiatrist (34.9%), been in inpatient psychiatric care (13.9%), been in counselling (46.8%) and been on medication ‘for their nerves’ (43.8%). Possible scores on the measure of disruptive behaviours ranged from 0 to 17, but actual scores ranged from 0 to 11 (M = 1.26, standard deviation = 1.63), with 50.9% denying having engaged in any of the behaviours.

Scores on the measure of disruptive behaviours in the medical setting are presented in Table 1 as a function of self-reported mental healthcare utilisation. Findings support an association between mental health problems and one specific form of aggressive behaviour – number of disruptive behaviours in the medical setting. Despite the potential limitations of self-report data (e.g. reluctance to disclose information related to shame/guilt), lack of information regarding psychiatric diagnoses and absence of reliability/validity of the Disruptive Behaviours Survey, findings suggest that primary care clinicians be alert to the possibility of aggressive and/or disruptive behaviours in the medical setting among patients with mental health histories, and to proactively approach these individuals with greater sensitivity and carefulness.

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References


Fertility is significantly reduced by female genital tuberculosis: a case series

Genital tuberculosis (TB) is an uncommon form of extra-pulmonary TB that substantially limits fertility. It is the primary site of disease in less than two percent of all TB cases. An Iranian study of genital TB found 75% of patients met criteria for infertility. We have sought to highlight the occurrence of this condition in Australian practice through a case series of patients diagnosed with genital TB, describing the clinical pattern of disease seen and concentrating on its impact on fertility. Cases were treated in the TB clinic at the Royal Melbourne Hospital. Patients were excluded from the case series if the TB was only urinary with no pelvic involvement.

Nine patients with genital TB were identified. Details of the clinical presentation and diagnostic procedures are presented in Table 1. All patients were born outside Australia and those patients who were tested were negative for HIV.

There were significant delays in diagnosis, possibly up to 31 years (patient 1). Most notably, patient 3 had a laparoscopy performed in Australia, which showed peritoneal granulomas on histology, but was not diagnosed with TB until 6 years later.

Infertility is defined as 1 year of unprotected intercourse without conceiving. GUTB had been regarded as being incompatible with later fertility. In this study six of nine patients appeared to have reduced fertility (Table 1). Four women had been infertile up until the point of TB diagnosis (although all other causes of infertility have not been excluded), one young women (patient 7) had significant ovarian damage and another, premature menopause (patient 1).

Two patients (patients 4 and 8) were able to conceive and deliver healthy babies in the year prior to diagnosis. A third patient (patient 3) was able to achieve a live birth with the use of *in vitro* fertilisation (IVF) having completed anti-tuberculous therapy 13 months earlier, after more than 5 years of unsuccessful IVF.

Genital TB causes between 3 and 17% of infertility in the developing world. A Nepalese study found infertility in more than 65% of those with genital TB. In our series, investigation of infertility led to the diagnosis of TB only in one case; however, in 6 of the 9 patients diagnosed with genital TB, abnormal fertility was present.

In TB endemic areas, fertile patients are frequently treated for TB if no other cause is found. In the developed world where IVF is frequently used for management of infertility, patients from TB endemic areas should be screened for TB with interferon gamma release assay and investigated for pelvic pathology consistent with this disease.

Restoration of fertility after treatment for pelvic TB has been documented infrequently. While up to 19% of women conceived after TB treatment, only 7% achieved live births. The use of IVF and ovarian stimulation has been shown to be effective in some cases. We have documented both restored fertility with successful IVF following TB treatment, and minimal impact of the disease in two patients who had live births up to 8 months prior to pelvic TB diagnosis.

In patients from TB-endemic areas it is important to consider TB as a cause of abdominal pain and infertility. Multiple modalities, including histology, culture and polymerase chain reaction, should be used to pursue this diagnosis. The failure to do so has the potential to lead to poor outcomes. This case series is a reminder that active TB can occur many years after the suspected exposure. If appropriately managed, it is compatible with successful childbirth, mostly using IVF.

**Acknowledgements**

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<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Birth country</th>
<th>Presentation</th>
<th>Effect on fertility</th>
<th>Imaging</th>
<th>Sample site</th>
<th>Histology</th>
<th>Culture</th>
<th>Polymerase chain reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>Turkey</td>
<td>Sterile pyuria, dysuria, flank pain and rigors</td>
<td>Three live births, amenorrhoea from 33 years of age</td>
<td>CT pyelogram: ureteric stricture, hydronephrosis, calcified fallopian tubes</td>
<td>Urine</td>
<td>Necrotising granulomas</td>
<td>+ve</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>Italy</td>
<td>Post-menopausal bleeding</td>
<td>Infertile throughout reproductive life. Investigated with curettage at 30 years of age, but no cause identified</td>
<td>USS: endometrial polyps and ovarian cyst</td>
<td>Ovary and endometrium</td>
<td>Necrotising granulomas</td>
<td>-ve</td>
<td>+ve</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>Turkey</td>
<td>Abdominal pain and fevers post miscarriage</td>
<td>Myometrial TB on endometrial histology after 3rd miscarriage and 5 years of unsuccessful IVF. After completion of TB therapy successful IVF pregnancy</td>
<td>USS: ovarian mass</td>
<td>Endometrium</td>
<td>Necrotising granulomas</td>
<td>+ve</td>
<td>(smear +ve)</td>
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<tr>
<td>4</td>
<td>23</td>
<td>Vietnam</td>
<td>Metromenorrhagia</td>
<td>Delivered healthy baby 8 months before diagnosis</td>
<td>USS: complex left ovarian cyst</td>
<td>Endometrium, Peritoneal fluid</td>
<td>Necrotising granulomas</td>
<td>+ve</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>Nepal</td>
<td>Abdominal pain and bloating</td>
<td>Infertile, bilateral salpingectomy, ovaries intact. Started IVF after completing TB therapy.</td>
<td>USS: ovarian mass</td>
<td>Ovary</td>
<td>Necrotising granulomas</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>Ethiopia</td>
<td>Abdominal wound with caseous discharge, pelvic pain, abdominal distension and menorrhagia.</td>
<td>Infertile. Previous abdominal surgery for cysts in Ethiopia, no clear diagnosis</td>
<td>CT abdomen: complex abdominal collection tracking to anterior abdominal wall</td>
<td>Abdominal wound discharge</td>
<td>Necrotising granulomas</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>Ethiopia</td>
<td>Abdominal pain and distension</td>
<td>Single ovary resected, not sexually active. Other ovary has cystic change on CT scan</td>
<td>CT abdomen: ascites, tubo-ovarian mass</td>
<td>Ovary and fallopian tube</td>
<td>Necrotising granulomas</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>Somalia</td>
<td>Abdominal pain and ascites</td>
<td>Delivered 8th child 5 months before diagnosis</td>
<td>CT abdomen: Mesenteric nodes</td>
<td>Peritoneal biopsy</td>
<td>Necrotising granulomas</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>India</td>
<td>Abdominal pain</td>
<td>Not tried conceiving</td>
<td>USS: 10 cm tubal abscess</td>
<td>Tubal abscess</td>
<td>Necrotising granulomas</td>
<td>+ve</td>
<td>+ve</td>
</tr>
</tbody>
</table>

CT, computed tomography scan; IVF, in vitro fertilization; USS, ultrasound scan.
Letters to the Editor

References

General correspondence

Coronary CT angiography for patients with stable chest pain in the Emergency Department; an appraisal of current and emerging evidence

The recent Medicare reimbursement of coronary computed tomographic angiography (CCTA) reflects the potential of this technology to result in significant cost-savings and improved management of patients with coronary artery disease, including those presenting to the emergency department (ED) with chest pain. In his recent editorial, Scott1 expresses concerns that CCTA is a ‘new test with possible unchartered hazards’, and implies that the use of CCTA in evaluating acute chest pain is a premature application of this technology.

More than 2000 patients have been specifically studied in the ED setting, including local Australian cohorts2–3 showing a pooled sensitivity of 92%, specificity of 89% and a very high negative predictive value of 99%. The principles to justify public spending outlined by Scott are supported by current evidence in CCTA: (i) accuracy, which is well established in large, multicentre randomised trials4–5; (ii) the ability to define the probability of disease in an individual patient6–8; (iii) altered clinical management through identification of coronary artery disease by CCTA and/or calcium scoring9–10, and (iv) provision of incremental prognostic data in large prospective cohorts with positive effects on downstream resource utilisation.9–10 Recent Australian cost-effectiveness studies have modelled the economic outcomes of CCTA in the ED. Kreisz et al.,11 found CCTA to be a cost-effective rule-out strategy patients at low-intermediate risk in the outpatient setting, and Priest et al.,12 recently confirmed that CCTA strategies have lower costs and higher quality-adjusted life years compared with stress electrocardiography (ECG), echocardiography and nuclear perfusion imaging.

Recently emerging data, such as the CT-STAT (Coronary computed Tomographic angiography for Systematic Triage of acute chest pain patients to Treatment) trial of 699 patients with acute chest pain in the ED,13 showed that CCTA resulted in a 54% reduction in time-to-diagnosis compared with SPECT, 38% lower cost and reduced radiation (P = 0.02). There was no difference in major adverse cardiac events. Contrary to the statement by Scott that ‘virtually all studies assess performance on first-generation 64-slice scanners’, prospective data from local Australian centres have been published using dual-source2 and broad-detector (320-slice) scanners specifically in the ED setting.9–10 Of note, the ‘triple-rule-out’ is not recommended, and CCTA is used primarily for evaluation of the coronary arteries in low-intermediate patients with suspected acute coronary syndrome.

In relation to radiation dose, recent Australian data have shown that CCTA with prospective ECG-gating results in 87.5% reduction in radiation dose with no change in image quality.14 Standard radiation dose for CCTA is approximately 3–8 mSv depending on patient size and scanner settings, significantly less than nuclear SPECT (~16 mSv15–16). In selected patients, dose can be reliably <1mSv17 using the latest scanners, which are now available in multiple centres around Australia.
We agree that no large, randomised outcomes trials have proven the comparative efficacy of CCTA with regard to hard outcomes, such as mortality, compared with standard investigations. Importantly, no chest pain assessment protocol or strategy (including stress ECG, SPECT and stress echo) has ever been shown to confer a mortality benefit.14 The PROMISE trial (clinicaltrials.gov NCT 01174550) is a National Institutes of Health-sponsored multicenter comparative effectiveness trial enrolling 10,000 patients, and is expected to define the cost-effectiveness and prognostic value of anatomic assessment with CCTA versus functional assessment with conventional stress testing.

In addition, CCTA may provide both anatomical and functional imaging within the same test. Australian data have evaluated ischaemia using adenosine-stress perfusion CCTA19 compared with invasive fractional flow reserve (FFR). Recently, novel strategies involving computational fluid dynamics to enable calculation of non-invasive fractional flow reserve from a standard CCTA dataset have been validated in comparison to invasive FFR,17 and are being evaluated in a prospective multicentre trial.20 CCTA, therefore, has future potential to provide comprehensive non-invasive assessment of coronary plaque, stenosis and lesion-specific ischaemia, but these strategies are not routinely available and have not been tested in the ED setting.

In summary, CCTA, when performed in appropriately selected and adequately prepared patients, provides timely, accurate and safe imaging of the coronary arteries in order to risk-stratify patients presenting to the ED with undifferentiated chest pain. This is supported by the recently updated, multipartite Appropriate Use Criteria for Cardiac Computed Tomography.23 CCTA is an established technology with a growing evidence base. Experienced providers who are proficient in CCTA acquisition, radiation reduction and image interpretation, coupled with optimal patient preparation, are the foundations to generate the highest quality images and to best inform clinical management decisions.

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References

Letters to the Editor

I thank Hamilton-Craig et al.1 for alerting us to very recent studies investigating 320-slice scanners in computed tomography coronary angiography (CTCA) assessment of chest pain in the emergency department, coronary flow data from CTCA images and decision analytic models in regard to cost-effectiveness. Evidence from clinical trials is pointing towards CTCA being useful as part of a rule-out algorithm for coronary artery disease (CAD) in low-risk patients presenting with acute chest pain.2,3 However, what is missing, as Hamilton-Craig et al. concede, are randomised trials proving efficacy of CTCA relative to standard investigations in optimising management and improving patient-important outcomes – outcomes that, in addition to all-cause mortality, include prevention of disease-related major adverse cardiac events and hospitalisations, as well as procedure-related complications, radiation exposure and quality of life.

The PROMISE trial (clinicaltrials.gov NCT 01174550) has such evaluation as its aim, recruiting 10 000 patients of intermediate risk in both ED and outpatient settings, randomising them to either initial functional (exercise electrocardiogram, stress echo or stress nuclear imaging) or anatomical (CTCA) assessment, and then evaluating clinical outcomes mentioned above at 2 years. Primary outcome results are expected in May 2012. The Scottish computed tomography of the heart trial (clinicaltrials.gov NCT 01149590) is also randomising 4000 patients referred to acute chest pain units to CTCA or usual care, and assessing outcomes at 6 months with results expected in July 2013. These trials will hopefully provide definitive data on which patients under what circumstances gain most from CTCA versus conventional approaches. While Hamilton-Craig et al. and other investigators working in tertiary academic centres will advance the technological capabilities of CTCA, it is large-scale pragmatic trials such as PROMISE that will define the management role of CTCA in patients representative of those encountered in routine clinical practice and undergoing CTCA in non-academic settings. Their findings, in turn, should inform decisions around CTCA eligibility for public funding.

In Australia, the recently introduced Medicare rebate for CTCA only applies to patients with stable chest pain symptoms consistent with coronary ischaemia, and who are at low to intermediate risk of CAD and would otherwise have been considered for coronary angiography. While I would have preferred the rebate was deferred until the results of the earlier trials were known, it is in keeping with growing evidence for CTCA being an accurate and cost-effective test for excluding significant CAD in low-risk ambulatory patients and obviating the need for further investigation.4 However, the rebate does not cover patients presenting to ED with acute chest pain, and Medicare may yet regret the current rebate in light of US studies reporting that publicly reimbursed CTCA, in the non-acute setting, is associated with more than twice as many downstream coronary procedures over...
6 months compared with stress testing, and 65% increase in resource utilisation with no decrease in mortality and only marginal decrease in absolute rates of acute myocardial infarction. This uncertainty clearly indicates the need for proper prospective trials over the long term in establishing the indications for CTCA in the management of acute chest pain.

References

Prehospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease

Wijesinghe et al. are to be congratulated on the publication of their retrospective audit of prehospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease (COPD), accepted for publication on 23 December 2009 and appearing in the August 2011 issue of Internal Medicine Journal. They concluded that ambulance administration of high flow oxygen to patients with acute exacerbations of COPD is associated with poor clinical outcomes, and that large randomised control trials of titrated oxygen therapy are urgently required.

We wish to point out that such a randomised control trial has been performed within Australasia, and its results were published after the date of acceptance of the Wijesinghe et al. article. This first randomised control trial of prehospital oxygen therapy for acute exacerbations of COPD has confirmed the long-held suspicion that high flow oxygen therapy in this situation is associated with increased mortality when compared with controlled oxygen delivery.

In this study of 405 people aged 35 years or older with breathlessness and a history or risk of COPD, paramedics were randomised to deliver usual high flow or titrated oxygen during transport to the Royal Hobart Hospital. In an intention to treat analysis of all patients, we found a significant difference between the two treatment arms for mortality (relative risk 0.42, 95% confidence interval 0.20–0.89; P = 0.02). Mortality was 9% (21/226) in the high flow oxygen arm compared with 4% (7/179) in the titrated oxygen arm. Titrated oxygen treatment reduced the risk of death from respiratory failure by 58% for all patients and 78% for patients with confirmed COPD, compared with high flow oxygen.

Our study has surely put the final nail in the coffin of high concentration oxygen for all, and provided hard evidence that we should be adhering to international guideline recommendations to keep arterial oxygen saturations ‘within the target saturation range’ of 88–92% for patients with COPD or other risk factors for hypercapnoea.

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Prehospital oxygen therapy in exacerbations of chronic obstructive pulmonary disease: the practical issues

We are responding to the paper by Wijesinghe et al.1 on prehospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease (AECOPD). This retrospective study of ambulance records was undertaken by hospital-based specialists without the prior knowledge or involvement of this ambulance service. Information was taken from forms intended to provide handover information to emergency department (ED) staff. The paper does not state exactly which oxygen saturations ‘at presentation to the ED’ were used, but the timing and accuracy of measurements taken in a moving ambulance would be subject to variation.

Standard prehospital treatment of AECOPD includes the administration of nebulised bronchodilators. The British Thoracic Society (BTS)2 accepts that ambulance services in western countries do not normally carry compressed air and that nebulisation with oxygen is routine. Therefore, according to the classification used in this study, all AECOPD patients will have received ‘high flow’ oxygen during prehospital nebulisation. In 2008, this ambulance service implemented the BTS recommendation that nebulisation with oxygen should be interrupted after 6 min to minimise hyperoxia.

A quarter of the patients in the study had previously required assisted ventilation, and half had a history of respiratory failure. Paramedics confronted by patients with severe dyspnoea of unknown cause will normally support or assist ventilation to correct hypoxia until the patient reaches the ED where previous records are available, end-tidal and blood gas tensions can be measured, and treatment can be tailored to the patient. Measuring an initial oxygen saturation on air would not be the first priority in a patient suffering significant respiratory distress.

AECOPD represents only one of many causes of prehospital dyspnoea. In 2007, the recognition of COPD patients was not facilitated by alert cards, which were first introduced in our area by Hutt Hospital in 2008.

The odds ratio of 1.2 reported for ‘high flow’ oxygen is much lower than for the categories of home nebulisation (2.4), long-term oxygen therapy (2.8), previous respiratory failure (2.6) or previous assisted ventilation (3.3). Patients with AECOPD who responded to ambulance and ED treatment, and were not admitted to hospital, were excluded from the study.

To say that the use of high oxygen flow rates ‘seems entrenched’ within our ambulance service is emotive, imaginative, and not substantiated by our own teaching and internal audit findings. Paramedics have a good understanding of the issue, basic trainees less so. Potentially affordable equipment that would permit portable air nebulisation in our ambulances has been sought for some time.

We consider it unprofessional for one group of healthcare workers to obtain and audit data produced by another without their knowledge and involvement.

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References

Reply

We thank Wood-Baker and colleagues for highlighting their landmark randomised controlled trial (RCT). As discussed in the accompanying *British Medical Journal* editorial, there is now robust level 1 evidence that controlled oxygen therapy titrated to achieve oxygen saturations of 88 to 92% substantially reduces the risk of death associated with high concentration oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease (AECOPD). However, there are two major obstacles to the implementation of this regimen. The first is to overcome the entrenched practice of delivering high concentration oxygen therapy in AECOPD. The extent of this behaviour was illustrated in the Australian RCT in which more than half of the patients with confirmed chronic obstructive pulmonary disease randomly assigned to the titrated oxygen group received high concentration oxygen at some stage during the ambulance transfer, in violation of the protocol, and despite 1 month of familiarisation and training of health professionals before commencement of data collection. The other obstacle is the delivery of high concentration oxygen through administration of bronchodilator through a nebuliser driven by oxygen. One alternative to this practice is to use air-driven nebulisers with titrated supplemental nasal oxygen, the regimen employed in the Australian RCT.

We also thank Swain and colleagues for raising these and other issues relating to the interpretation of clinical data in our audit. We recognise that clinical documentation in emergency situations may not be ideal, but nevertheless, there was a significant association between increasing PaO₂ at presentation to the emergency department and worse outcome in our audit. In regard to the strength of the association with oxygen administration, the odds ratio of 1.2 is per 1 L/min oxygen flow, which equates to an odds ratio of 3.0 per 6 L/min oxygen flow (the difference between 2 L and 8 L/min oxygen flow), which is similar to the odds ratios reported for other risk factors. In comparing odds ratios, another consideration is how common the risk factor occurs, and in this regard, 49% of patients in whom the oxygen flow rate was clearly documented had received oxygen ≥8 L/min in our audit. In addition, some of the risk factors used to adjust the estimates for imbalance related to the non-experimental study design are not modifiable, whereas administration of oxygen is under the control of medical care. With regard to initial priorities, we do not concur with the view that measuring initial room air oxygen saturation would not be important when attending a patient suffering respiratory distress. It is a critical vital sign to both assess risk and enable a informed assessment of whether oxygen therapy is indicated.

Looking forward, the challenge will be to achieve a paradigm shift in practice worldwide, so that titration of oxygen therapy to achieve an oxygen saturation target of 88 to 92% becomes the standard care in AECOPD, thereby minimising the risks of both hypoxaemia and hyperoxaemia.

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References


Treatment of refractory neurosarcoidosis with TNF-inhibitors: what lies ahead?

We read with interest the case series on the treatment of refractory neurosarcoidosis with infliximab.1

We were interested to know whether the serum and cerebrospinal fluid angiotensin converting enzyme or other makers of sarcoidosis might have been ascertained (such as increased cerebrospinal fluid CD4/CD8 lymphocyte ratios, lysozyme and β2-microglobulin), as these can have a role in monitoring disease activity, and in supporting a diagnosis2 if a patient (e.g. Case 1) declines biopsy. Likewise, a gallium or positron-emission tomography scan may indicate accessible disease worthy of biopsy, for example, salivary glands or lymph nodes.

Sarcoidosis refractory to glucocorticosteroids is an important and difficult area, and although there have not been any randomised controlled treatment trials for isolated neurosarcoidosis, there is now a large body of evidence from placebo-controlled studies that anti-TNF-α agents have a relatively modest effect in modulating this disease, which is disappointing given the logical choice of TNF antagonists in sarcoidosis.3–5 Nonetheless, individual trials of therapy may be worthwhile as in the refractory cases reported, if monitored carefully, and the therapy discontinued quickly if ineffective, particularly with the awareness that tuberculosis might be unmasked as being the true diagnosis, rather than sarcoidosis. We also note that Pereira et al. tested azathioprine in two of their patients although did not assess anti-malarials.1 Azathioprine, as well as chloroquine and hydroxychloroquine have also been reported as being useful in a few small case series of neurosarcoidosis,2,6 but no clinical trial data exist. Hopefully, better agents that target CD4+ type 1 helper T-cell (Th1) immunity and associated sarcoid inflammatory pathways will become available as the immunology of this fascinating disease becomes apparent.4,7

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