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Donation and transplantation of organs and tissues is one of the greatest miracles of modern medicine, having opened the way to effective, proven treatments for many diseases previously incurable. The gift of an organ can not only relieve suffering but also provide a rare opportunity for good to be salvaged from tragedy, and for altruism and nobility to shine through the darkness in what is otherwise an uninterrupted vista of self-interest and greed. What is more, remarkably, the outcome is not only noble and ethical but also cheaper and more cost-efficient than other methods of treatment. In societies divided by so many contentious issues, this is one on which there can be almost complete unanimity: organ donation is a social good that should be supported, along with whatever steps are necessary to increase its effectiveness.

The powerful rhetoric underlying organ donation is familiar to us all. There is only one problem: even with all the hyperbole and good news stories associated with it, donation rates for organs and tissues in almost every developed country in the world are insufficient to meet demand. Even with the almost unanimous encouragement of policy-makers and health professionals, too few people agree – either through advance directives or by granting permission on behalf of their deceased relatives – to make organs and tissues available for transfer to other individuals. Various explanations for this state of affairs have been proposed: it is speculated, for example, that it results from inadequate education, unjustified fears, irrational superstitions or lack of understanding of the concept of brain death. Public campaigns, promotional schemes and incentives have all been tried in attempts to overcome the scarcity, but with a few exceptions, success has been limited. In many cases, this failure to bring the organ donation miracle to fruition has come to be regarded as a source of national shame. Australia provides a particularly egregious example. For at least 20 years, organ donation rates have languished in the bottom third of the Organisation of Economic Cooperation and Development (OECD) donor rankings. In addition, whereas many other countries have improved their statistics over the years – the most spectacular being Spain, which has doubled its donation rate since 1990 – in Australia, the figures have been largely static. Indeed, it has even been argued that publicly available data paint an excessively optimistic picture by understating the number of people genuinely in need of kidney transplants. The poor figures have defied numerous, expensive strategies to change them, including the establishment of a consent registry in 2005, the funding of an American-style ‘collaborative’ in 2006–2009, repeated attempts to streamline hospital processes and the technical infrastructure, and the establishment of the Australian Organ and Tissue Authority with a government grant of $153 million in 2008. All that seems to be left is a shift to an opt-out system of presumed consent, which has been seemingly successful in some other countries, although this is seen as a last and likely unpopular resort. Some solace has been taken from the belief that the failure, at least in part, is a paradoxical reflection of other successes, an effect of dramatic improvements in stroke and road trauma mortality which have eroded two of the main sources of supply of donor organs.

The rhetoric is so ingrained that few of us think to question it. Unfortunately, despite the undisputed merits of donation and transplantation, the account just presented does not tell the whole story. For all the good intentions of those who promote it, the public representation of organ donation and transplantation has failed to acknowledge crucial facts and has ignored or silenced concerns deeply felt by the community. There is no doubt that this failure has contributed to the present perceived crisis. It is not true, for example, that poor donation rates are the result of inadequate knowledge and education about the virtues of transplantation: surveys have repeatedly demonstrated high levels of awareness of the benefits of donation and the need for organs. There is no evidence that opposition from religious groups in general undermines acceptance of organ and tissue donation. Even the extra freedom supposedly inherent in opt-in systems of consent does not seem to be a factor because careful analysis shows that, when controlled for other factors, there is little difference between rates in countries using opt-in and opt-out decision-making systems. In a paper in this issue of the Journal, Bendorf et al. dispose of another popular theory, referred to above, often quoted in Australia and elsewhere, to which they refer as the ‘failure because of success hypothesis’: that
poor donation rates are the result of the otherwise welcome improvements in road safety and survival after stroke which have eroded two of the main sources of donor organs. Despite the superficial plausibility of this hypothesis – deaths from road trauma and stroke really have improved – the authors show through analysis of data from Australia and other OECD countries that there is no correlation between these variables and availability of donor organs. Indeed, in some countries, the falls in road trauma and stroke deaths have been accompanied by marked increases in donor rates, including several in which the improvements have been considerably greater than those in Australia.

The compelling message conveyed by all these studies is that there is no single solution to the problem of organ donation rates that is likely to be applicable in all settings. Simple formulae and increasingly vigorous public exhortations are unlikely to be effective. Instead, what is needed is examination of the concerns of specific individuals and communities, and the fostering of a public debate that is not limited by the rhetoric and ideology that has come to dominate the field. Openness to local concerns is of particular importance in a country like Australia, which is characterised by a wide diversity of cultures and social perspectives. In each case, the relevance of potentially modifiable variables identified in research around the world needs to be assessed. For example, the need for enhanced provision of information, quality care of potential donors, explanations of brain death, separation of the request for donation and clinical care, and the use of experts to manage family discussions; other factors, such as ethnicity, patient age and cause of death, are more difficult to modify. In multiethnic, multicultural societies, varying attitudes and needs of different groups are likely to be major factors: indeed, it is possible that while for some groups saturation has been reached, for others the message has not even started to penetrate.

An additional possibility also needs to be considered, that the evident discrepancy between the apparent unanimity in the dominant discourse about donation and transplantation and poor donation rates suggests that many community members have concerns they feel are not being addressed. It is possible that the triumphalist discourse about miracles and gifts of life has succeeded in creating an illusion of consensus that obscures an underlying disquiet about the many complex and perplexing issues raised by the new medical practices. If this is true, doctors, public health officials and the media need to step back from the ideology they are propagating and start to listen more carefully to the reservations being experienced by the people in the communities they are trying to convince.

There is evidence to support this view. When asked directly, many individuals confess to a deep scepticism about some of the key elements of the ideology of organ donation, that death is no more than a physiological event that can be defined and redefined to suit the convenience of technicians and public officials, that the body – alive or dead – is no more than a collection of reusable parts to be circulated and utilised in the most efficient way, and that even our worst, most painful experiences of grief and pain are just another part of the inexorable chain of supply and demand that keeps the economy functioning. There is, for many, a deep – and understandable – sense of uneasiness about the social, emotional and spiritual implications of organ transfer, which is seen as part of an inexorable movement, supported by modern medicine, towards the commodification of the body and the extirpation of the meanings, feelings and secret possibilities that have traditionally resided within it. Many are disquieted by the appearance of an elaborate bureaucracy of organ transfer and the thriving, lucrative economy it has generated around the world. There is widespread scepticism about the motives underlying public investment in organ donation which, while proclaiming a commitment to the alleviation of suffering, is assumed really to be directed primarily to reducing the costs of treating chronic diseases.

The natural and ancient concern about the meaning and significance of death and bodily tissues cannot be eliminated by the introduction of new clinical criteria of a technical nature, new legal statutes or expensive social marketing campaigns that proclaim traditional beliefs to be no more than superstition. For many people, the dead body is not merely a cadaver, and its organs and tissues are not merely inert biological materials, devoid of cultural and spiritual significance. For all the scientific language, many transplant patients continue secretly to regard the living, functioning organ within them as a form of the continued life of the donor, as a strange intruder within their own bodies.

The progress of medicine always comes with a philosophical price, but whether for an individual that price is worth paying is not always straightforward. The maximisation of organ and tissue donation rates raises a wide range of social and ethical issues that need to be fully recognised and accepted in public debates. The new, complex set of social relationships that are established through the medium of cadaveric donation must take these concerns and misgivings into account, and avoid limiting their expression through the application of a panoply of euphemisms about the nature of death and the body, about harvesting of tissues, gifts or miracles. The issues discussed in the article by Bendorf et al. may well represent the tip of an iceberg of wishful thinking
driven by a paternalistic commitment to improve donation rates that has generated decades of public policy failure. If community uncertainty is not addressed, the rates will not improve. A fresh public debate about organ donation that searches out and respects people’s misgivings and fears is more likely to generate outcomes with which society will be comfortable.

References

REVIEW

Chest ultrasound in practice: a review of utility in the clinical setting

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Key words
ultrasonography, lung, pleura, chest tube, respiratory insufficiency.

Abstract
Clinician-performed chest ultrasound is rapidly entering clinical practice in the fields of intensive care, respiratory medicine and acute medicine. Ultrasound is clearly useful in the diagnosis and characterisation of pleural diseases. It is also critical in improving the safety of pleural interventions. More recently, attention has also focused on the use of lung ultrasound. While the normal aerated lung is not well imaged by ultrasound, lung pathology reaching the pleura often provides an ‘acoustic window’ for a number of lung conditions. Lung ultrasound is useful to diagnose pneumothorax, interstitial and alveolar lung abnormalities, and pleurally based lung masses. There is some evidence that integrating routine chest ultrasound into clinical practice has benefit in the emergency and intensive care settings. In the future, chest ultrasound is likely to become an essential physician skill, and training requirements are evolving in light of current developments.

Introduction
Interest in chest sonography by physicians has grown rapidly, informed by recent developments. First, it is now acknowledged that ultrasound guidance is critical for the safety of pleural interventions. Second, just as interventional specialists have acquired proficiency with endobronchial ultrasound, they have also become comfortable applying ultrasound from outside the thorax. Third, a range of portable and affordable equipment is now available. Finally, it is increasingly recognised that many thoracic pathologies are amenable to ultrasound diagnosis. In some instances, sonography is superior to other radiological investigations.

‘Chest ultrasound’ is a term that encompasses the sonographic examination of both pleura (pleural ultrasound) and lung (lung ultrasound). In this article, we review the practice of chest ultrasound performed by nonradiologist physicians when undertaken to improve the safety of pleural interventions and the accuracy of medical diagnoses.

Ultrasound basics
Ultrasound waves (typically between 2 and 8 MHz) are generated by passing an electrical current through piezoelectric crystals within an ultrasound transducer. The resulting waves may be reflected back to the ultrasound probe by objects located in its path. The time delay between the generation of the ultrasound signal and its detection indicates the distance of the object from the probe, whereas the intensity of the returning signal indicates the acoustic nature of the object.

The intensity of a reflected signal may be depicted on a monitor by the Amplitude of an image (A-mode) or the Brightness of a pixel (B-mode). If the distance of the object from the probe changes during scanning, this Motion may be depicted over time on a X-axis using M-mode ultrasound.

The way in which an ultrasound wave is reflected back to the transducer depends on how it interacts with body tissues. Reflection occurs when acoustic impedance suddenly changes at a tissue interface, such as between solid chest wall and aerated lung, or between the fluid of a pleural effusion and diaphragm. Such specular (mirror-like) reflection is depicted on the monitor by a high-intensity (hyperechoic) signal.

Scatter occurs within the heterogeneous texture of a solid organ, such as the liver. Only some of the scattered...
waves are reflected back to the transducer, weakening the signal intensity. Refraction occurs when a wave continues on through tissues with different acoustic impedances that change its direction. Attenuation occurs when waves are absorbed by body tissues, such as bone, and converted to heat, casting dark acoustic shadows distally. The Doppler effect describes the frequency shift of the wave when an object (usually blood) is travelling towards (upward shift) or away (downward shift) from the transducer.

**Normal lung**

To obtain optimal sonographic views of the thoracic contents, we suggest that two key manoeuvres are rotation of the scapulae and rotation of the ultrasound probe. First, the bony scapulae can be rotated upwards out of view by having the patient place one or both hands behind the head. However, this manoeuvre is often uncomfortable (and for some patients, unachievable) and may be omitted at the sonographer’s discretion. Second, the probe can be rotated diagonally until aligned longitudinally within an intercostal space, thereby avoiding the bony ribs. (An equally acceptable alternative is to use a microconvex probe with a footprint small enough to fit between rib spaces regardless of its orientation.)

It should be admitted that these technical comments reflect the authors’ personal bias rather than any universally accepted convention. There are in fact many differences among sonographers in terms of their preferred scanning position (erect vs supine), probe orientation (vertically/longitudinally or transversely rather than aligned along a rib space) and image depiction (some, as is our practice, present the hemidiaphragm on the right of the screen regardless of whether the left or right pleural cavity is scanned; others do not). Each individual practitioner or institution will need to thoughtfully standardise their own practice.

**Lung artefact**

A bright line of specular (mirror-like) reflection occurs at the pleural interface between solid chest wall and air-filled lung. The change in acoustic impedance between these two tissues is so great that almost all ultrasound energy is reflected with consequently little penetration into the lung itself. Any ultrasound waves that do penetrate the lung are then absorbed due to the unfavourable attenuation coefficient of air.

Because of these two factors, the on-screen depiction of structures deep to pleura is artefactual. The importance of this is that significant lung abnormalities that are not in direct contact with the pleura may be present in a patient, even though the screen of the monitor is filled by normal lung artefact.

Normal lung artefact is due to the characteristics of the pleural interface and comprises a diffuse ‘snowstorm’ appearance, with superimposed horizontal lines known as A-lines, or reverberation artefact (Fig. 1). These A-lines are due to ultrasound waves bouncing (reverberating) one or more times between the pleural interface and more superficial structures (such as skin) before returning to the probe. Thus, their distance below the pleural line is often a multiple of the distance between skin and pleura.

![Figure 1](image-url) Normal lung. (A) Ultrasound view transverse to ribs demonstrating rib shadows. (B) Ultrasound view longitudinal to a rib space demonstrating normal lung artefact deep to the chest wall. IC, intercostal.
**Lung sliding**

**Normal lung sliding**

‘Lung sliding’ refers to the cyclical movement of normal lung artefact with respiration. It could be argued that ‘pleural sliding’ may be a more accurate term because the finding actually represents movement of the normal visceral pleura.

**Loss of lung sliding**

Lung sliding may be abolished by breathhold, hyperinflation because of airways disease, pleural adhesions or pneumothorax. Conversely, the presence of lung sliding rules out a pneumothorax at that site.¹ A recent meta-analysis suggests a higher sensitivity and equivalent specificity of clinician-performed sonography for pneumothorax compared with plain chest radiography.² In the supine position, ultrasound is clearly superior to radiography.³ However, computed tomography (CT) is superior to ultrasound in the detection of pneumothorax and remains the gold standard for this condition, at least in the post-lung biopsy setting.⁴

There are two important caveats to the use of ultrasound for diagnosing pneumothorax. First, other conditions such as chronic obstructive pulmonary disease may mimic pneumothorax.⁵ Proceeding to chest-tube drainage on the basis of sonographic findings alone in such patients would obviously lead to serious adverse consequences. Second, ultrasound is unable to give information on the size of pneumothorax, only its presence or absence. Because treatment decisions are often linked to the size of pneumothorax, this is an obvious limitation to the utility of ultrasound in this setting.

Loss of lung sliding can be confirmed and recorded using M-mode sonography (Fig. 2). The normal dynamic artefact of lung sliding is represented by a granular appearance (‘sea-shore’ sign), whereas loss of lung sliding is represented by a screen of horizontal lines (‘bar-code’ sign).

In incomplete pneumothorax, ‘lung point’ refers to the sonographic transition between where lung sliding is present and where it is absent.⁶ Pathologically, this represents the location where lung that is adherent to parietal pleura begins to fall away into the thoracic cavity.

**Lung curtain**

This term refers to the edge of normal lung artefact visible at the costophrenic angles (Fig. 3). On inspiration, the descent of lung artefact transiently obscures deeper structures, such as liver, spleen and kidneys, reminiscent of a theatre curtain drawn shut to hide the stage behind it.

Lung curtain may be higher than expected with hemidiaphragm elevation, lower in patients with hyperinflation, paradoxical in hemidiaphragm paralysis, and altered or even absent in pleural effusion.

**Pleural ultrasound**

Sonography is extremely useful in the detection, quantification and characterisation of pleural fluid (Fig. 4). It is essential to the safety of pleural interventions, and this is probably its primary use for clinicians.
Diagnostic pleural ultrasound

Detection

Ultrasound has been used for the detection of pleural fluid since the 1960s. Compared with conventional radiography, ultrasound is more sensitive and specific for the presence of pleural fluid. This is particularly so in critically ill patients where the quality of chest radiography may be suboptimal. Clinicians may achieve a proficiency approaching that of radiologists in detecting pleural fluid. In one series of 960 ultrasound examinations, clinician-performed ultrasound was as accurate in detecting pleural fluid as procedures performed by radiologists.

Differentiation

On occasion, the differentiation of pleural effusion from pleural thickening may be difficult. In such circumstances, referral to a radiologist is the best course of action for most clinician sonographers. For the more experienced practitioner (such as one meeting ‘Level 2’ standards, see later under ‘implementing chest ultrasound’), two special manoeuvres may be useful in this situation. First, M-mode sonography can detect a cyclical change in the depth of a pleural effusion with respiration. The characteristic sinusoidal movement of visceral pleura seen on M-mode sonography supports a diagnosis of pleural effusion rather than pleural thickening, and this has been described as the ‘sinusoid sign’ (Fig. 4). Second, the presence of ‘fluid-colour’ on Doppler interrogation of a pleural effusion can also distinguish it from pleural thickening.

Quantification

The volume of pleural fluid may be estimated sonographically with the patient either supine or upright, and these estimations are superior to radiological estimation. Such calculations may be useful when deciding whether sufficient fluid is present to warrant drainage for dyspnoea (although there are obviously other clinical considerations that influence this decision). One simple formula is to multiply the lateral subpulmonic height of the effusion in centimetres (with the patient upright) by a factor of 90 to give an estimated volume in mL. This and other formulae are only applicable to free-flowing effusions (Fig. 5).

Characterisation

Effusions may be anechoic or echogenic (complex). In general, transudative effusions are always anechoic, whereas exudative effusions may have either appearance. Effusions may be free-flowing or exhibit septations or loculations (Fig. 6). In empyema, it is suggested that the presence of septa may predict a higher risk of failure of small-bore catheter drainage and possibly increased mortality, but more data are needed in this area.

In some cases, associated pleural thickening or nodules may be present (Fig. 7). In a region with a low incidence of tuberculosis, the presence of pleural thickening or nodularity is highly predictive of malignant pleural effusion.

Interventional pleural ultrasound

Pleurocentesis

Traditionally, clinicians have selected pleural puncture sites for thoracocentesis on the basis of radiology review.
and clinical examination. However, there is now convincing evidence to support the superiority of ultrasound localisation over clinical localisation.\textsuperscript{19} It is difficult (if not impossible) to differentiate dullness on percussion because of pleural fluid from dullness on percussion due to subdiaphragmatic organs, such as liver or spleen; the inability to make this crucial distinction may lead to solid organ puncture. In one study comparing the safety of site selection by clinical examination versus ultrasound, one-in-six puncture sites selected on the basis of clinical findings alone would have resulted in pneumothorax or solid organ puncture.\textsuperscript{19} Of note, clinicians who participated in this study were members of a respiratory department, and the seniority of the clinician did not influence the accuracy of puncture site selection.

There is also high-level evidence for improved clinical outcomes with ultrasound-guided pleurocentesis. A recent systematic review of over 8000 pleural aspirations calculated that the risk of pneumothorax from pleurocentesis is reduced by two-thirds when assisted by ultrasound localisation (odds ratio 0.3).\textsuperscript{20} On this basis, we would recommend ultrasound guidance as standard of care for pleurocentesis.

**Intercostal catheter placement**

Less objective data exist to support the use of ultrasound for chest-tube placement than is available for pleurocentesis. Instead, the argument for ultrasound localisation in this scenario is based more on the significant risks of this more complex procedure and the documented occurrences of incorrect anatomical tube placement in clinical practice.

Hazards of chest-tube insertion include inadvertent organ puncture and death. Chest tubes have been accidentally and unfortunately placed into every possible major thoracic and upper abdominal organ. In one survey, two-thirds of acute hospitals in the United Kingdom reported a serious adverse event because of chest-tube insertion in the preceding 5 years, and half of the events involved chest-tube insertion into the wrong anatomical location or on the wrong side.\textsuperscript{21} Although not conclusively proven, it is highly likely that the use of ultrasound to guide chest-tube placement for pleural effusions would dramatically reduce the risk of incorrect site selection. Accordingly, current guidelines now highly recommend the routine use of ultrasound for all chest tubes placed for pleural effusions.\textsuperscript{22} (It should be emphasised that the same recommendation does not apply to chest tubes placed for pneumothorax.)

While ultrasound use improves anatomical localisation for chest-tube placement, this in itself is insufficient to guarantee a safe outcome. Competence in ultrasound should not be equated with competence in chest-tube insertion. Rather, the complexity of chest-tube insertion also requires a high level of operator skill and an adequately supported environment. For example, there are as yet no data that ultrasound prevents intercostal artery laceration, which relates more to the site selection for entry and good technique. For optimal results, it is therefore essential that chest tubes are only inserted when clinically indicated, by experienced operators, in an appropriate environment and with relevant imaging including ultrasound guidance.\textsuperscript{22}

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**Figure 6** Loculated pleural effusion. ‘E’ indicates the loculated effusion with multiple septations (white arrows). This patient had a malignant pleural effusion. L, liver; M, mediastinum.

**Figure 7** Pleural nodule. ‘N’ indicates the 2.5-cm pleural nodule. In addition, the diaphragmatic pleura are diffusely thickened (‘T’). This patient had metastatic breast cancer. E, effusion; L, liver.
Clinic-performed sonography

At acute hospitals (where pleurocentesis and chest-tube insertion is most often performed), radiology services are sometimes unable to meet the demand for ultrasound site marking within the desired time frame. There has therefore been a move towards clinician-performed ultrasound for site localisation at the time of the pleural intervention. Ultrasound localisation at the time of the procedure also removes the risk that either patient movement or a significant delay between the time of localisation in radiology and the time of pleural intervention on the ward may render the marked site inaccurate.

In practice, the implementation of routine clinician-performed ultrasound (together with standardised procedural training) reduced the rate of pneumothorax because of pleurocentesis from 8% to 1% in the respiratory department of the Mayo Clinic. In another series, this time from Oxford, the major complication rate of more than 500 ultrasound-guided pleural interventions performed by respiratory physicians was 0.4%, comparable with that performed by radiologists. These studies demonstrate that nonradiologist physicians, when appropriately trained, can perform ultrasound-guided pleural procedures as safely as radiologist sonographers.

Lung ultrasound

Traditionally, chest ultrasound has focused mainly on pleural pathology. In more recent times, attention has also turned to lung pathology that may also be detected sonographically. European centres in particular have been pioneers in describing and delineating the utility of lung ultrasound.

Consolidation

The normal aerated lung is difficult to image because the dramatic change in acoustic impedance between chest wall and lung results in specular reflection of ultrasound waves at the pleura. However, consolidated lung has a tissue density and echo-texture similar to liver, analogous to pathological hepatisation. This removes the change in acoustic impedance at the pleural interface, and ultrasound waves pass directly into the affected lung (Fig. 8a,b). Within the consolidated area, hyperechoic (white) foci may be visible, again representing a change in acoustic impedance, but this time at the tissue interface between solid lung and air-filled bronchi. The distal margin of a consolidated area often displays an irregular serrated edge. In the emergency setting, ultrasound examination is often able to detect consolidation that is occult on conventional chest radiography.

Subpleural consolidation on ultrasound does not always indicate pneumonia. The differential diagnosis includes pulmonary masses and pulmonary infarction. In some instances, pulmonary masses may have a smoother distal edge (Fig. 8c,d). In this scenario, ultrasound is more accurate than CT in diagnosing chest wall invasion.

Pulmonary infarcts due to thromboembolism may also have a more regular appearance than true consolidation and may be wedge-shaped, rounded or quadrangular. Larger infarcts may have a serrated edge and a central hyperechoic focus (Fig. 8e,f). The sensitivity of chest ultrasound for pulmonary infarct due to thromboembolism is disputed. In some hands, chest ultrasound is reported to be 74% sensitive and 95% specific for pulmonary infarction. In other hands, the most common finding in the presence of pulmonary embolus was a normal lung ultrasound examination. The latter study took place in intensive care, and the difficulty of examining critically ill patients in the supine position may explain the lower sensitivity for pulmonary infarcts. At present, there is insufficient evidence to support the routine use of chest ultrasound for diagnosing pulmonary infarcts due to pulmonary embolus. The main consideration for the clinician is not to forget pulmonary infarct as a differential of sonographically detected consolidation.

Comets

Lung ultrasound is able to detect interstitial thickening due to a range of pathologies. The characteristic findings on sonography are vertical hyperechoic lines extending from pleura to the bottom of the screen known as ultrasound lung comets or B-lines (Fig. 9). Comets are artefacts formed by reflections of the ultrasound beam from thickened interlobular septa. In normal individuals, occasional comets may be visible posteriorly just above the diaphragm.

Diffuse comets may be caused by interstitial pulmonary oedema or pulmonary fibrosis. In a series of 250 patients in intensive care, the presence of comets had a sensitivity of 93% and a specificity of 93% for the interstitial syndrome (comprising acute respiratory distress syndrome), pulmonary oedema and interstitial lung disease). Focal comets may be present in patients with pneumonia or focal fibrotic processes.

Central venous pressure

While this examination is technically outside the chest, the jugular venous pulse is often of clinical relevance to the management of patients with lung pathology. The ability to determine the height of the jugular venous pulse has always been considered an important clinical skill.
Figure 8  Differential diagnosis of lung consolidation. Panels (A) and (B) show the corresponding ultrasound and computed tomography (CT) images of an area of pneumonic consolidation (‘C’). There is a central air bronchogram (white arrow) and an irregular distal edge (black arrow). Panels (C) and (D) show the corresponding ultrasound and CT images of a pleurally based mass (‘M’) invading chest wall. There is a central hyperechoic area suggestive of an air bronchogram (white arrow) and a smooth regular distal edge (black arrow). Panels (E) and (F) show the corresponding ultrasound and CT images of a pulmonary infarct (‘I’). There is a central hyperechoic area (white arrow) and an irregular distal edge (black arrow). On CT, the pulmonary infarct ‘I’ is distinguished from adjacent compressive atelectasis ‘A’ by the lack of contrast enhancement. Ax, axillary tissue; E, pleural effusion.
However, there are many instances when clinical examination may be difficult, such as the critically ill obese patient. In this setting, it has been shown that the internal jugular vein can be easily seen on ultrasound and the venous collapse point determined (Fig. 10). The height of the collapse point can then be measured above the sternal angle in exactly the same way as with clinical determination. A jugular venous pressure obtained by ultrasound has been shown to reflect accurately the jugular venous pressure obtained by clinical examination.34

Chest ultrasound in clinical practice

The current challenge to the clinician is no longer to determine the diagnostic accuracy of ultrasound for different thoracic pathologies; we have presented abundant data demonstrating excellent tests characteristics for different lung conditions. The major question now is whether and how chest ultrasound should be integrated into existing clinical pathways. An additional complication is that the role and usefulness of chest ultrasound may well differ depending on the clinical setting and what investigations have already been performed. In this section, evidence for the role of diagnostic chest ultrasound in different hospital settings will be reviewed.

Emergency departments

A recent study from Italy35 examined the use of chest ultrasound as a screening test in emergency patients presenting with dyspnoea. Four hundred and four consecutive patients presenting during shifts worked by the single sonographer author were included. The majority of the patients were subsequently admitted to hospital (84% to the wards, 5% to short-stay observation). The final diagnosis was not assessed. Rather, the concordance between screening ultrasound and screening chest radiography was calculated. Kappa values were greater than 0.7 for free pleural fluid, pulmonary oedema, consolidation, pulmonary fibrosis and pneumothorax. One hundred and fifty-seven patients had a normal ultrasound examination, and of these, 90% had normal chest radiographs.

The authors of this study conclude that chest sonography could replace radiography in the future as an initial screening test for dyspnoea in emergency patients. However, they acknowledge their study limitations of a single operator, the variable test characteristics depending on pathology and the lack of cost effectiveness data.

Intensive care

The utility of chest ultrasound has been explored in 260 consecutive patients admitted to intensive care with undifferentiated acute respiratory failure. The patients were examined in the semirecumbent (or in the 35 intubated patients, supine) position. Using a simple 3-minute chest protocol (with extension to lower limb venous examination when indicated), the ultrasound diagnosis was reported to be correct in 90% of cases.30 Diagnoses included pneumonia, airways disease, cardiogenic pulmonary oedema, pulmonary embolism and pneumothorax.

This study does present some limitations; the authors had excluded from analysis 16 patients with no final diagnosis, 16 patients with a combination of two or more diagnoses, and nine patients with rare diagnoses, such as interstitial lung disease, massive pleural effusion, fat embolism and tracheal stenosis. Interestingly, ARDS did

Figure 9 Lung ‘comets’. Lung comets, also known as ‘B lines’ (C) are indicative of an interstitial syndrome. This patient had extrinsic allergic alveolitis, but pulmonary oedema is a much more common aetiology.

Figure 10 Central venous pressure. The collapse point of the internal jugular venous pulse is clearly visible (white arrow). The vertical height of the jugular venous pressure can then be measured from this point relative to the sternal angle. ICA, internal carotid artery; IJV, internal jugular vein.
not seem to feature in this group (or else were not differentiated from cardiogenic pulmonary oedema), and there were no cases of diaphragm or pericardial pathology. It therefore appears as though the reported utility of ultrasound in this setting may be overstated.

A more recent study examined 42 mechanically ventilated patients who underwent chest radiography and chest ultrasound prior to a clinically scheduled chest CT, which was then referenced as the diagnostic gold standard. Compared with plain radiography, ultrasound had higher sensitivity and specificity for consolidation, interstitial syndrome, pleural effusion and pneumothorax, with a diagnostic accuracy exceeding 90% for all these conditions. These authors did not attempt to provide an aetiopathological diagnosis for the syndromic findings of consolidation and interstitial syndrome.

However, three-quarters of the patients had admission diagnoses of either sepsis or trauma so it may not be possible to apply these findings to other intensive care unit populations. The indication for chest CT was not described, and no pulmonary emboli were diagnosed in any of the patients.

The data thus far in intensive care practice therefore support the use of chest ultrasound as a useful adjunctive investigation for acute respiratory failure, with excellent test characteristics (when compared with plain chest radiography) for common causes of respiratory failure. In many cases, ultrasound may yield findings that render further radiology unnecessary, but it is unlikely that ultrasound will completely replace current radiological investigations.

In both the emergency and intensive care settings, it is likely that CT will remain the gold standard for complex lung pathology. Future studies should focus on determining which patients undergoing ultrasonography may safely have further testing by CT withheld.

Implementing chest ultrasound

For physicians to acquire and develop safe chest ultrasound skills, the mentorship of a local radiologist is absolutely essential. The Royal College of Radiologists in the United Kingdom recommend that physicians entering the field should acquire theoretical knowledge and attend a relevant thoracic ultrasound course, followed by the observation of 20 cases and the performance of 30 cases under the supervision of a radiologist. These are the stated requirements for ‘Level 1’ practice. (Practitioners may then work towards ‘Level 2’ requirements, which involve performing at least 100 examinations and a much greater depth and breadth of knowledge and practice.) Australasian entry-level recommendations are similar; the Australasian Society of Ultrasound in Medicine offers a certificate in pleural ultrasound requiring attendance at an accredited course, followed by 20 supervised examinations.

While clinicians interested in performing chest ultrasound should certainly obtain these entry-level qualifications, it should be noted that the guidelines are not based on evidence and do not in themselves guarantee competence. In fact, it is entirely possible that some clinicians may require significant extension to this training.

Even after competence is considered to be achieved, radiologist mentorship should continue for the purposes of continuing education, quality assurance and audit. Furthermore, the limitations of a nonradiologist in interpreting ambiguous images should be acknowledged and expert help sought whenever needed. Even experienced clinician sonographers refer difficult cases to radiologists in about 5% of cases.

Conclusion

Pleural ultrasound has a proven role in improving the safety of pleural procedures and should be offered as standard of care in this setting. Ultrasound also offers advantages over conventional radiography in the detection, quantification and characterisation of pleural effusions.

Lung ultrasound has excellent test characteristics for the diagnosis of consolidation, interstitial syndrome and elevated central venous pressure. Data are continuing to accumulate on how best to integrate lung ultrasound into clinical practice. When added to conventional investigations, there is some evidence for benefit in the emergency department and in the intensive care setting.

In the future, chest sonography is likely to be an essential skill for the physician, and training requirements are likely to evolve with advances in the field.

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Explaining failure through success: a critical analysis of reduction in road and stroke deaths as an explanation for Australia’s low deceased organ donation rates

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Key words
organ donation, public safety, brain death, traffic fatalities, stroke.

Abstract

Background/Aim: During the past two decades, Australian federal and state governments have funded many initiatives to bolster organ donation. Despite large investments of time, effort and money, Australia’s deceased donation rate is in the bottom half of the Organisation for Economic Co-operation and Development countries and has only marginally increased from 11.9 donors per million people (pmp) in 1990 to 14.9 donors pmp in 2011. An often-cited explanation for this situation is that Australia’s success in increasing levels of public health and safety through reduced traffic and stroke fatalities has reduced its number of potential deceased organ donors. We refer to this as the ‘Failure Because of Success’ hypothesis. Although commonly accepted, this hypothesis is largely untested.

Methods: By analysing data from international donation and transplantation organisations and international public health and safety organisations, we compared historical deceased organ donation rates with traffic and stroke fatality rates in Australia and the seven countries with the world’s highest deceased organ donation rates (Spain, Portugal, France, USA, Belgium, Austria and Italy).

Results: Traffic fatality rates across all countries in the study have fallen dramatically during the time period, with Spain having the lowest traffic fatality rates. Stroke fatality rates demonstrate similar reductions, with France showing the lowest cerebral vascular accident mortality rates.

Conclusion: When compared with countries with the world’s highest deceased donation rates, Australia’s improvements to public health and safety through reductions in traffic and stroke fatalities were neither unique nor exemplary and do not provide an adequate explanation for its low organ donor rates.

Introduction

Organ transplantation is a well-established treatment for many chronic diseases, with the potential to save lives and significantly improve the quality of life of severely ill people. Unfortunately, the demand for organs exceeds supply, and despite Australia’s excellent record in organ transplantation outcomes and Australian federal and state governments’ continued investment of substantial resources to improve donation rates, Australia’s deceased organ donation rate continues to languish in the bottom half of the Organisation for Economic Co-operation and Development (OECD) donor rankings (Fig. 1). While much discussion has centred on recent improvements to Australia’s organ donation rates, Australia’s 2010 deceased donor rate of 13.8 donors per million people (pmp) is less than one-half of (world-leading) Spain’s 2010 rate of 32 donors pmp (in 1989 both Australia and Spain had virtually identical deceased donor rates). Australia’s low donation rate is frequently explained by reference to its success in increasing levels
of public health and safety, which have directly reduced the number of potential organ donors.5–8

With the exception of a relatively small, but increasing number of patients who donate organs after cardiac death, virtually all solid organs for transplant in Australia are retrieved from brain dead donors.9 In Australia, the types of donor death are tracked and categorised into six broad categories (each with its own subcategories), which largely parallel the types of donor deaths tracked in many other OECD countries. These are: strokes (cerebral vascular accidents (CVA), road trauma (RT), non-road trauma, cerebral tumour, hypo/hyper anoxia and other (unspecified)).9–17 Of these, the majority of deceased donors are the victims of CVA and RT. (The percentage of these deaths is broadly similar across most OECD countries (Fig. 2a–c).

Over the past several decades, Australian RT fatalities have steadily fallen from 13.66 deaths per 100 000 population in 1990 to 6.8 in 200918 (Fig. 3). Rates of death from CVA in Australia have similarly declined from 61.2 per 100 000 population in 1990 to 35.2 in 200619 (Fig. 4). The fact that these significant reductions in death rates from RT and CVA have occurred parallel to a long period of stasis in Australian deceased organ donation rates has supported lay and professional claims that Australia’s failure to improve organ donation rates is due to success in saving people’s lives through improvements in public health and safety, thereby depleting our pool of potential organ donors.5–8 We refer to this notion as the ‘Failure Because of Success’ hypothesis.

The validity of this assumption has generally been accepted as self-evident and true despite the fact that the quantum of the impact of RT and CVA deaths on overall organ donation rates has not been fully examined. In this paper, we examine this argument by comparing the RT death, CVA death and deceased donation rates for seven leading donor countries with those from Australia.

Methods

Using published reports9–11,13,14 and data from the International Registry of Donation and Transplants complemented with unpublished data from several other sources,12,15–17 we analysed the annual deceased organ donation rates for 54 countries from 1990 through to 2009. We then extracted data for the seven leading donor countries, which were Spain, Portugal, France, USA, Belgium, Italy and Austria. For the purposes of this study, we define the term ‘leading donor countries’ as those countries whose deceased donor rates exceeded 20 donors per million population (pmp) for at least 5 of the 10 years between 2000 and 2009. These countries’ deceased donation rates were then compared with that of Australia for the same time period (Puerto Rico, which showed the greatest
Figure 2 (a) Percentage of donor death caused by road trauma fatalities.9–17 (b) Percentage of donor death caused by cerebral vascular accidents (CVA) fatalities.9–17 (c) Percentage of donor death caused by road trauma and CVA fatalities (combined).9–17

- Australia, Spain, Portugal, France, USA, Belgium, Austria, Italy.

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improvement in deceased donation rates of all the countries during the time period analysed is not included because we were unable to find reliable data on CVA and RT fatality rates for the period under study).

RT fatality rates from the International Road Traffic and Accident Database (IRTAD) for the leading donor countries and for Australia were then compared for the same time period (1990 through 2009). A RT fatality was defined as death where RT was the primary cause of the death, occurring within 30 days of a traffic accident.

Stroke (CVA) death data from OECD Health Statistics Database for the leading donor countries and Australia was also compared for the same time period. CVA deaths were defined as a death whose cause was listed as International Classification of Diseases codes (ICD 10) I60 through I69.

**Results**

**RT mortality**

Figure 3 shows that all eight countries had significant reductions in RT fatality rates from 1990 to 2009. During the past 20 years, the trend for RT fatality rates for the majority of the countries studied has essentially merged. Spain, at 5.9 fatalities per 100,000 population is the
lowest, with both Australia and France next at 6.8, followed closely by Italy, Austria and Portugal at 7.1, 7.6 and 7.9 respectively (Table 1). Australian RT fatality rates improved significantly during the past 20 years, and although it started from a lower (safer) base, its improvement lags significantly behind that of many other leading donor countries. Australia ranks sixth in terms of rate percentage reduction in RT mortality (50% reduction). The USA shows the smallest net reduction of RT fatality rates, dropping from 17.88 per 100 000 population in 1990 to 12.25 in 2008 (31% reduction). Spain and Portugal show the greatest improvement with each having reduced its RT fatality rate by more than 70%. Spain, Portugal and France’s performance in increasing road safety is particularly noteworthy given the dramatic increases in deceased donation rates that occurred in these countries during the same time period (see Fig. 5).

CVA mortality

All eight countries examined have achieved steep reductions in CVA fatality rates during the time period studied (see Fig. 4). While the incomplete datasets in the OECD database records make analysis of CVA fatality rates beyond the 2006 time period difficult, certain trends are evident. Portugal shows a surprisingly high CVA death rate – several times that of other countries (i.e. in 1990, Portugal’s CVA mortality rate was 204.7 per 100 000 population while that of Spain was 68.2, Australia’s was 68.2 and the USA was 47.4) (Table 2). Of the eight countries included in the analysis, as of 2004 (the latest year most countries reported), Australia ranks in the middle in CVA fatality rates with 40.2 CVA deaths per 100 000 population per year, while France, the USA and Austria show the lowest CVA fatality rates with 30.6, 35.7 and 40.1 respectively. Therefore, as is the case with RT fatalities, reductions in CVA fatalities do not appear to have compromised the leading donor countries’ ability to maintain, and in most cases, dramatically improve their organ donor rates.

Deceased organ donation rates

All countries, with the exception of Australia and Austria, demonstrated significant increases in their deceased organ donation rates during the study period (see Fig. 5). Italy showed the highest percentage rate improvement at more than 238% from 1993 to 2009. Spain, Portugal, France and the USA also showed dramatic increases to their deceased donation rates (Spain, from 17.8 in 1990 to 34.0 in 2009; Portugal from 15.0 in 1993 to 31.0 in 2009; France from 17.1 in 1993 to 24.2 in 2009 and the USA from 17.9 in 1992 to 24.0 in 2009) (Table 3). Overwhelmingly, these countries

Table 1 Road trauma fatalities by country 1990–2009 (deaths per 100 000 population)

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% Reduction from 1990 to 2009 level

†At time of publication, Belgium had not reported its 2009 road trauma fatality rate to the International Road Traffic and Accident Database. This number represents its 2008 rate.
demonstrated steady, progressive improvement in rates of deceased organ donation throughout the study period.

With the exception of the 13.2% decrease observed in Austrian donations during the study period, the sustained and significant increases in donation rates in all other leading donor countries are independent of the steady and notable improvements (reductions) observed in their RT and stroke fatality levels.

**Discussion**

Whether measured in relative or absolute terms, Australia’s performance in increasing levels of public health and safety through achieving significant reductions in RT and CVA deaths is neither unique nor exemplary when compared with the improvements seen in many of the leading donor countries analysed in this study. Importantly, most of the world’s highest-performing donor

**Table 2** Cerebral vascular accidents fatalities by country 1990–2008

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<tr>
<th>Year</th>
<th>Australia</th>
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<td>% Reduction from 1990 to last year reported</td>
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International Classification of Diseases codes I60–I69, deaths per 100 000 population, age standardised.
countries have succeeded in improving public safety and reducing mortality from cerebrovascular disease while concurrently increasing their deceased organ donor rates. With one exception (Austria), their achievements demonstrate that success in improving public health and reducing both RT and CVA deaths does not necessarily compromise success in substantially raising deceased organ donation rates. Success in improving public safety through reducing RT and CVA deaths does not, therefore, adequately appear to explain failure to achieve improvements in organ donation rates. Success in improving public safety through reducing RT and CVA deaths does not, therefore, adequately appear to explain failure to achieve improvements in organ donation rates. (It is theoretically possible, of course, that management of CVA and RT in Australia differs from other leading donor countries and that neurological outcomes, including a diagnosis of brain death, in such circumstances, are also different. However, there are no data to suggest that this is true, and even if it were, the impact on donation rates would be minimal at best.)

This raises a series of troubling questions. The first is, how could a ‘failure because of success’ hypothesis, such as we have described have gained such political, medical and lay traction and been so widely adopted as factually correct without being subjected to rigorous examination? The second is whether there is, or has been, a ‘cost’ to our donor rates through uncritical acceptance both of this hypothesis and the idea that Australia is somehow ‘different’ to other western democracies in terms of improvements made to public health and safety.

While Australia’s achievements in improving levels of public health and safety are laudable, and, as some evidence in both Spain and the UK demonstrates, might have shrunk the potential donor pool by reducing the overall number of Australians who would potentially become brain dead, very recent evidence from Spain shows that this shrinkage in the potential donor pool can be more than compensated for through implementation of hospital-wide donor best practice recommendations and through the development of systemic approaches to organ donation that include, but are not limited to, the identification and management of donors in hospitals. The fact that many leading donor countries have been successful at improving deceased donation rates, while at the same time achieving impressive improvements in public health and safety, suggests that improvements in public health and safety are not a sufficient explanation for Australia’s low organ donor rates. Indeed, the success of these countries in achieving both improvement in public health and safety and high deceased organ donation rates suggests that they have been able to ‘do more with less’.

We believe that continued acceptance of this failure because of success hypothesis prevents Australia from acknowledging that success in increasing public health and safety is not incompatible with success in achieving high organ donation rates. We hope that by demonstrating that simultaneous improvements to both public safety and organ donation is not only possible, but

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% Increase from first reported donation rate

<5.0  91.0  108.7  41.5  34.0  18.9  <13.1  238.1
common among the world’s leading donor countries, we can shift Australia’s attention on to evidence-based explanations for why Australia continues to have such a low supply of organs for transplantation and away from this convenient mythology.

Acknowledgements
The authors wish to express their sincere thanks and gratitude to the International Traffic Safety Data and Analysis Group, the EuroTransplant Foundation, the Société Belge de Transplantation, the Centro Nazionale Trapianti, the Organización Nacional de Trasplantes, the Autoridade para os Serviços de Sangue e da Transplantação and ShareLife Australia for their generous assistance and support.

References
4 de Lago M. Organ donors and transplantations decrease in Spain, the leading country in both. *BMJ* 2011; 342: 242.
Congenital heart disease-associated pulmonary arterial hypertension: preliminary results from a novel registry

M. L. Rose,1,2 G. Strange,3,6 I. King,1,2 S. Arnup,2,4 S. Vidmar,2,4 C. O’Donnell,9 F. Kermeen,8 L. Grigg,5 R. G. Weintraub1,2 and D. S. Celermajer6,7

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Key words
congenital heart disease, pulmonary arterial hypertension, Eisenmenger syndrome, registry.

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Abstract
Background/Aims: Pulmonary arterial hypertension (PAH) frequently accompanies childhood congenital heart disease (CHD) and may persist into adult life. The advent of specific PAH therapies for PAH prompted formation of a national Australian and New Zealand registry in 2010 to document the incidence, demographics, presentation and outcomes for these patients.

Methods: This multicentre, prospective, web-based registry enrols patients with CHD-associated PAH being followed in a tertiary centre. The inclusion criteria stipulated patient age ≥16 years, a measured mean pulmonary arterial pressure >25 mmHg at rest or echocardiographical evidence of PAH or a diagnosis of Eisenmenger syndrome, and followed since 1 January 2000. A single observer collected standardised data during a series of site visits.

Results: Of the first 50 patients enrolled, 30 (60%) were female. The mean age (standard deviation (SD)) at the time of PAH diagnosis or confirmation in an adult centre was 27.23 (10.07) years, and 32 (64%) patients are currently aged >30 years. Fourteen (28%) patients were in World Health Organization Functional Class II and 36 (72%) in Class III at the time of diagnosis. Forty-seven of 50 (94%) had congenital systemic-pulmonary shunts, and 36 (72%) never underwent intervention. Thirteen (26%) had Down syndrome. Confirmation of PAH by recent cardiac catheterisation was available in 30 (60%) subjects. During follow up, a total of 32 (64%) patients received a PAH-specific therapy.

Conclusions: CHD associated with PAH in adult life has resulted in a new population with unique needs. This registry will allow documentation of clinical course and long-term outcomes for these patients.

Introduction
In Australia, the approximate number of adults living with congenital heart disease (CHD) has been estimated at 40 000, and now exceeds the number of children and adolescents with CHD. This number is consistent with epidemiological observations from a national European CHD registry. This number continues to expand, as does the complexity of CHD patients surviving to adult life. As medical management and surgical techniques continue to advance, children previously deemed unsuitable for cardiac surgery are undergoing corrective and palliative procedures. As a result, an increasing population of children with CHD is surviving into adulthood, many of whom will require further medical or surgical management for residual or progressive complications.

Early epidemiological studies of CHD suggested low incidences of about four to five cases per 1000 live births; however, this figure included only the most severe cases referred to specialist referral centres in the USA in an era where paediatricians’ CHD expertise was relatively basic, rigorous diagnostic testing was underutilised and surgical intervention was less sophisticated. Since then, estimates of the incidence of CHD has progressively increased with currently reported incidences of 12–14 cases per 1000

On behalf of the Australian and New Zealand Adult Congenital Heart Disease Pulmonary Arterial Hypertension Registry.
Funding: Actelion Australia Pty Ltd provided financial sponsorship for this registry. They had no role in the study design, data collection and analysis, manuscript preparation, or manuscript review.
Conflict of interest: None.
live births, or higher, reported. In approximately 6% of adults with congenital heart defects, pulmonary arterial hypertension (PAH) develops, the most extreme example being Eisenmenger syndrome (ES). CHD has emerged to be one of the commonest associated causes of PAH. A diagnosis of PAH in adults with CHD is associated with more than twofold higher risk for all cause mortality and a threefold higher rate of health service utilisation, compared with CHD without PAH.

The advent of targeted therapies that influence the key pathogenic pathways involved in PAH has given rise to new therapeutic considerations for patients previously not deemed suitable for such management, such as adults with CHD-associated PAH. Arteriolar vasoconstriction and vascular remodelling represent the therapeutic targets of currently available medications that include endothelin receptor antagonists, prostanoids and phosphodiesterase inhibitors.

In 2010, a dedicated Australian and New Zealand registry for adults with CHD and PAH was established. The aims of the registry include the following:
1. To describe the prevalence of CHD associated with PAH, as seen in specialist adult CHD (ACHD) centres,
2. To describe the demographics of adults with CHD and coexisting PAH,
3. To understand management patterns and treatment responses to conventional and PAH-targeted therapies, and
4. To describe survival and to develop prognostic variables that may permit risk stratification and early identification of those who are at greatest risk of a poor outcome.

We report on the features of the registry and on the first 50 patients entered into the registry.

### Materials and methods

The registry seeks to enrol cases of CHD associated with PAH in subjects aged at least 16 years at time of visit in a specialist centre and who have been seen in a specialist centre at least once since 1 January 2000. This includes subjects who were initially diagnosed prior to that date, as well as subjects who were referred or diagnosed since 1 January 2000. Potential study subjects were identified through ACHD and PAH tertiary referral centres through the lead clinician at each site using existing local databases. Additional cases were recruited by sending a flier to all cardiologists on the mailing list of the Cardiac Society of Australia and New Zealand. Human Ethics approval was obtained from all participating centres.

For the purpose of the registry, PAH has been defined as a mean pulmonary artery pressure of >25 mmHg and a pulmonary artery wedge or left atrial pressure <15 mmHg diagnosed on the basis of cardiac catheterisation. For those patients without a diagnostic cardiac catheter, a combination of clinical and echocardiographical criteria has been utilised (e.g. a patient with ES who has an unrepaired septal defect).

Standardised data fields collected from identified cases are shown in Table 1. Data entry was undertaken by a single experienced investigator (GS) during a series of site visits to each participating centre. The information entered includes both retrospective data and the data obtained during prospective follow up.

PAH classification was entered according to the Venice Classification (2003), which was the most recent iteration at the time the registry was constructed. The study protocol imposes no requirement for participants to undergo any procedures or therapies beyond normal

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**Table 1** Summary of data collected for study

- Date of birth, year of congenital heart disease (CHD) diagnosis, date of first symptom onset of pulmonary arterial hypertension (PAH), year of first definite diagnosis of PAH and date of confirmation of PAH in adult centre (usually time of first visit)
- Classification of PAH, World Health Organization (WHO) functional class (FC) and symptoms (exercise intolerance, syncope, congestive heart failure, cyanosis) at presentation
- Details of underlying diagnosis and interventions performed
- Predisposing factors (separate from underlying diagnosis)
- Results of baseline diagnostic investigations, including abdominal ultrasound, nuclear lung ventilation/perfusion scan, pulmonary function tests, sleep study, computer tomography scanning, pathology testing including connective tissue and other serology
- Echocardiographical data: right ventricular (RV) size, wall thickness and ejection fraction indexed to body surface area, and estimated RV systolic pressure
- 6-min walk test (6MWT), oxygen saturations and Borg score
- Cardiac catheterisation data: baseline right atrial mean, pulmonary arterial (PA) mean, PA wedge, cardiac output, pulmonary vascular resistance and vasoreactivity testing
- Drug therapy, including date commenced, dose and duration of therapy
- Clinical reviews, including WHO FC status, symptoms, echocardiographical, 6MWT and chest X-ray data
- Tracking of unplanned hospitalisations relevant to PAH and CHD
- Status/outcome (alive/dead/transplantation)
patient care. It is anticipated that follow-up data on all subjects will exceed a minimum of 2 years.

The data collected for this study are summarised in (Table 1).

All data are collected through web-based technology with multilayered encrypted security on to a centralised registry database. The registry is an easily accessible system with registered users entering data from the participating adult hospitals.

The project has been operational since early 2010, with data entry and collection at this stage occurring from tertiary centres in Australia. Data input from each centre is through the Internet, and the database is accessed only by medical and nursing staff intimately involved in the care and management of adults diagnosed with CHD and PAH. Data entry is password-protected and can be entered at regular intervals or retrospectively as desired with the database administrator tracking data entry. Tracking of patient status through clinical review and associated testing has generally been entered on a six monthly to annual basis, as available.

At the time of writing, the registry has currently enrolled approximately 150 individuals, mainly from New South Wales, Victoria and Queensland since April 2010. This recruitment figure is expected to rise steadily in 2011, as more centres receive ethics approval and enrol patients with follow-up data. It is anticipated that more than 200 adults with CHD and PAH will be entered by the end of 2011.

The investigators ensure consistency of diagnosis, organise follow up for patients without recent follow-up data and will solicit cases from general practitioners, adult physicians and transplant centres around Australia to actively promote population-based data. The team will also search and collect autopsy data from computerised coronial data compiled by the Australian Bureau of Statistics. Following up patients for the registry requires a committed and collaborative approach from both the treating physicians and staff entering data.

Data analysis

Data is summarised using descriptive statistics. All data are reviewed and cleaned at three monthly intervals using STATA version 11.0 (Stata Corp., College Station, TX, USA) under the supervision of an experienced epidemiological statistician. Percentages, and means or medians are used to summarise categorical and continuous variables respectively.

Results

Following data entry on the first 50 cases, minor additions to the database fields and the mechanisms for reporting were made after a team consensus. With further refinements, more subjects continue to be entered, highlighting the complexity of this registry. Some of these complexities relate to entering data on patients who carried a diagnosis of PAH forward, from childhood to adult life (and a new adult care centre).

The following is an interim review of data from the first 50 patients entered.

During the early data entry phase, five hospitals in Eastern Australia entered the first 50 patients, as represented in (Fig. 1).

Current age distribution at 1 January 2011

The age of the 50 patients on the registry at January 2011 is represented in Figure 2, showing almost half of the subjects aged 30–39 years of age. Otherwise, the age groupings are relatively evenly distributed.

Table 2 shows the demographic details of the first 50 subjects.

Utilisation of medical therapies

At latest follow up, a total of 32 of the 50 patients (64%) was receiving a PAH-specific therapy, including an endothelin receptor antagonist in 32 and/or a phosphodiesterase type 5 inhibitor in five; five were receiving combination (two or more) PAH-specific therapies. Anticoagulants were being used in five (10%) and diuretics in seven (14%) patients.

Discussion

We report on the set-up of an ACHD and PAH registry together with data on the first 50 patients entered. Traditionally, management of ACHD and PAH have operated
as two quite specific entities, CHD predominantly managed by cardiologists and PAH often by respiratory physicians. Current guidelines recommend a multi-disciplinary team approach to CHD management.\textsuperscript{11}

The coexistence of new targeted therapies and advancing surgical interventions for CHD raises some important clinical issues.\textsuperscript{10} Some individuals ‘labelled’ as having relatively fixed physiology related to CHD and associated PAH, and those with no other therapeutic options available may now require re-evaluation for optimal management.

We have begun to characterise a population of patients that has few reports in the literature. The advent of specialist combined CHD/PAH clinics in some tertiary centres has arisen in part because of the seemingly increasing but poorly defined patient numbers of adults with CHD and PAH. With improved survival in this population, increasing therapeutic options and the number of adolescents transitioning to adult centres, the demand for such specialist clinics will likely continue to increase.

Patient registries such as ours are therefore becoming increasingly significant, as CHD and PAH affect young people with a poorly defined natural history. In the current era in which PAH targeted therapies are becoming more accessible to a broader spectrum of patients, understanding the population is more important than previously thought. Examination of retrospective data to explore the possible underutilisation of potentially beneficial therapies in patients with CHD and associated PAH, alongside the more conventional therapies, may change therapeutic practices and promote consistency between centres. The authors of a recent review of registries within Australia concluded by saying, ‘clinical registries provide the most credible information about quality of care’.\textsuperscript{12} Real-world outcomes for adults with PAH being treated with Bosentan have recently been described from an Australian registry.\textsuperscript{13}

The construction of a registry for adults with CHD and PAH was difficult in part because of the complexity of the underlying CHD lesions involved. Data pertaining to individual dates of CHD diagnosis and dates of first PAH diagnoses some decades earlier and the methods utilised for such diagnoses were diverse. Furthermore, sourcing data from individuals managed in the community for many years is problematic, and therefore, only the information in records from their referral centre could be utilised during data collection. So far, the data entry has been performed by a single person, potentially reducing variability in interpretation of patient data and maximising consistency.

Furthermore, management issues surrounding transition and access to medical care, treatment of arrhythmias, heart failure, reoperation/intervention, pregnancy and contraception, psychosocial/neuropsychological, and insurance concerns are all relevant to adults with CHD and PAH. Transition appears to be a critical period in the management of young adults with associated poorer outcomes if unsuccessfully transitioned to an ACHD centre. In our early data, we expose a mean adult centre date of PAH confirmation of 27 years, exposing a possible interval of some 10 years lost in transition from paediatric to adult specialty care. With improved survival and increasing complexity of CHD patients surviving into adulthood,
seamless transition into specialised ACHD clinics appears to be an emerging critical issue. A more comprehensive understanding of the current profile of this patient group will support appropriate transition programmes by identifying the resources and infrastructure necessary to link dedicated ACHD clinics from paediatric facilities.

Healthcare providers need to understand prevalence and natural history to plan for effective services provision. Epidemiological data representative of PAH associated with CHD are limited and at times underrepresented in PAH registries, highlighting the demand for further research to understand prevalence and natural history. This in turn should promote consensus among treating centres, facilitate planning of patient services and ultimately optimise management of this complex group of individuals.

General agreement exists that registries comprise a significant foundation in housing data that contribute in investigating less common medical conditions. However, data on long-term outcome are scarce because of the lack of large, national registries that operate over a period of years.

Examples of international PAH registries include the French PAH registry,14 the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management,13 and the Scottish morbidity and mortality registry on PAH.16 In PAH registries, the relative proportion of patients with PAH and CHD appears to be rather variable. These registries, in particular, highlight the need for rigorous registries to extrapolate more precise estimates of prevalence of PAH associated with CHD. For example, all hospitalisations for PAH in the Scottish population were examined to determine the epidemiological features of PAH. These data were compared with expert data from the Scottish Pulmonary Vascular Unit revealing almost half the rate of CHD-associated PAH between these two populations and a 12-fold difference from that of the French registry.15

The Belgian ES registry17 was a national project to ‘optimise patient care and to provide epidemiological information regarding PAH and CHD in Belgium’. Similarly, this web-based registry housed data on demographics details, clinical, technical and therapeutic strategies. Ninety-one individuals with ES were identified and enrolled, with an estimated prevalence of 11 per million inhabitants. These data are similar to that found within the Scottish hospitalisation records, but clearly, if the reported numbers of adults with CHD and the proportion of those surviving is increasing, this may underrepresent the true burden of this disease. Almost half of the study subjects were classified with Down syndrome who had worse functional capacity; significantly fewer such patients, however, were treated with PAH-specific therapies. A registry of this patient population will go some way in improving possible differences in care.

The Euro Heart Survey, on ACHD, is a retrospective, multicentre study describing a European cohort of almost 1900 adults with CHD receiving treatment at referral centres in which 531 (27%) of patients suffered from PAH and 231 cases had typical ES.18

In Australia, there is a paucity of research performed in this group of patients with ACHD-related PAH. Hence, our ability to identify and track such individuals and to extrapolate any data about this unique patient group has been inadequate.

Until now, there has not been a dedicated registry for adults with CHD and PAH in Australia or New Zealand. This registry is the first of its kind to be established and implemented here, and should ultimately provide a unique platform for collaborative research and an interdisciplinary forum among participating tertiary and secondary institutions. Furthermore, evidence-based protocols and standardisation of care across this vast country is likely to be enhanced by establishment of a comprehensive national registry.

Limitations

As is the case with most registries, important selection bias is acknowledged. It is challenging to obtain a true population-based registry, including cases from rural and community areas across Australia. With this considered, most cases at this interim phase have been selected through the tertiary ACHD centres along the east coast of Australia. At the time of writing, enrolment from each Australian States and New Zealand is being planned.

Conclusions

The establishment of a CHD and PAH registry for adults will offer a variety of information for healthcare providers, researchers and healthcare agencies. The registry aims to provide current and accurate information about adults living with CHD and PAH in Australia and New Zealand, promoting standardisation and consensus on the approach in managing this expanding and challenging group. An ongoing focus of the registry will be to provide a pool of patients for relevant clinical research and genetic studies. The ultimate goal of this registry is to improve patient care and service provision for this very complex and unique cohort of individuals.
References

Hepatitis B status in migrants and refugees: increasing health burden in Western Australia


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Key words
chronic hepatitis B, migrant, refugee, viral factor, Western Australia.

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Abstract

Background: In light of increasing migration from endemic countries with chronic hepatitis B (CHB), this study describes the changing epidemiology of CHB patients born outside Australia referred to a tertiary hospital in Western Australia. It aims to stratify risk and progression to cirrhosis and hepatocellular carcinoma according to viral factors and to provide an indication of the growing burden of disease and current and future treatment costs.

Methods: Demographic, serological and biochemical data were obtained from patients with CHB between July 2002 and December 2008. Hepatitis B virus DNA quantification was performed to assess baseline viral loads in the patients. Total cost estimates for surveillance and treatment are based on probabilities of the population anticipated to be at a given stage of the disease in a given year.

Results: There is a progressive increase in referrals (n = 478) with the majority coming from Asia (57%) and Africa (35%). The mean age of Africans is 11 years less than that of Asians, with a lower proportion of Africans having hepatitis B virus DNA > 2000 IU/mL compared with Asians (36.7% vs 54.3%). Approximately 50% of CHB patients referred are at risk of cirrhosis and hepatocellular carcinoma unless treated. Without treatment, a substantial increase in cost over 10 years (from $401 460 to $2 027 078) is estimated at 400%.

Conclusion: This study highlights the increasing burden of CHB in Western Australia, from people born in endemic countries, in particular, the direct costs of treatment. It will help to develop strategies that can be tailored to Western Australia with appropriate allocation of resources.

Introduction

Chronic hepatitis B (CHB) is an important public-health problem in Australia with increasing migration from endemic areas. In Australia, approximately 90 000 to 160 000 people are infected with CHB. Seventy-five percent of those infected with CHB are Asians, with people born in China and Vietnam making up about half of all the cases of CHB. Although there is increasing migration to Western Australia (WA) from countries where hepatitis B virus (HBV) infection is endemic, there are limited data on the epidemiological characteristics of CHB patients in WA.

People with CHB are at risk of developing liver-related morbidity, including cirrhosis, liver failure and liver cancer. People with chronic HBV infection have a 10-fold to 100-fold greater risk than those not infected of developing primary liver cancer (hepatocellular carcinoma or HCC), which is the fifth most common cancer and the third most common cause of cancer-related mortality worldwide. A screening strategy for liver cancer that takes into account the level of viral load has been suggested by the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study, which showed that an elevated serum HBV DNA level of >10^6 copies/mL (2000 IU/mL) is a strong predictor of liver cancer risk, independent of any other markers of activity, such as hepatitis B e-antigen (HBeAg), alanine aminotransferase (ALT) and cirrhosis. HBV DNA > 10^6 copies/mL (2000 IU/mL) is also associated with disease progression to cirrhosis.

Early detection of HBV through screening and treatment has the potential to reduce the incidence of liver-related morbidities. Migrants or refugees who are found to have hepatitis B infection offshore are given a health undertaking which requests that they contact the Department of Immigration and Citizenship after arrival.
in Australia. However, this process is not mandatory. The current surveillance guidelines recommend six monthly ultrasound and α-fetoprotein levels in all Asian males above the age of 40 years, and in Africans, above the age of 20 years.9 In Australia, there are two major therapeutic options for treatment, pegylated interferon-α (PEG-IFN-α) for a period of 12 months or oral nucleoside (or nucleotide) analogues of an indefinite period. Under the usual treatment protocols in Australia for CHB, many persons with HBV who meet the criteria of an elevated ALT and active viral replication (positive HBV DNA) are treated with nucleoside/nucleotide analogues, such as entecavir. Given the numbers of people with HBV in WA and the age profile, the cost effectiveness of different types of treatment is an important consideration for health policy and planning.10

The aims of this study were to determine the epidemiology of CHB patients born outside Australia referred between July 2002 and December 2008 to the Liver Service at Royal Perth Hospital (RPH) and to stratify risk with progression to cirrhosis and HCC according to viral factors. Using data collected on CHB patients, we provide an indication of the cost of surveillance and treatment for the CHB patients both at the current time and in 10 years.

Methods

Epidemiological data and viral factors

All patients born outside Australia with hepatitis B surface antigen (HBsAg) between July 2002 and December 2008 were included. Other coexisting liver diseases, including other viral infections were excluded by standard clinical, laboratory, imaging and histological studies. Patients with delta infection were not excluded as HBsAg-positive patients were not tested for delta infection routinely. Demographic data, including age, gender, country of origin and migrant status for those with CHB were obtained and entered into a database. All laboratory tests were performed at PathWest Laboratory Medicine, WA. Serological testing for HBsAg was used to identify patients with hepatitis B. Patient sera were tested for HBsAg, core antibody and surface antibody by COBAS Core II system (Boeringer Mannheim/Hoffmann la Roche, Pleasanton, CA, USA). Of those that were HBsAg positive, the HBeAg and antibody to e-antigen were tested. Liver function tests, including ALT, were obtained for each patient. ALT level of 40 U/L was chosen as the upper limit of normal in this study. Tests for HBV DNA were performed using the COBAS AmpliPrep/COBAS TaqMan HBV Test (version 2.0). Viral loads were expressed as IU/mL.

During the period July 2002 to December 2008, 468 consecutive patients born outside Australia with positive HBsAg were referred to and attended the Liver Service. Of the total, 33% were refugees, and 67% were non refugees. Sixty-five % of the refugees came from Africa. A refugee is someone who ‘owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group, or political opinion, is outside the country of his nationality’ and enters Australia on a humanitarian visa.11 This paper uses the epidemiological data of the two largest groups from the total population sample: East Asians, numbering 266 and Africans, numbering 166.

Cost analysis

There are two costs associated with management of the condition: treatment and surveillance. We use a Markov model of HBV infection disease progression to assess the clinical and economic consequences of alternative HBV treatment in the East Asian and African populations. In order to assign costs to stages of the progression of the disease, five cost components were identified. These were outpatient visits, outpatient pathology, outpatient imaging, drugs and inpatient procedures.12 The sources of the data were the Medicare Benefits Schedule (a list of rebates for services obtained under Medicare, Australia’s public-health insurance scheme), the Pharmaceutical Benefits Scheme and the Diagnosis Related Groups (DRG) cost report for Western Australian public hospitals.13 The costs applied to the numbers in the sample population at any given time are the actual direct costs of treatment. Indirect costs of travel time, lost production for both patients and carers were not included.

Results

Descriptive epidemiology

There has been a progressive rise in referrals to the Liver Service at RPH from nine in 2002 to 187 in 2008. Table 1 and Figure 1 show the referrals to Liver Service at RPH between the years 2003 and 2008. Out of the 468
patients, the majority (57%) came from East Asia, with 28% from Vietnam and 11% from Burma. Thirty-five per cent were from Africa, with 21% born in Sudan (Table 1). The 468 patients comprised 278 males and 190 females. The mean age was 38 years and the range was 14 to 89 years. Figure 2 shows the age range of the referrals from 2003 to 2008.

Viral factors

The mean age of the Africans was 11 years less than that of the Asians. The proportion of the East Asians with an elevated ALT level and HBV DNA > 2000 IU/mL was higher than that for the Africans. Of the Africans, 36.7% had HBV DNA > 2000 IU/mL compared with 54.3% of the Asians. Of the East Asians and the Africans, 24.8% and 16.9% were HBeAg positive respectively.

On multivariate analysis, after adjusting for age, gender and refugee status, Africans were less likely to have viral load >2000 IU/mL in comparison with South-East (SE) Asians (P < 0.05; odds ratio (OR) 0.315). Similarly, Africans were less likely to have ALT < 40 (P < 0.05; OR 0.480). Females were less likely to have an ALT > 40 (P < 0.05; OR 0.480), SE Asians had an increased ALT compared with the African females (OR 5.4).

Of the East Asians, 42.5% had elevated ALT > 40 and positive HBV DNA compared with 28.3% of the Africans. Out of the 468, 77 had undergone liver biopsy, with six of them found to have a fibrosis score of 4 (cirrhosis), and 38 were found to have significant fibrosis (F2–F4). Patients underwent liver biopsies if ALT is elevated in the presence of positive HBV DNA or radiological evidence of cirrhosis in the absence of coagulopathy, and hence, the estimate of cirrhosis is not accurate.

Numbers and cost of treating cohort now and in 10 years

The size and characteristics of the populations were based on the data in Table 2. The Markov model (Fig. 3) is a version of the model developed by Hutton et al. and Kanwal et al. The Markov model accounts for the dynamics and complexities of the progression of the

*Table 2 Identification of patients at high risk of complications and eligible for treatment: Asians and Africans*

<table>
<thead>
<tr>
<th></th>
<th>East Asian (n = 266)</th>
<th>African (n = 166)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean and standard deviation)</td>
<td>41 ± 14</td>
<td>30 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>HBeAg positive</td>
<td>24.8% (66/266)</td>
<td>16.9% (28/166)</td>
<td>NS</td>
</tr>
<tr>
<td>HBV DNA &gt; 2000 IU/mL</td>
<td>54.3% (138/254)</td>
<td>36.7% (58/158)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>ALT &gt; 40 U/L</td>
<td>41.4% (110/266)</td>
<td>27.7% (46/166)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>ALT† &gt; 40 U/L &amp; presence of HBV DNA</td>
<td>42.5% (113/266)†</td>
<td>28.3% (47/166)§</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

†Patients with elevated alanine aminotransferase (ALT) and positive hepatitis B virus (HBV) DNA are eligible for treatment under S100. §29.9% with HBV DNA > 2000 IU/mL. ¶14.6% with HBV DNA > 2000 IU/mL. HBeAg, hepatitis B e-antigen; NS, not significant.
disease from HBV to cirrhosis to liver cancer and death. The rates at which progression occurs are taken from a number of published studies conducted in various countries over different time periods (Table 3). As a result, there is a range of probabilities that can be applied to the progression of the disease through its various stages.

In the analysis later, we assume the transition rates from one stage of the disease to another are the same for all ethnic groups, as rates for different ethnic groups were not available in the published studies. These transition probabilities assume that drug therapies were not used for treatment. The transition probabilities would change with the use of drug therapies by slowing down the progression of the disease by enabling seroconversion in some patients.

The estimated number of persons who were and will be at various stages in 2010 and 2020 are based on the initial numbers in the Asian and African populations from Table 2 with the transition probabilities applied to these numbers from Table 3. A healthcare funder perspective was taken, and all future costs and health outcomes were discounted at 5% per annum, as is conventional in the literature.16 The estimated numbers are shown in Table 4. The total cost estimates (Table 5) are based on the numbers (or probabilities) of the population anticipated to be at a given stage of the disease in a given year multiplied by the direct cost of the treatment. As the DRG costs are taken from the Western Australian DRG reports, they include oncosts to account for hospital costs that are not directly related to treatment, such as administration, laundry and other ‘hotel’ costs.

The results in Table 4 show that costs increase by 400% over 10 years, from $0.4 to $2 million. This number is conservative, given that it is based on the size of the cohort in Table 2 and does not include the addition of new cases. Moreover, the cost does not include the administration of entecavir and/or interferon. The costs of drug therapies are considerable. Interferon, for example, costs approximately $22 651 per year per person (Table 5), but if successfully applied, does slow down the progression of the disease.

**Discussion**

The expanding Asia–Pacific- and African-born population settling in Australia with chronic HBV is projected to produce increasing HBV-related HCC cases through 2020. The evidence that suppression of HBV replication could
limit disease progression needs to inform the development of a public-health response. This study clearly demonstrates that between 2002 and 2008, there is an increase in referrals of foreign-born patients with HBV to the Liver Service at RPH. In another study, three-quarters of the 2617 refugees entering WA between January 2003 to December 2004 came from Africa.\textsuperscript{17} Hepatitis B carrier state was seen in 6.4\% of sub-Saharan Africans, 6.5\% of SE Asians and 6.8\% of North Africans, compared with a 2004 population-based study estimate of hepatitis B carriage in the Australian population of 0.87\%.\textsuperscript{18} Those with high viral load (HBV DNA > 2000 IU/mL) are at high risk of developing cirrhosis and HCC and require monitoring and treatment. In our study, about 50\% of patients are at risk of cirrhosis and HCC unless treated. A significantly lower proportion of Africans had HBV DNA > 2000 IU/mL compared with SE Asians (36.7\% vs 54.3\%). In our cohort, the mean age of Africans was 30 years. Indeed, the American Association for

<table>
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<tr>
<th>Table 4</th>
<th>Estimated treatment costs by stage of progression without drug therapy</th>
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<tbody>
<tr>
<td></td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>Annual unit cost per person ($)</td>
</tr>
<tr>
<td>Surveillance</td>
<td>1790</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>13 685</td>
</tr>
<tr>
<td>Liver failure</td>
<td>90 000</td>
</tr>
<tr>
<td>HCC</td>
<td>13 700</td>
</tr>
<tr>
<td>Total</td>
<td>401 460</td>
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</table>

2020 prices are equal to 2010 prices adjusted by 2.5\% per year. Annual unit costs of liver failure and hepatocellular carcinoma (HCC) are based on annual costs of treatment from Access Economics.\textsuperscript{16} The cost of liver failure includes an estimate for liver transplant on the assumption that 50\% of cases receive transplantation. The HCC total cost per annum is similar to that used by Butler et al.,\textsuperscript{12} table 20. Direct costs of compensated cirrhosis include surveillance.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Estimated treatment costs by type (2010 prices)</th>
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<tbody>
<tr>
<td>Type of treatment</td>
<td>Details</td>
</tr>
<tr>
<td>Outpatient pathology</td>
<td>HBeAg and anti-HBe (4 × pa)</td>
</tr>
<tr>
<td></td>
<td>liver function test (ALT) (4 × pa)</td>
</tr>
<tr>
<td></td>
<td>HBV DNA (4 × pa)</td>
</tr>
<tr>
<td>Outpatient imaging</td>
<td>Ultrasound and α-fetoprotein per year</td>
</tr>
<tr>
<td>Surveillance</td>
<td>—</td>
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<tr>
<td>Drug therapy and associated outpatient visits</td>
<td>Entecavir per year§</td>
</tr>
<tr>
<td></td>
<td>Specialist consultation (4 × pa)</td>
</tr>
<tr>
<td>Total (entecavir)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Interferon per complete treatment</td>
</tr>
<tr>
<td></td>
<td>Specialist consultation (8 × pa)</td>
</tr>
<tr>
<td></td>
<td>Nurse consultation (8 × pa)</td>
</tr>
<tr>
<td>Total (PEG-IFN)</td>
<td>—</td>
</tr>
<tr>
<td>Inpatient costs</td>
<td>Compensated cirrhosis</td>
</tr>
<tr>
<td></td>
<td>With co-morbidities</td>
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<tr>
<td></td>
<td>Without co-morbidities</td>
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<tr>
<td>Liver failure</td>
<td>Total average costs per DRG episode:</td>
</tr>
<tr>
<td></td>
<td>With co-morbidities</td>
</tr>
<tr>
<td></td>
<td>Without co-morbidities</td>
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</tbody>
</table>

†Total costs = direct costs plus of overheads estimated as 20\% of total. Overhead of 20\% is based on the range of overheads in DRG report.\textsuperscript{15} §Tenofovir is an alternative drug therapy to entecavir, which is not listed separately here as it is of similar effectiveness and cost to entecavir. ALT, alanine aminotransferase; AUD, Australian dollar; DRG, Diagnosis Related Groups; HBe, antibodies to HBe antigen; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; MBS, Medicare Benefits Schedule; NA, not applicable; pa, per annum; PBS, Pharmaceutical Benefits Scheme; PEG-IFN, pegylated interferon; —, not available.
the Study of Liver Diseases has recommended commencing HCC surveillance at the age of 20 years for Africans, while in Asian males, at the age of 40 years. The reported host and viral risk factors associated with increased rates of cirrhosis and HCC include the presence of HBeAg, older age (longer duration of infection), increased ALT level, diabetes mellitus, co-infection with the hepatitis delta virus, carcinogens, such as aflatoxin, HBV genotypes (C, D, F) and core promoter mutation (prevalence of the T1762/A1764 mutation in the basal core promoter region increases with the progression of liver disease, and this mutation is significantly associated with the development of HCC in both genotypes B and C).19–22

If the higher risk of HCC in Africans could be stratified by genotype or mutations in hepatitis B, then the age at which monitoring for HCC may be modified in the future. This would then lead to a role for genotyping for hepatitis B in clinical practice. Genotypes A and D occur frequently in Africa, whereas B and C are prevalent in Asia. One study from India suggests that genotype D may predict the occurrence of HCC in young HBV carriers. Indeed, further studies on risk factors, including genotypes are required to explain the higher incidence of HCC independent of viral load in African patients.

Entecavir and tenofovir are the preferred first-line therapeutic options for oral therapy, with adefovir as add-on therapy for patients with lamivudine resistance. In 2010, entecavir cost $384.30 per month, and many patients remain on it indefinitely. The alternative treatment is PEG-IFN, which costs $25 000 for 48 weeks. The compliance with the interferon therapy is more difficult due to the unpleasant side-effects of the treatment. The costs associated with the drug therapies are detailed in Table 5. Of those eligible for drug therapy, approximately 10% use interferon.

A smaller proportion is HBeAg positive (24.8% East Asians and 16.9% Africans), which means that the higher proportion of HBeAg-negative people will require indefinite entecavir treatment. The administration of either entecavir (including equivalent drugs) or PEG-IFN impacts on the progression of CHB to cirrhosis, liver failure and HCC as per the Markov model in Figure 3. It should be noted that entecavir has an HBeAg seroconversion rate after 4 years of 19.5%. The seroconversion rate of PEG-IFN after 4 years has been shown to be 25%. This means that approximately 20% of those who qualify for drug therapy after 4 years will no longer require treatment, if they are HBeAg positive. The remaining 80% who do not have seroconversion will progress to more advanced stages of the disease with higher associated costs of treatment (as per Table 5). The impact of the drugs is to offer the individual a chance of acquiring an immune response to the disease or slower progression.

Several studies have been carried out overseas on the cost effectiveness of entecavir in the treatment of HBV patients. Entecavir has been found to be a cost-effective therapy in studies based in Poland, Sweden, Spain, Hong Kong, China and the United States.15–21 The Polish study uses some of the data from the REVEAL-HBV study, which is a Taiwanese-based study of the largest natural history cohort study in patients with CHB.24 The authors of the Polish study concluded that administration of entecavir results in a substantial decrease in CHB-related complications, leading to reduced costs and an increase in life years and quality-adjusted life years (QALYs).

The results in Table 4 show that cost increases by 400% over 10 years, from $0.4 to $2 million. These estimates are based on the size of the cohort from 2008 (from Table 2), which remains relatively static over the 10 years. There are reductions in the size of the cohort, associated with deaths, but there are no increases that would be associated with ongoing migration and an increasing incidence in the refugee and migrant community within Australia.

The costs over the 10 years do not include costs of drug therapies but do include costs of regular surveillance by a specialist team. Robotin et al., in their study of Asian-born populations in Australia, estimate higher costs associated with targeted pharmacological management of patients at highest risk but also a more favourable cost-effectiveness ratio per QALY gained compared with the current practice of surveillance alone.16

The transition rates for cost estimations in Table 4 assume that the progression through the disease is the same for both ethnic groups. Changes in practices and procedures between now and 2020 may have an impact on the cost estimation, which may be either cost decreasing or cost increasing. As much of the innovation in medical practice tends to be cost increasing, we conclude that the cost estimation in Table 4 is quite conservative.

The economic burden of HBV infection is considerable because of the high morbidity and mortality costs associated with the progression of the infection to cirrhosis and liver cancer or subsequent need for transplantation. In the case of the refugee and migrant community in WA, the indirect burden of lost work days and productivity and costs imposed on family members and support networks is likely to be considerable as the refugee and migrant population with the disease is relatively young. Data to analyse the indirect burden are lacking or of poor quality, and few studies estimating the indirect costs have been undertaken.25 In a 1997 South Korean study, the total annual cost was estimated to be US$959.7 million, with 13.2% of the total attributable to prevention, 20.9% of the total indicating the cost imposed on society indirectly and the remaining 65.9% was the direct costs.26
One of the main limitations of this study is that it only addresses people with CHB born outside Australia and does not include indigenous and other high-risk groups already residing in WA.

Conclusions

With increases in referrals from foreign-born patients with CHB, this study gives us important information for engaging high-risk groups. Approximately 50% of CHB patients referred are at risk of cirrhosis and HCC unless treated. Further studies on risk factors as well as routine genotyping in clinical practice are required to explain the higher incidence of HCC in African patients. This study gives an indication of the increasing economic burden of CHB patients, especially the direct burden of treatment. Without treatment, there is likely to be a substantial increase in costs associated with the infection over the next 10 years.

References

8 Bloeje IH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; 130: 678–86.
Dialysis in public and private hospitals in Queensland
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Key words
dialysis, hospital, private, public, Queensland.

Abstract
Background: Clinical outcomes for patients treated in public and private hospitals may be different.
Aim: The aim of the study was to compare the characteristics and outcomes of patients receiving dialysis at public and private hospitals in Queensland.
Methods: Incident adult dialysis patients in Queensland registered with the Australia and New Zealand Dialysis and Transplant Registry between 1999 and 2009 were classified by dialysis modality at either a public or private hospital. Outcomes were dialysis patient characteristics and survival.
Results: Three thousand, three hundred and ten patients commenced dialysis in public hospitals, 1939 haemodialysis (HD) and 1371 peritoneal dialysis (PD). Seven hundred and ninety-three patients commenced dialysis in private hospitals, 757 HD and 36 PD. Compared with public HD, private HD patients were older, had more coronary artery disease and less diabetes, and were more likely to live in an urban area. Public HD patients were more likely to be obese and referred late to a nephrologist. Nearly all indigenous patients were managed in public hospitals. Private patients were more likely to have an arteriovenous fistula or graft at first HD ($P < 0.001$) but not after excluding late referrals ($P = 0.09$). Public hospitals provided longer HD sessions and more HD hours per week for all age groups except 75+ years. Compared with public hospital HD, patient survival adjusted for multiple variables was comparable for private hospital HD (hazard ratio 1.20 (95% confidence interval 0.98–1.46, $P = 0.07$)) but worse for public PD (hazard ratio 1.14 (95% confidence interval 1.05–1.24, $P = 0.002$)).
Conclusion: Private HD patients are older and less likely to be diabetic than public patients. Patient survival is worse for public PD than public HD.

Introduction
The Australian Health Care System is broadly divided into a public hospital sector funded by government and a private hospital sector funded by individuals, mainly through health insurance. While there are many similarities between the systems, there are also differences. Comparison of the two systems was recently completed by the Australian Government Productivity Commission.1

There have been some publications comparing clinical outcomes for patients treated in public and private hospitals. Rates of obstetric interventions are lower in public hospitals,2 but perineal injury and newborn outcomes are better in private hospitals.3 Survival from colorectal cancer is better for patients in the private sector.3 Public hospital patients are less likely to have coronary angiography or revascularisation following acute myocardial infarction.1 There are no publications comparing dialysis in public and private hospitals in Australia.

Dialysis is provided in both sectors of the health system and comprises 34.82% of same day admissions in the public sector and 8.29% in the private sector.1 However, unlike public hospitals that generally provide all modalities of dialysis including home-based therapies, such as home haemodialysis (HHD) and peritoneal dialysis (PD), the private sector mainly provides facility-based haemodialysis (HD). In the past, a small number of patients was funded by the Department of Veteran’s Affairs for PD in private hospitals. Funding is different between sectors with public facilities generally having a set budget or some form of activity-based funding, whereas private facilities are reimbursed on a per-treatment basis. The aim of this study was to compare public and private hospital dialysis patient characteristics and survival outcomes.

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Methods
The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) collect data on all patients receiving renal replacement therapy in Australia and New Zealand. This study included all adult patients registered with ANZDATA who commenced dialysis in Queensland between 1 January 1999 and 31 December 2009. Data on the treating hospital and treating nephrologist were used to categorise patients as undergoing dialysis at a public or private hospital. Patients were classified by dialysis modality at day 90 of treatment as hospital or satellite HD (ICHD), HHD, or PD (including continuous ambulatory PD and automated PD).

Patient characteristics at commencement of dialysis among the ICHD and PD groups in the public and private setting were compared. Comparisons were made using the chi-squared or Fisher’s exact test, as appropriate, for categorical variables and the median test for continuous, non-normally distributed variables. The frequency of comorbid conditions among these groups was compared using logistic regression, including adjustment for age. Patient survival was compared using Cox regression analysis, including adjustment for age, gender, body mass index, smoking status, late referral, coronary artery disease, diabetes, lung disease, cerebrovascular disease, peripheral vascular disease, primary renal disease, indigenous status and remote area index. Proportional hazards assumptions were checked by Schoenfeld residuals and scaled Schoenfeld residuals examined by formal hypothesis test and graphically. At the end of the study period, patient measures of dialysis effectiveness, and frequency and length of dialysis periods were compared among the ICHD, HHD and PD groups in the public and private setting. All analysis was carried out using Stata 11.0 (StataCorp, College Station, TX, USA). This study has been approved by a human research ethics committee.

Results

Baseline characteristics
During the study period, 3310 patients commenced dialysis in public hospitals and 793 in private hospitals. Treatment at commencement of dialysis occurred at 14 public HD centres, 8 private HD centres, 13 public PD centres and 6 private PD centres. Of the public hospital patients at day 90 of treatment, 1939 were on ICHD, 1371 PD and 0 HHD (no patients were recorded as being established on HHD by day 90 of treatment and are included in the ICHD numbers). Of the private hospital patients at day 90 of treatment, 757 were on ICHD and 36 PD.

Patient characteristics at commencement of dialysis are shown in Table 1. Public patients were younger, less likely to have coronary artery disease or a functioning arteriovenous fistula (AVF)/graft at commencement of HD, but more likely to be of indigenous background, and be a current smoker. Public hospital patients were more likely to have diabetes. Obesity was most prevalent among the public HD group. Estimated glomerular filtration rate (eGFR) was lower at dialysis start in public patients. Patients living in outer regional or remote/very remote regions of Queensland were nearly all treated in public hospitals, reflecting the absence of private dialysis facilities in these areas. The majority of private patients lived in a major city or inner regional area, corresponding to Brisbane or the Gold Coast.

Table 2 shows the primary renal disease for public and private hospital patients. Public patients were more likely to have diabetes and glomerulonephritis but less likely to have a vascular cause for end-stage kidney disease (ESKD).

Table 3 shows characteristics for patients on dialysis and alive at the end of the study period. Haemoglobin, phosphate and calcium phosphate products were not different among groups. Serum calcium was lower in public HD and PD but not HHD compared with private HD. Most patients having ICHD in either system undertook HD thrice weekly or less, whereas public HHD patients undertook more frequent dialysis. Table 4 shows total weekly HD hours by age group at study end. Public hospitals provided longer HD sessions for all age groups, except 75+ years (data not shown), and more HD hours per week for all age groups, except 75+ years. HHD patients mainly had 15 or more hours/week of HD.

Patient survival
There were 1716 deaths during the study period, including 737 public HD patients, 386 private HD, 569 public PD and 24 private PD. Cause of death was different between groups (Table 5), with withdrawal from treatment being most prevalent among the private HD group. Cardiac causes were more common among the PD groups. Compared with public HD, unadjusted survival was worse in private HD with a hazard ratio of 1.57 (95% confidence interval (CI) 1.33–1.85, \( P < 0.001 \)) and private PD with a hazard ratio of 1.58 (95% CI 1.33–1.89, \( P < 0.001 \)) but not significantly different in public PD with hazard ratio 1.14 (95% CI 0.98–1.32, \( P = 0.08 \))

After adjusting for confounders, compared with public HD, the hazard ratio for death in private HD was 1.20 (95% CI 0.98–1.46, \( P = 0.074 \)), public PD 1.14 (95% CI 1.05–1.24, \( P = 0.002 \)) and private PD 0.96 (95% CI 0.78–
1.19, $P = 0.73$). Adjusted survival is shown in Figure 1. The power for detecting the observed difference between public HD and private HD was 68%. When looking at HD only, and including vascular access at first HD and HD hours/week in the Cox regression analysis, the hazard ratio for private HD was 1.16 (95% CI 0.94–1.43, $P = 0.18$) compared with public HD.

**Discussion**

This study has shown that public HD patients have better survival outcomes than public PD patients in Queensland. Private HD patients have very different characteristics to public HD and a trend towards poorer survival.

Why was survival for patients on public PD worse than public HD? Randomised trials comparing HD and PD have lacked statistical power, suffered poor recruitment or been pilot studies to test the feasibility of a large trial. Several observational studies have been published, usually based on large databases. Bloembergen et al. looked at the United States Renal Data System and found PD associated with a 19% higher all-cause mortality rate than HD. Our data show a high rate of diabetes in public hospital patients. Survival on PD has been reported to be

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Public HD</th>
<th>Private HD</th>
<th>Public PD</th>
<th>Private PD</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1939</td>
<td>757</td>
<td>1371</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>59.9</td>
<td>60.6</td>
<td>53.5</td>
<td>66.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years) at first dialysis (median ± IQR)</td>
<td>60.2 (48.5–71.4)</td>
<td>74.8 (63.4–80.9)</td>
<td>60.6 (47.1–70.6)</td>
<td>78.0 (67.8–81.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indigenous (%)</td>
<td>20.5</td>
<td>0.5</td>
<td>16.6</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>3.3%</td>
<td>3.6%</td>
<td>5.7%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal (18.5–24.9)</td>
<td>34.5%</td>
<td>39.6%</td>
<td>37.9%</td>
<td>27.8%</td>
<td></td>
</tr>
<tr>
<td>Overweight (25–29.9)</td>
<td>29.8%</td>
<td>33.6%</td>
<td>31.5%</td>
<td>50.0%</td>
<td></td>
</tr>
<tr>
<td>Obese (30+)</td>
<td>32.4%</td>
<td>23.3%</td>
<td>24.9%</td>
<td>22.2%</td>
<td></td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>13.9</td>
<td>4.6</td>
<td>13.1</td>
<td>5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Region (RAI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major city</td>
<td>49.1%</td>
<td>86.0%</td>
<td>53.1%</td>
<td>83.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inner regional</td>
<td>24.6%</td>
<td>13.2%</td>
<td>16.1%</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Outer regional</td>
<td>22.0%</td>
<td>0.7%</td>
<td>23.7%</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Remote/very remote</td>
<td>4.3%</td>
<td>0.1%</td>
<td>7.2%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease (%)</td>
<td>14.8%</td>
<td>15.6%</td>
<td>13.4%</td>
<td>30.6%</td>
<td>0.021</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>39.9%</td>
<td>49.3%</td>
<td>34.1%</td>
<td>55.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease (%)</td>
<td>13.7%</td>
<td>15.2%</td>
<td>12.1%</td>
<td>22.2%</td>
<td>0.089</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>27.2%</td>
<td>30.5%</td>
<td>22.2%</td>
<td>19.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>44.8%</td>
<td>27.9%</td>
<td>38.0%</td>
<td>33.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late referral (%)</td>
<td>29.9</td>
<td>22.3%</td>
<td>22.0%</td>
<td>16.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR at start ml/min (median ± IQR)</td>
<td>6.8 (5.0–9.2)</td>
<td>8.4 (6.3–11.4)</td>
<td>7.0 (5.2–9.3)</td>
<td>7.3 (5.0–9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AVF/AVG at first HD (%)</td>
<td>39.2</td>
<td>49.1%</td>
<td>—</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AVF/AVG at first HD – late referral excluded (%)</td>
<td>51.6</td>
<td>56.7%</td>
<td>—</td>
<td>—</td>
<td>0.087</td>
</tr>
</tbody>
</table>

AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; eGFR, estimated glomerular filtration rate; HD, haemodialysis; IQR, interquartile range; PD, peritoneal dialysis; RAI, remote area index; —, not applicable to PD.

<table>
<thead>
<tr>
<th>Primary renal disease</th>
<th>Public HD</th>
<th>Private HD</th>
<th>Public PD</th>
<th>Private PD</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>n = 1939</td>
<td>n = 757</td>
<td>n = 1371</td>
<td>n = 36</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>20.5%</td>
<td>18.2%</td>
<td>22.8%</td>
<td>8.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vascular</td>
<td>12.3%</td>
<td>21.1%</td>
<td>12.3%</td>
<td>27.8%</td>
<td></td>
</tr>
<tr>
<td>Cystic</td>
<td>6.8%</td>
<td>6.6%</td>
<td>7.4%</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>5.1%</td>
<td>3.4%</td>
<td>5.5%</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>33.1%</td>
<td>17.2%</td>
<td>29.1%</td>
<td>19.4%</td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td>7.8%</td>
<td>12.8%</td>
<td>9.1%</td>
<td>16.7%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14.3%</td>
<td>20.6%</td>
<td>13.9%</td>
<td>13.9%</td>
<td></td>
</tr>
</tbody>
</table>

HD, haemodialysis; PD, peritoneal dialysis.

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worse than HD for patients with diabetes. An analysis of ANZDATA examined survival based on dialysis modality at day 90 of treatment but also with an ‘as treated’ analysis. The authors found that PD treatment may be advantageous initially but may be associated with higher mortality than HD after 1 year. PD was not separated into continuous ambulatory PD and automated PD for this study, as no differences in outcome have been found between these modalities.

Potential advantages of home dialysis (PD and HHD) for patients include quality of life, flexible dialysis times and control of disease state. For healthcare providers, increasing PD rates has been shown to reduce dialysis costs. A recent change to funding dialysis in Queensland public hospitals introduces a home dialysis target with penalties for not achieving the 50% benchmark. Australia has a high rate of home dialysis by international standards, with more patients being treated with PD than HHD. Efforts to increase home dialysis may lead to limitation of patient choice, increased PD uptake by patients who are better suited to ICHD or leaving patients on PD longer than appropriate, changes that may result in increased adverse PD outcomes. Improved home dialysis support services may facilitate achieving higher PD and HHD uptake. Nephrologists need to be aware of the survival differences shown in

### Table 3 Patient characteristics at 31/12/2009 (alive and receiving dialysis)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Public HD</th>
<th>Public HHD</th>
<th>Private HD</th>
<th>Public PD</th>
<th>Private PD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>851</td>
<td>154</td>
<td>263</td>
<td>338</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/L) (median ± IQR)</td>
<td>115 (106–124)</td>
<td>116 (110–126)</td>
<td>117 (110–123)</td>
<td>114 (103–122)</td>
<td>114</td>
<td>0.109</td>
</tr>
<tr>
<td>Ferritin (mcg/L) (median ± IQR)</td>
<td>397 (208–663)</td>
<td>308 (131–569)</td>
<td>420 (174–655)</td>
<td>240 (123–472)</td>
<td>1978</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transferrin saturation (%) (median ± IQR)</td>
<td>24 (17–33)</td>
<td>23 (16–29)</td>
<td>27 (21–36)</td>
<td>23 (18–31)</td>
<td>18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mmol/L) (median ± IQR)</td>
<td>2.23 (2.11–2.35)</td>
<td>2.34 (2.21–2.42)</td>
<td>2.33 (2.21–2.48)</td>
<td>2.24 (2.12–2.36)</td>
<td>1.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phosphate (mmol/L) (median ± IQR)</td>
<td>1.60 (1.28–2.00)</td>
<td>1.63 (1.27–2.00)</td>
<td>1.58 (1.27–1.90)</td>
<td>1.63 (1.39–1.98)</td>
<td>1.1</td>
<td>0.199</td>
</tr>
<tr>
<td>Calcium phosphate product (mmol²/L²)</td>
<td>3.58 (2.84–4.41)</td>
<td>3.80 (2.89–4.60)</td>
<td>3.68 (2.88–4.45)</td>
<td>3.73 (3.02–4.46)</td>
<td>1.2</td>
<td>0.173</td>
</tr>
<tr>
<td>URR &gt;70%</td>
<td>69.3%</td>
<td>62.2%</td>
<td>73.2%</td>
<td>—</td>
<td>—</td>
<td>0.153</td>
</tr>
<tr>
<td>HD ≤3×/week (%)</td>
<td>97.8</td>
<td>30.5</td>
<td>97.0</td>
<td>—</td>
<td>—</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Note: Because of small numbers in private PD, only the median value is recorded. HD, haemodialysis; HHD, home haemodialysis; IQR, interquartile range; PD, peritoneal dialysis; URR, urea reduction ratio; —, not applicable to PD.

### Table 4 HD hours/week by age group (alive and on HD at 31/12/09)

<table>
<thead>
<tr>
<th>Age group</th>
<th>HD hours/week Public HD (n = 851)</th>
<th>Public HHD (n = 154)</th>
<th>Private HD (n = 263)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>&lt;12</td>
<td>6.6%</td>
<td>0.7%</td>
<td>20.2%</td>
</tr>
<tr>
<td></td>
<td>12–13.4</td>
<td>29.5%</td>
<td>4.6%</td>
<td>50.2%</td>
</tr>
<tr>
<td></td>
<td>13.5–14.9</td>
<td>18.7%</td>
<td>5.2%</td>
<td>14.8%</td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>45.2%</td>
<td>89.6%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Age &lt;55</td>
<td>&lt;12</td>
<td>2.0%</td>
<td>0</td>
<td>27.3%</td>
</tr>
<tr>
<td></td>
<td>12–13.4</td>
<td>21.1%</td>
<td>1.1%</td>
<td>45.5%</td>
</tr>
<tr>
<td></td>
<td>13.5–14.9</td>
<td>14.2%</td>
<td>5.3%</td>
<td>4.6%</td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>62.7%</td>
<td>93.7%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Age 55–64</td>
<td>&lt;12</td>
<td>6.2%</td>
<td>0</td>
<td>11.8%</td>
</tr>
<tr>
<td></td>
<td>12–13.4</td>
<td>23.9%</td>
<td>7.3%</td>
<td>52.9%</td>
</tr>
<tr>
<td></td>
<td>13.5–14.9</td>
<td>22.1%</td>
<td>5.0%</td>
<td>17.7%</td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>47.8%</td>
<td>87.5%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Age 65–74</td>
<td>&lt;12</td>
<td>8.3%</td>
<td>5.9%</td>
<td>26.3%</td>
</tr>
<tr>
<td></td>
<td>12–13.4</td>
<td>36.1%</td>
<td>11.8%</td>
<td>40.8%</td>
</tr>
<tr>
<td></td>
<td>13.5–14.9</td>
<td>22.2%</td>
<td>5.9%</td>
<td>15.8%</td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>33.5%</td>
<td>76.5%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Age 75+</td>
<td>&lt;12</td>
<td>15.6%</td>
<td>0</td>
<td>17.6%</td>
</tr>
<tr>
<td></td>
<td>12–13.4</td>
<td>49.2%</td>
<td>50.0%</td>
<td>55.7%</td>
</tr>
<tr>
<td></td>
<td>13.5–14.9</td>
<td>18.0%</td>
<td>0</td>
<td>15.3%</td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>17.2%</td>
<td>50.0%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

HD, haemodialysis; HHD, home haemodialysis.
this study and direct efforts in identifying and rectifying possible causes.

Private HD patients were older than public patients. Private health insurance for hospital treatment covered 40.1–42.6% of the Queensland population between 2000 and 2009 inclusive. Examining private health insurance rates by age reveals that in those over age 45, the lowest private health insurance rate was in the 75+ group, the group most likely to have private HD. Therefore, private insurance status does not explain the age difference between public and private HD. This study has no data on how many patients treated in public hospitals were covered by private health insurance. It is possible that younger patients with private health insurance were diverted to public hospitals for HHD or PD (private health funds do not cover home dialysis therapies).

Diabetes was less common in private HD. This study cannot explain this finding, but it is possible that patients with longstanding chronic disease have been under the care of public hospitals for many years before commencement of dialysis, or may have become financially less well-off and forfeited membership of private health funds. Indigenous patients were underrepresented in private HD, reflecting the poor socioeconomic status of this group and the absence of private HD in regional and remote Queensland. Private HD patients were more likely to die as a result of withdrawal from dialysis than public HD patients. This was associated with patient age, as cause of death and dialysis withdrawal rates in patients aged 75+ were not different among groups.

There was a trend towards poorer survival for private HD compared with public HD. The public hospitals provided more hours of HD per week, except among the 75+ year old group. Dialysis Outcomes and Practice Patterns Study data have shown improved survival for HD of >240 min each treatment, with a 7% lower relative risk of mortality for every 30 min extra session length. However, the Hemodialysis (HEMO) study did not show improved survival with a larger delivered dialysis dose, although the time on dialysis only increased from 190 to 219 min each session. The reason for the shorter dialysis hours in private hospitals is unknown. Queensland Health, which manages the public hospitals, developed a Collaborative for Health Improvement from 2004 to 2007. This Collaborative allowed benchmarking of clinical key-performance indicators throughout the public hospital dialysis facilities and may have improved standards of care and possibly outcomes. A subanalysis of the HD data alone shows a reduction in the relative risk of private HD compared with public HD when including vascular access at first dialysis and dialysis hours per week in the multivariable model.

Whether the different methods of remuneration in public and private hospitals contribute to treatment differences is unknown. In private hospitals, health funds pay a set price per HD session to the hospital and medical staff are remunerated a fee for service. This structure may impact dialysis session duration, frequency, eGFR at dialysis start or commencing dialysis in patients with a perceived poor prognosis. While medical staff report that financial considerations are not among the main reasons

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Public HD</th>
<th>Private HD</th>
<th>Public PD</th>
<th>Private PD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>n = 737</td>
<td>n = 386</td>
<td>n = 569</td>
<td>n = 24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac</td>
<td>34.9%</td>
<td>32.9%</td>
<td>39.5%</td>
<td>41.7%</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>8.7%</td>
<td>7.3%</td>
<td>9.1%</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>6.0%</td>
<td>7.3%</td>
<td>5.5%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>12.2%</td>
<td>6.2%</td>
<td>13.4%</td>
<td>12.5%</td>
<td></td>
</tr>
<tr>
<td>Withdrawal</td>
<td>33.5%</td>
<td>43.5%</td>
<td>26.0%</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4.8%</td>
<td>2.9%</td>
<td>6.5%</td>
<td>4.2%</td>
<td></td>
</tr>
</tbody>
</table>

HD, haemodialysis; PD, peritoneal dialysis.
for directing patients to a dialysis modality, the literature suggests that financial remuneration is the most important non-medical factor to guide modality selection. This may result in patients who see a private physician being offered private HD as the only treatment modality, even if they are suitable for HHD or PD. On the other hand, these patients may choose private HD even if capable of performing home-based therapy to continue care with the same specialist. The Australian Government has attempted to encourage home dialysis by provision of a rebate to nephrologists, for services provided outside usual clinic appointments. The rebate commenced in November 2005, and data suggest large variations in uptake among states. So far, there has been no change in home dialysis rates across Australia.

The private hospitals performed well in a number of areas. The rate of commencement of HD with a functional AVF was higher in private, although the difference was not significant after correcting for late referral of patients. The main modifiable reason for a dialysis patient commencing HD without a functional fistula is failure of timely referral to a vascular surgeon by the treating nephrologist. Perhaps, the structure of clinics in public hospitals impairs timely referral for vascular access creation. This study has several limitations. This analysis was only performed for dialysis care in Queensland because of variations in practice across Australia. Private health insurance rates in Queensland are below the national average. In Queensland, private HD facilities were easily identifiable, and patients receiving dialysis treatment in private hospitals generally undertake the majority of their care in private facilities. This is not the case elsewhere, and hence, there is uncertainty as to whether the results of this study can be extrapolated to the entire country. Second, ANZDATA does not collect information on individual dialysis prescriptions, the severity of comorbidities, medication usage, socioeconomic status or hospitalisation. Third, we adjusted for many patient characteristics, but it is possible that confounding remained. Fourth, ANZDATA does not record those who died from ESKD but did not undertake dialysis. Finally, mortality is not the sole reason for an individual to select a type of dialysis, and other factors may have been critical in decisions made, such as transport, location, time, quality of life, patient satisfaction, local expertise, funding, health insurance status and geography.

**Conclusion**

This observational registry analysis shows that treatment with HD in public hospitals in Queensland was associated with better patient survival than public PD. Private HD patient characteristics are different to public hospital patients. The reasons for these differences are unknown. Both systems should collaborate to improve health outcomes for dialysis patients whether treated publicly or privately. Patients should be offered dialysis modality choice regardless of public hospital funding model or health insurance status.

**Acknowledgements**

The authors gratefully acknowledge the contributions of the Australian and New Zealand nephrology community in providing information for and maintaining the ANZDATA database. The data reported here have been supplied by ANZDATA. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of ANZDATA.

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Prospective randomised trial of endobronchial ultrasound-guide sheath versus computed tomography-guided percutaneous core biopsies for peripheral lung lesions

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Key words
lung neoplasm, endobronchial ultrasound, bronchoscopy, CT-guided core biopsy, patient satisfaction.

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Abstract
Aim: To determine diagnostic rate, complications and patient tolerability of endobronchial ultrasound-guide sheath (EBUS-GS) and computed tomography (CT)-guided percutaneous core biopsy for peripheral lung lesions.

Methods: Lesions >1 cm diameter on CT were randomised to either EBUS-GS or CT-guided biopsy. Excluded were patients with severe chronic obstructive airway disease, lesions touching visceral pleura or hilum, and patients with symptoms needing bronchoscopic evaluation. Patients completed preprocedure and postprocedure questionnaires on tolerability.

Results: Of 64 participants (mean lesion size 29 ± 16 mm), 57 completed the study. Diagnostic sensitivity was 67% for EBUS-GS and 78% for CT-guided biopsy (P = not significant). In those with negative results, in the EBUS group, nine had a CT-guided biopsy as a cross-over, seven of which were positive. In the CT group, four had cross-over EBUS-GS of which three were diagnostic. Sensitivity for malignancy was 17/23 for EBUS-GS (74%) and 23/26 (88%, P = not significant). For lesions <2 cm, CT-guided biopsy had a significantly better diagnostic yield (80% vs 50%, P = 0.05). In EBUS-GS cases, for lesions with an air bronchogram, sensitivity was 89%. Pneumothorax and intercostal catheter insertion occurred in three and two cases, respectively, for EBUS, and 10 and 3 cases for CT-guided biopsy (P = 0.02 for pneumothorax). Nine unexpected admissions occurred after CT-guided biopsy compared with three after EBUS-GS. Overall, tolerability was high for both groups; however three patients had moderate-to-severe pain after CT-guided biopsy.

Conclusions: In lesions <2 cm, CT-guided biopsy had higher yields; however, EBUS-GS had better tolerability and fewer complications.

Introduction
In the investigation of a peripheral lung lesion, the choice of investigation is usually between bronchoscopy or computed tomography (CT)-guided transthoracic needle aspiration/biopsy.1 However, no study has ever made a direct comparison of the two methods. The reasons for choosing either bronchoscopy or CT first would include lesion size and location.2,3 Bronchoscopy is usually done first for lesions that are more centrally placed and potentially accessible. However, conventional bronchoscopy for such pulmonary lesions, which are not endoscopically visible has a poor yield of at best 30–40% for malignancy.4,5 Endobronchial ultrasound-guide sheath (EBUS-GS) transbronchial lung biopsy improves yields in these cases to 70–85%.6 EBUS-GS is a safe procedure with low rates of pneumothorax or bleeding after biopsy, both approximately 1–5%.7–10

One retrospective comparison of transthoracic needle aspiration biopsy (TTNA) with EBUS-GS in the diagnosis of peripheral pulmonary lesions showed that EBUS-GS was better for more central lesions and TTNA was better for peripheral lesions touching the visceral pleura.11 EBUS-GS specimen positivity was 8/23 (35%) for subpleural lesions and 86/117 (74%) for lesions not touching the pleura, P < 0.001. Pneumothorax rate for EBUS-GS of 2% was significantly lower than that for TTNA (22%), P < 0.01.11 A prospective study was therefore designed comparing transthoracic CT-guided core biopsy and EBUS-GS where peripheral lesions touching

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the visceral pleura were excluded, as such lesions would be best served by a CT-guided approach. Such a study would also enable us to assess prospectively other factors in procedure selection. In addition, our national practice is often to refer to CT-guided biopsy first perhaps because of a perception that it is a better tolerated procedure. Accordingly, this study compares the patient tolerability of the two procedures and is the first such report.

**Materials and methods**

The study received Institutional Review Board Ethics Committee approval (Approval number 2007/065) in line with National Health and Medical Research Council research guidelines. All patients gave written informed consent, and patient anonymity was preserved. Subjects were patients referred to our tertiary referral teaching hospital in Thoracic Medicine public outpatients department, with a lung nodule on chest X-ray (CXR) or chest CT for tissue diagnosis. For inclusion, lesions had to be greater than 1 cm in maximum dimension. Lung function testing and assessment of fitness for either procedure were performed. Exclusion criteria were severe airflow obstruction with forced expiratory volume in 1 s <40% predicted (consistent with British Thoracic Society guidelines for TTNA), bullous lung disease obscuring access to the lesion, patients with symptoms requiring bronchoscopic investigation (such as cough or haemoptysis), and bleeding diathesis or other standard contraindication to procedures, such as active ischaemic heart disease. Regarding lesion location, perihilar lesions (either touching or associated with hilar structures) were excluded and had bronchoscopy. Lesions touching the visceral pleura were excluded except if they extended into the lung at least 3 cm radially towards the hilum. Also if the radiologist considered that the lesion was inaccessible because of overlying bony structures, the patient was excluded. Patients referred from a chest physician at private clinics who had consented patients outside the hospital to EBUS-GS were excluded.

Suitable patients were then randomised to either EBUS-GS or percutaneous biopsy by random number allocation. The protocol required a cross-over test to be performed if the first test was negative, unless clinical circumstances dictated no need for further tissue sampling. Primary endpoints were statistically significant differences in diagnostic yield and pneumothorax rate by procedure type. Pneumothorax was defined as visible pneumothorax on CXR, requiring an additional CXR over that normally done at 4 h postprocedure because of concern about the pneumothorax size or symptoms, or one requiring hospital admission. Occasionally, tiny pneumothoraces can be seen on CT at the time of the TTNA, but these were not in themselves regarded as complications for the purpose of the study. Statistical analysis was with a chi-squared difference in frequency. To demonstrate a 20% difference in pneumothorax rate at a significance level of 0.05 with a power of 80%, it was estimated that 75 patients would be needed in each group. A positive histological diagnosis meant either proof of malignancy or a defined benign pathology, such as granuloma or localised pneumonia. With such diagnoses, a true benign nature was demonstrated if there was radiological improvement or demonstrated X-ray stability over 6 months. If pathology only demonstrated normal bronchial mucosa, this was regarded as a non-diagnostic (negative) result.

Secondary endpoints included differences in patients’ tolerance, and other complications and resource utilisation using validated questionnaires. Preprocedure and postprocedure interview forms were sent with the patient to be filled in within 12–24 h of the procedure. These included validated visual analogue scales regarding patient acceptance of the procedure. With respect to perilesional haemorrhage (sometimes seen on CT at the time of TTNA), this was only regarded as significant if there was associated haemoptysis, cough or the need for admission because of hypoxaemia or other concern.

Equipment used for EBUS-GS were 2- or 1.7-mm Olympus min probes (UM S20-20R and S20-17R, Olympus, Tokyo, Japan) and Olympus ultrasound processor (EUM60, Olympus). Video bronchoscopes were 6- or 4.9-mm outer diameter, with 2.8- and 2-mm diameter biopsy channels respectively (BF 1T 180 or P180, Olympus). Image intensifier X-ray fluoroscopy guidance was also used to observe forceps and brush sampling. For percutaneous biopsy, all subjects had core biopsies using a coaxial approach, meaning only one passage of the needle (Speedybell, Biopsybell, Mirandola, Italy) through the pleura was made. Needle size was either 18G or 20G, and one to three passes with a 2-cm throw were made depending on the subjective visual assessment of the size and quality of the specimen and the CT image showing the needle within the target lesion. Bronchoscopies were done either under conscious sedation or with laryngeal mask airway anaesthetic support. Choice of anaesthesia depended on whether this was controlled by a thoracic physician (conscious sedation) or an anaesthetist (who usually prefers general anaesthetic). This was not randomised, however, in the study; half of the bronchoscopy lists have anaesthetic cover and half do not, and patients were placed on the next available list. For percutaneous CT-guided biopsy, sedation was at the discretion of the radiologist; however, no anaesthetic cover was available in radiology. CT-guided procedures were done with either no sedation or conscious sedation.
Results

During the study period from September 2007 to March 2011, 235 patients were referred with peripheral lung lesions. After exclusions, there were 64 patients randomised. Figure 1 lists the reasons for exclusion, as per the study protocol. Table 1 summarises the patients randomised to EBUS-GS or CT-guided biopsy. Thirty-three patients were randomised to EBUS-GS and 31 to CT-guided biopsy. Following randomisation, in the CT biopsy group, three lesions had reduced in size on CT prior to the date of procedure booking, meaning that a procedure was not done. In addition, in this group, four patients refused to go on with the CT-guided biopsy having been randomised; this included three patients who changed their mind and preferred to have a bronchoscopy, and one patient who refused the procedure while in the CT room before any intervention was done. This meant that of the 31 patients randomised to CT-guided biopsy, 24 had this as a first procedure. The final tissue diagnoses obtained for the total 57 patients were primary lung cancer in 40, localised pneumonia in 5, chronic granuloma in 6, localised fibrosis in 5 and lymphoma in 1.

Table 1 Details of randomised patients

<table>
<thead>
<tr>
<th>Patient details</th>
<th>EBUS-guide sheath</th>
<th>TTNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Age</td>
<td>66 ± 9 years</td>
<td>67 ± 9 years</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>22/11</td>
<td>17/14</td>
</tr>
<tr>
<td>Lesion size (largest dimension)</td>
<td>26.8 ± 17 mm</td>
<td>32 ± 15 mm</td>
</tr>
<tr>
<td>Lesions &lt;2 cm, %</td>
<td>11 (33%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Lesion in upper lobe</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Lesion in middle or lower lobe</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

EBUS, endobronchial ultrasound; TTNA, transthoracic needle aspiration biopsy.
For the initial procedure, diagnostic results were obtained in 22 of 33 EBUS cases (67%) and 19 of 24 CT biopsy cases (78%, \( P > 0.1 = \text{not significant (NS)} \)). Where percutaneous biopsy was nondiagnostic, four patients had EBUS-GS as a ‘cross-over’ procedure, and of these procedures, three were diagnostic. Where EBUS-GS was nondiagnostic, nine patients had CT-guided biopsy, and of these, seven patients were diagnostic. Taking all procedures (initial and cross-over), there were 37 EBUS-GS and 33 CT-guided procedures done. For EBUS-GS, diagnostic material was obtained in 25/37 (68%), and for CT-guided biopsy, diagnosis was obtained in 26/33 = 79%, \( P > 0.1 = \text{NS} \). The sensitivity for malignancy by all procedures was 17/23 for EBUS-GS (74%) and 23/26 (88%, \( P > 0.1 = \text{NS} \)).

Table 2 lists the results for lesions of \(<2\) cm in maximum dimension, which shows a significant improvement for CT-guided biopsy versus EBUS-GS in obtaining a tissue diagnosis in these small lesions. Table 3 shows results of EBUS-GS based on the presence or absence of an air bronchogram within the lesion. There was a highly significant improvement in EBUS-GS if there was an air bronchogram. Figure 2 gives an example of a lesion with an air bronchogram.

At the bronchoscopy for EBUS-GS, three patients had additional significant pathology identified other than the identification of the peripheral pulmonary lesion. Such identification occurred with the usual bronchial inspection prior to deployment of the EBUS probe. In one patient, there was an endobronchial carcinoma in situ proven by endobronchial biopsy that was removed with the main primary tumour at surgery. In another patient, a small amount of endobronchial lymphoma was visible providing extra biopsy material to complement the peripheral mass biopsy that showed lymphoma. In a third patient, there was proximal extension of a malignant lesion into a sixth-order bronchus allowing additional direct biopsy; this normally would not have been visible with a standard-sized bronchoscope and could not have been predicted from the CT scan prior to the procedure.

Table 2 Results of EBUS GS and TTNA based on size of lesion – includes both the initial test and cross-over tests

<table>
<thead>
<tr>
<th>Lesion size</th>
<th>EBUS GS</th>
<th>TTNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 2 ) cm</td>
<td>6/12 (50%)</td>
<td>8/10 (80%) ( P = 0.05 )</td>
</tr>
<tr>
<td>All lesion sizes</td>
<td>25/37 (68%)</td>
<td>26/33 (79%)</td>
</tr>
</tbody>
</table>

EBUS-GS, endobronchial ultrasound-guide sheath; TTNA, transthoracic needle aspiration biopsy.

Table 3 Results of EBUS GS based on the radiological feature of presence or absence of an air bronchogram within the lesion on the CT. Includes both the initial test and cross-over tests

<table>
<thead>
<tr>
<th>Lesion appearance</th>
<th>Positive pathology by EBUS GS</th>
<th>Negative pathology by EBUS GS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air bronchogram present in lesion</td>
<td>17*</td>
<td>2</td>
</tr>
<tr>
<td>Air bronchogram not present in lesion</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

\*\( P = 0.003 \). CT, computed tomography; EBUS-GS, endobronchial ultrasound-guide sheath.

Figure 2 (a) Air bronchogram within a lesion on computed tomography scan in right middle lobe. (b) Corresponding endobronchial ultrasound guide sheath image of probe deployed within the lesion immediately before biopsy.
Table 4 Complications from all procedures. Pneumothorax defined as that requiring additional test or intervention other than just a standard postprocedure chest X-ray. Perilesional haemorrhage defined as that causing symptoms or hypoxia or requiring admission.

<table>
<thead>
<tr>
<th>Complication</th>
<th>EBUS-GS, n = 37</th>
<th>TTNA, n = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>3</td>
<td>10, p = 0.02</td>
</tr>
<tr>
<td>Insertion of ICC or aspiration of pneumothorax</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Significant perilesional haemorrhage</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Procedure not completed</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unexpected admission (not including ICC)</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>All unexpected admissions</td>
<td>4 (11%)</td>
<td>9 (27%), p = NS</td>
</tr>
</tbody>
</table>

EBUS-GS, endobronchial ultrasound-guide sheath; ICC, intercostal catheter; NS, not significant; TTNA, transthoracic needle aspiration biopsy.

Table 4 shows the complications from all 70 procedures including cross-overs. Overall, there was a significantly higher number of pneumothoraces in the CT biopsy group. In the EBUS-GS group, of the three pneumothoraces, two had an intercostal catheter (ICC) inserted, and one had aspiration of the pneumothorax and admission. Perilesional haemorrhage occurred in three patients in the CT biopsy group. In the EBUS-GS group, there was an episode of aspiration of gastric contents immediately at the commencement of the procedure. The aspirated material was successfully removed immediately with the bronchoscope, and the procedure was stopped, that is, not completed. It was later revealed that the patient had eaten in the fasting period before the procedure and did not reveal this despite being asked during preprocedure checks. Overall, regarding unexpected admissions, there were four in the EBUS-GS group and 11 in the CT biopsy group; this result was not significantly different. Duration of admission was 1–3 days.

Results of the patients’ tolerance of the two procedures are shown in Table 5. Overall, there was a good return rate with the questionnaires. Generally, both the procedures were well tolerated with all patients describing the procedure as well tolerated or moderately well tolerated overall. There were some patients who experienced pain; of course, some of this was as a result from an ICC being placed after the procedure. However, there were three patients in the CT biopsy group who experienced moderate-to-severe pain despite not having an ICC inserted. When asked ‘Would you have the procedure again?’, there were three patients in the CT biopsy group (none of them having received conscious sedation) who said that they would never have it again, whereas no patients in the EBUS group gave this response.

The sedation for the procedure showed significant differences in that, only 13% of the TTNA group had some intravenous conscious sedation, whereas all patients in the EBUS group had either conscious sedation (36%) or an anaesthetist delivered general anaesthetic (64%).

Of the 171 excluded patients, the final diagnosis was known in 169. There were 92 malignant and 77 benign diagnoses. Tissue diagnosis was obtained in 138 cases, with the remaining 31 being the confirmation of benign disease over X-ray follow up. Of the 138 cases, bronchoscopy obtained the tissue diagnosis in 108 (EBUS-GS in 77, EBUS transbronchial needle aspiration (TBNA) in 23, and endobronchial biopsy 8), CT-guided fine-needle aspiration in 18 and surgical open lung biopsy in 12.

Discussion

This prospective series has shown a trend to better histological confirmation with CT-guided core biopsy, which was statistically significant for lesions <2 cm in diameter. However, this was accompanied by a higher incidence of pneumothorax and unexpected admission rate with percutaneous CT-guided biopsy. EBUS-GS results were in line with published data and were certainly higher than would be expected with standard bronchoscopy alone for these small lesions.9 Eberhardt et al. reported some success with lesions of 20 mm or less; however, like us, the diagnostic yield was relatively lower than for larger lesions (46%), and this supports our recommendation for CT-guided biopsy in these lesions.17 Importantly, also we showed that EBUS-GS was well tolerated and that occasional patients experienced significant pain with percutaneous biopsy.

In our study, there were three cases where unexpected endobronchial lesions were observed. This gives some support in performing the bronchoscopic EBUS approach first to allow such inspection. Importantly, also, we did not randomise patients with pulmonary symptoms, such as cough, because such patients need an exclusion of
endobronchial pathology. Seijo commented that bronchoscopy should be the first test in the evaluation of patients with suspected lung cancer, as unexpected endobronchial pathology can be detected. We would conclude that for investigation of a peripheral pulmonary lesion, CT-guided biopsy should be performed as the first procedure where lesions are less than 2 cm in diameter. Most other cases would best have EBUS-GS first, particularly because of the possibility of finding unexpected pathology. Where pneumothorax would be poorly tolerated or seems more likely to occur (such as in patients with significant emphysema and bullae), it would be best to perform EBUS-GS as the first procedure. Lesions with air bronchograms would also be best served by EBUS-GS first. Using these factors would be a very simple way to stratify many of these cases. We expect that both methods will be complementary.

In terms of study limitations, we did not reach the target of 75 patients; however, nonetheless, we were able to show a 20% difference in pneumothorax rate that was both statistically different and, in our view, clinically significant. Furthermore, we were able to show significantly better yields with CT-guided biopsy for lesions less than 2 cm in diameter. Another possible limitation is that radiologists evaluated the CT before study inclusion. While this might suggest a bias in favour of CT-guided biopsy, only 11 of the 171 exclusions were due to this. Most of the radiological exclusions were on the basis of factors determined from the previous nonrandomised study. Also, Yeow et al. showed in a series of 660 cases of CT needle biopsy that the best predictor of avoiding pneumothorax was a lesion that touched the visceral pleura. Therefore, we considered that such patients should have CT fine-needle sampling and be excluded from our study. However, the high exclusion rate of our study does make broad applicability difficult. In effect, the results apply only to lesions in the ‘middle third’ of the lung, that is, neither touching the visceral pleura nor the hilum.

The follow-up results of excluded patients show the very high yield of EBUS-GS and bronchoscopy procedures in general, and that CT TTNA was not used as a fall back in cases that were more marginal or difficult.

The issue with level of sedation and interpretation of the comfort scores was problematic in that anaesthetic cases would be expected to have less procedural discomfort. However, our use of either conscious sedation or general anaesthetic is in line with widespread, common, bronchoscopic practice. We conclude therefore that there need be no aversion in referring for an EBUS-GS procedure on the basis that it is less well tolerated than transthoracic biopsy. In fact, we found very good tolerance for the EBUS-GS procedure. Others have shown tolerability for bronchoscopic procedures using the instruments of Diette et al., and our results are commensurate with theirs, including the key question whether they would ever have the procedure again.

An alternative to EBUS-GS is electromagnetic navigation (EMN) and steerable directed catheter biopsy. Such procedures require more equipment, and overall, the diagnostic yields are comparable with EBUS-GS. Pre-procedure virtual bronchoscopy planning of the correct route to a given small lesion can be done prior to EBUS-GS. This gives a directed route to the lesion without the need for additional hardware, which is required for EMN.

In 2007, Gould et al. published a guideline on behalf of the American College of Chest physicians of recommendations for biopsy of peripheral lesions of >10 mm. They commented, ‘In general we suggest that TTNA be the first choice unless the procedure is contraindicated or the nodule is inaccessible. We suggest that bronchoscopy be performed (first) when an air bronchogram is present or in centres with expertise in newer guided techniques (such as EBUS GS)’. Our study is the first to compare directly results of these small lesions between CT-guided biopsy and EBUS-GS.

Our results support EBUS-GS as the first test where there is an air bronchogram present in the lesion. This feature suggests that the EBUS probe in the bronchus (and subsequent biopsy forceps) will be surrounded by pathology. Seijo et al. recently reported a series of transbronchial biopsy of peripheral lesions using EMN. Where there was an air bronchogram, the success rate was significantly higher at 79% compared with 31% where the bronchus sign was not present.

Our study showed significantly fewer pneumothoraces in the EBUS-GS group. The EBUS picture shows that the biopsy forceps will be inside the lesion, meaning the forceps will not touch the visceral pleura, thereby limiting the risk of pneumothorax. Additionally, the 2-mm guide sheath itself limits any bleeding – it is left in for 2 min after the biopsy, which allows for tamponading of this candidate bronchus.

**Conclusion**

Our results favour EBUS-GS as the first test for lesions with an air bronchogram and in lesions larger than 2 cm. Where pneumothorax is a high risk, EBUS-GS is favoured as the first test. We favour EBUS-GS as the first test in other patients with heavy smoking history because of the possibility of detecting occult endobronchial pathology, although this is tempered by a lower yield for the peripheral lesions of <2 cm.
References


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Essential, but at what risk? A prospective study on central venous access in patients with haematological malignancies

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Key words
central venous catheter complication, haematology, infection, thrombosis, immediate complication.

Abstract

Aims: Central venous catheters (CVC) are integral to modern haematology practice; however, they are associated with a range of complications. This prospective study aimed to determine the rate of CVC-related complications and risk factors in haematology patients, who are vulnerable because of their underlying pathology and treatments.

Methods: All inpatients that had a non-tunneled CVC inserted in a 14-month period in the haematology ward at St Vincent’s Hospital were enrolled. Complications (immediate and late), demographics, type of device, insertion technique and duration of dwell, were examined using multivariate analysis.

Results: One hundred and seventy-four CVC in 84 patients were recorded, representing 3016 catheter-days. At least one complication was found in 43 (24.7%) patients. Immediate complications occurred in 13 (7.5%) insertions, with a higher rate in those inserted after ≥2 attempts compared with one (P = 0.02). Catheter-related bloodstream infection occurred at a rate of 7.6 per 1000 catheter-days, with acute lymphoblastic leukaemia associated with a higher rate (P = 0.02), and subclavian vein CVC had a lower rate compared with other locations (P < 0.01). Thrombosis was found in seven (4.0%) patients, with subclavian CVC carrying an increased risk (P = 0.02).

Conclusions: This prospective observational study found almost a quarter of haematology patients experience a CVC-related complication. An association was found with a number of attempts at insertion and immediate complications; other risk factors included anatomical location, underlying disease and duration of catheterisation. The relatively high complication rate, compared with reports of non-haematology patients, highlights the need to improve CVC management, a vital part of care for this population.

Introduction

Central venous catheters (CVC) have become an integral tool in modern haematology practice. Although there are obvious benefits to their use in this setting, immediate, infectious and thrombotic complications can occur, which have the potential to increase patient morbidity and mortality, with large financial costs to the health system¹.

It has been estimated that over 15% of patients undergoing CVC insertion experience an immediate or long-term complication, the most common being catheter-related bloodstream infection (CR-BSI) and thrombosis.²,³ Serious sequelae of these include endocarditis, septic emboli, pulmonary embolism and haemorrhage, causing significant morbidity and contributing to overall mortality burden.⁷ An Australian study carried out in 1994 estimated CR-BSI lengthens hospital stay by 18.7 days and costs an extra $14 000.¹

However, most studies have been carried out on heterogenous patient groups, such as patients with solid tumours and in intensive care unit, using different catheter types (peripherally vs centrally inserted) in varying anatomical locations and using different definitions of complications. Haematology patients are unique in their susceptibility to complications because of the likely presence of marrow failure, thrombotic tendencies, intensive chemotherapy and prolonged immunosuppression. A few recent Australian studies have been...
published outlining the risk factors associated with CVC-related infection and thrombosis; however, they do not address all complications and most were not specific to haematology patients. This study aimed to determine prospectively the rate of all non-tunneled CVC-related complications and their risk factors in a haematology unit, with an intention of using this information to improve the practices of using CVC.

**Materials and methods**

**Recruitment and data collection**

This study was prospectively carried out between June 2008 and July 2009 in a single centre, with approval of the institution’s Human Research and Ethics Committee. All inpatients with CVC insertions during this period were recruited. Information from standardised data collection forms were electronically collated. Data collected for each patient-episode included: indication, insertion details (place, number of attempts at insertion, type of device), anatomical location, reason for removal and duration of dwell. Patient details that were collected included demographic information, clinical indicators of infection such as fevers, rigors or hypotension over the time the CVC was in situ, CVC dressing changes and documentation, blood and CVC tip culture results, presence of neutropenia and/or thrombocytopenia and relevant radiological investigations (e.g. ultrasound venous duplex studies).

**CVC procedure and definitions**

A CVC was defined as a silicone or polyurethane catheter that is inserted into a large vein, with the tip of the catheter usually terminating in the superior vena cava. PIVC catheters were excluded for the purpose of this study. Each CVC insertion was counted as a discrete episode and patients having repeated catheter insertions were documented as separate episodes.

All procedures were performed by dedicated operators (Clinical Nurse Consultant for IV access; anaesthetics consultants and registrars) in the recovery ward, according to the institutional guidelines. Briefly, the types of devices used include Cook Spectrum antibiotic-impregnated catheters (minocycline and rifampin) with three or five lumens, and ArrowGard chlorhexidine-silver sulfadiazine-impregnated catheters with two or four lumens; the choice of number of lumens was determined clinically. All devices were inserted under sedation, using strict aseptic Seldinger technique. Antiseptic used was 0.5% chlorhexidine in 70% alcohol, and CVC were dressed with a clear occlusive dressing (Opsite IV 3000; Smith and Nephew, Melbourne, Vic., Australia) with a Biopatch antiseptic-impregnated sponge encircling the insertion site. Use of ultrasound guidance was at the discretion of the operator. CVC position was confirmed radiographically before use. According to the institution’s guidelines, CVC sites and dressings were inspected daily, and dressings were routinely changed twice per week. In line with current evidence, CVC were not changed on a scheduled basis, but were only removed because of clinical suspicion of infection, mechanical failure, or when no longer required.

Immediate complications included all those adverse events that occurred within 24 hours of CVC insertion and as a direct result of the procedure. Where more than one complication occurred in the same patient in the same procedure, they were counted as separate events. In cases where one patient had more than one catheter on separate occasions, subsequent complications in these were also counted as separate events.

CR-BSI were defined using descriptions from the Australian Commission on Safety and Quality in Healthcare, requiring an intravascular catheter to be present within 48 hours of the episode of BSI and that the organism(s) not be related to an infection at another site. Thromboses were defined as those identified by diagnostic imaging prompted by clinically significant and relevant symptoms and signs.

**Statistical analysis**

Rates of infection were analysed per 1000 catheter-days, using the equation

\[
\text{Number of BSI in patients with CVC} \times 1000 = \frac{\text{Number of CVC days}}{\text{Number of BSI in patients with CVC}}
\]

Quantitative parameters were expressed as means ± standard deviation. Univariate analysis was performed using t-test for continuous and Chi-squared for categorical variables respectively. Multivariate analysis was carried out using binary logistic regression with stepwise removal of insignificant variables, with odds ratios (ORs) and 95% confidence intervals (CI) provided. Variables analysed included age, sex, diagnosis, body mass index, number of attempts at insertion, duration of catheterisation, presence of neutropenia (neutrophils <0.5 × 10⁹/L) or thrombocytopenia (platelets <50 × 10⁹/L) and anatomical location. All analyses were performed in consultation with a biostatistician using IBM SPSS Statistics 18 (IBM Australia, Sydney, NSW, Australia). A P-value of <0.05 was considered to indicate statistical significance.
Results

There was a total of 174 CVC in 84 patients, representing 3016 catheter-days. The demographic and catheter characteristics are shown in Table 1. The most common indication for CVC insertion was bone marrow transplantation for acute myeloid leukaemia (AML) or non-Hodgkin lymphoma. Ultrasound guidance was used in 46 (26.4%) CVC insertions, 40 of these for those placed in the internal jugular (IJ) vein.

A total of 43 complications occurred in the 174 CVC, representing 24.7% of insertions. Immediate complications occurred in 13 (7.5%) insertions: eight being arterial punctures, one pneumothorax, two haematoma and two incorrect positioning resulting in failure to insert the CVC.

As shown in Table 2, the number of attempts at insertion was associated with immediate complications (six times higher rate for ≥2 attempts compared with one attempt). In a multivariate logistic regression model, it was found that CVC inserted in one attempt were associated with significantly fewer immediate complications compared with those inserted after two or more attempts, OR 0.22 (95% CI 0.06–0.76) (P = 0.02).

There were seven (4.0%) episodes of thromboses; three of these occurred consecutively in one patient with a known history of venous thromboembolism, which necessitated the catheter to be removed and subsequently replaced. The mean time to thrombosis was 20 ± 11 days (range 6–41 days). There was a significantly higher rate of thromboses in the subclavian (SC) vein (8.2%) compared with IJ (1%), OR 2.05 (P = 0.02).

Ninety-seven (55.7%) CVC were removed because they were no longer needed; 43 (24.7%) were removed because of clinically suspected infection, of which 23 were subsequently confirmed to be CR-BSI by the above criteria. One hundred and fifteen (66%) catheter tips were cultured on removal of the CVC. There were 23 cases of CR-BSI in this cohort, with an infection rate of 13.2%, or 7.6 per 1000 catheter-days. The interval between insertion of the CVC and the detection of CR-BSI ranged from 6 to 59 days (median 21 days). The cumulative incidence of infection was 21% at day 30 (Fig. 1).

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Episodes</th>
<th>Number of patients</th>
<th>Female, n (%)</th>
<th>Age, mean ± standard deviation (SD) (range)</th>
<th>BMI on day of insertion, mean ± SD (range)</th>
<th>Duration of catheterisation, mean ± SD (range)</th>
<th>Indication, n (%)</th>
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<tr>
<td></td>
<td>174</td>
<td>84</td>
<td>28 (33.3)</td>
<td>49 years ± 15 (19–77)</td>
<td>25.3 ± 4.6 (13.0–41.5)</td>
<td>17.3 ± 9.7 days (2–59)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Episode</th>
<th>4 (2.3)</th>
<th>2 (18%)</th>
<th>4 (36%)</th>
<th>23.3 ± 19 (12–35)</th>
<th>4.6 ± 1.5 (3–6)</th>
<th>2.0 ± 0.6 (1.5–2.5)</th>
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</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>15 (17.9)</td>
<td></td>
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<tr>
<td>Allogeneic/MUD</td>
<td>41 (48.8)</td>
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<tr>
<td>Chemotherapy</td>
<td>28 (33.3)</td>
<td></td>
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<tr>
<td>AML, n (%)</td>
<td>30 (35.7)</td>
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<tr>
<td>NHL</td>
<td>27 (32.2)</td>
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<tr>
<td>MM</td>
<td>7 (8.3)</td>
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<tr>
<td>ALL</td>
<td>6 (7.4)</td>
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<tr>
<td>CLL</td>
<td>5 (6.0)</td>
<td></td>
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<tr>
<td>Other</td>
<td>9 (10.8)</td>
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<tr>
<td>Patients with neutropenia, n (%)</td>
<td>140 (80.5)</td>
<td></td>
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<tr>
<td>Duration (mean)</td>
<td>10.5 days</td>
<td></td>
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<tr>
<td>Patients with thrombocytopenia</td>
<td>137 (78.7)</td>
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<tr>
<td>Duration (mean)</td>
<td>12 days</td>
<td></td>
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<tr>
<td>Location</td>
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</tr>
<tr>
<td>Internal jugular</td>
<td>96 (55.4)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Subclavian</td>
<td>73 (52.3)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Femoral</td>
<td>5 (2.9)</td>
<td></td>
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<tr>
<td>Catheter type</td>
<td></td>
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</tr>
<tr>
<td>Tunnelled, non-coated</td>
<td>4 (2.3)</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Antibiotic-coated (Cook)</td>
<td>156 (89.7)</td>
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<tr>
<td>Chlorhexidine-silver</td>
<td>14 (8.0)</td>
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<tr>
<td>sulfadiazine-coated (ArrowGard)</td>
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</tbody>
</table>

Table 2 Univariate analysis of factors associated with immediate complications

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No immediate complication (n = 161)</th>
<th>Immediate complication (n = 13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (mean)</td>
<td>25.5</td>
<td>23.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Catheter location</td>
<td>Internal jugular n (56%) 90</td>
<td>6 (46%)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Femoral n (23%) 4</td>
<td>1 (81%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subclavian n (42%) 67</td>
<td>6 (46%)</td>
<td></td>
</tr>
<tr>
<td>Number of attempts</td>
<td>One n (79%) 129</td>
<td>5 (45%)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Two n (15%) 25</td>
<td>2 (18%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Three+ n (63%) 9</td>
<td>4 (36%)</td>
<td></td>
</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphoid leukaemia; MM, multiple myeloma; MUD, matched unrelated donor; NHL, non-Hodgkin lymphoma.

Multivariate analysis revealed that the underlying diagnosis and location of the CVC correlated with infective risk; those with acute lymphoblastic leukaemia (ALL) and CVC located in the IJ vein were more likely to become infected. Of those with ALL, 41.7% acquired a CR-BSI, with OR of 5.0 for infection (1.32–18.92, P = 0.02).
Furthermore, the mean dwell time was significantly longer for ALL compared with the non-ALL group (30 vs 17 days; \( P = 0.002 \)). A significant association between longer duration of catheterisation and CR-BSI was found, with the mean duration to be 22.6 days in those with CR-BSI compared with 16.5 in those without (\( P = 0.05 \)). CVC located in the SC vein had a significantly lower rate of infection compared with those located in the IJ or femoral veins (OR 0.11, 0.03–0.52, \( P = 0.004 \)). The CVC type (number of lumens, antibiotic or antiseptic-coated), presence of neutropenia, and treatment type (bone marrow transplant vs chemotherapy alone) were found not to be statistically significant risk factors for infection.

**Discussion**

This is, to our knowledge, the first prospective study examining all types of complications of CVC in haematology patients in Australia. Up to a quarter of insertions had a complication, in spite of recommended preventative measures taken during CVC insertion, management and removal. It is considerably higher than the predicted 15% by McGee and Gould for all patients (i.e. not specific to haematology).\(^3\) A meta-analysis specific for haematology patients found incidence of infection and asymptomatic thrombosis of up to 20 and 34%, respectively.\(^4\) There are few data published from studies carried out specifically in haematology patients regarding immediate complications; Cortelezzi et al. stated a rate of 9.6%, although risk factors were not reported.\(^4\)

We found the incidence of immediate complications to be 7.5% of CVC insertions, lower than rates reported elsewhere in haematology and non-haematology patients.\(^2\)\(^,\)\(^4\) Two or more attempts at insertion is associated with a statistically higher immediate complication rate. Although the association is not causative and the two events are not strictly independent of each other, the statistical analysis is still informative. This relation has been attributed to the fact that multiple punctures cause small haematomas, which alter anatomic reference points thus hindering accurate CVC placement.\(^3\) However, this may also be a surrogate for patients with difficult anatomy or operators with a lower level of experience.

Neither anatomical location nor body mass index influenced the rate of immediate complications.\(^3\)\(^,\)\(^5\)\(^,\)\(^15\) This would suggest that unless a patient has a clear contraindication (such as chronic obstructive pulmonary disease, conferring a much higher morbidity burden in the event of a pneumothorax), or a previous site of radiation, then the anatomical site chosen should depend on the patient, noting the individual variations in anatomy based on ultrasound imaging, as well as operator preference and ease of use. However, SC CVC would be preferred as they are generally more comfortable for the patient and have a lower rate of CR-BSI; this must be balanced by the consideration for higher rate of thromboses. Other studies have shown that operator experience is related to the risk of immediate complications occurring.\(^3\)

We found a CVC-related BSI occurred in 13.2% of devices, with a CR-BSI rate of 7.6 per 1000 catheter-days. Worth et al. reported a rate of 7.5 per 1000 catheter-days in patients with haematological malignancies.\(^10\) Other studies report a lower estimate, including a set of retrospectively collected data from 10 NSW hospitals showing a rate of 1.86 per 1000 catheter-days.\(^16\) A study carried out by Mollee et al. in cancer patients with solid tumours and haematological malignancies found a CR-BSI of 2.5 per 1000 catheter-days.\(^11\) However, the majority of these lines was peripherally inserted central catheters and tunnelled lines, with only 13.7% (154 of 1127 lines) being non-tunnelled CVC.\(^11\) Furthermore, those with haematological malignancies were found to have the highest rate of complications in this study.\(^11\) The widely divergent results are due partly to case definitions,\(^5\) methodology and catheter type, with a higher overall complication rate resulting from a more inclusive estimation, a homogenous population, and one method of CVC insertion in this study.

This study found that underlying disease, duration of catheterisation and anatomical location were significant risk factors for the development of CR-BSI (see Table 3). Although a lower rate of CR-BSI associated with SC CVC and the importance of underlying disease relating to the propensity to develop CR-BSI have been consistently reported,\(^2\)\(^,\)\(^3\)\(^,\)\(^8\)\(^,\)\(^10\) there are divergent results with regards to duration of catheterisation. Some studies report a higher rate of CR-BSI with increasing length of site use,\(^8\)\(^,\)\(^10\) whereas Worth et al. found that the number of days a CVC remains in situ was not associated with a higher complication rate.\(^10\) Our findings would suggest an association between risk of infection and a longer duration of
catheterisation for non-tunnelled catheters. However, prolonged catheterisation may be confounded by severity of illness.¹²

The higher rate of CR-BSI associated with IJ and femoral CVC compared with SC is supported by most other studies.²,³,¹⁰,¹⁹ Anatomically, IJ CVC are more prone to positional variation; practically, dressings are less likely to adhere because of facial hair, neck movements and therapeutic manipulations. The higher rate of CR-BSI among patients with ALL is possibly secondary to the prolonged treatment course (as shown by the significantly longer mean duration of catheterisation), and use of high doses of corticosteroids, leading to defective immune mechanisms as well as impaired skin barrier. As there was only a small number of ALL patients in our series, this association needs corroboration with future studies. In addition, we were unable to test the hypothesis that cumulative steroid exposure, in particular relation to ALL, is associated to CR-BSI.

The overall rate of symptomatic thrombosis of 4% is within the range of published data, showing an incidence of 1.2–13%.⁶ In our patient group, CVC located in the SC vein were more than twice as likely to experience a thrombosis as those in the IJ or femoral location, although this is based on a small number of observations. It is possible that SC CVC follow a sharper curve than IJ CVC, resulting in wall adherence.¹³ Previous studies have had differing results with regard to the risk of thrombosis of IJ compared with SC CVC.¹⁹,²⁰

This study forms a basis for future trials designed to examine interventions and strategies aimed at minimising catheter related complications in a randomised setting. For example we were unable to examine the effect of a patient’s co-morbidities and confounding factors such as diabetes, previous CVC use or BSI episodes, on complication rates.

Conclusion

This prospective observational study of non-tunnelled CVC usage found a relatively high overall complication rate of CVC in haematology patients as compared with reports that include non-haematology patients. Patients with haematological malignancies are especially vulnerable because of their underlying pathology and nature of their treatments and should be regarded separately to the general patient population. The risk factors for complications of non-tunnelled CVC, were associated with anatomical location, underlying disease, duration of dwell, and the insertion procedure. This study highlights the improvements that are needed to make venous access, a vital part of care delivery, safe for haematology patients.

Acknowledgements

The authors are grateful to Ian Nivison-Smith for his input and assistance with statistical analysis; Nick Yates, Nick Yacopetti and the anaesthetics department for their information regarding CVC procedures at St Vincent’s Hospital and their feedback; and the staff and patients of the haematology and bone marrow transplant unit at St Vincent’s Hospital.

References

Effects of methylnaltrexone in patients with narcotic bowel syndrome: a pilot observational study

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Key words
opiate, constipation, abdominal pain, fatigue, 
\(\mu\)-opioid receptors, \(\mu\)-opioid antagonist.

Abstract
Background: Narcotic bowel syndrome (NBS) describes disabling chronic severe abdominal pain that worsens despite continuing or escalating doses of opiates. Therapy is very limited.
Aim: To examine effects of blocking peripheral \(\mu\)-opioid receptors on the symptomatology of patients with NBS and its safety.
Methods: An open-label observational study was performed in four women with NBS. After a 2-week run-in period, patients were treated for 12 weeks with 8–12 mg methylnaltrexone bromide subcutaneously every other day, increasing to daily if there was poor response. Patient and physician assessment was documented, and patients completed an eight-symptom visual analogue scale weekly and the Functional Assessment of Chronic Illnesses Therapy-Fatigue questionnaire for fatigue. Patients were observed for 4 weeks following withdrawal of the drug.
Results: One patient was unable to tolerate the study medication because of worsening pain after injection, and withdrew. Two showed clear benefit with reduction of symptoms overall, pain, bloating, distension, nausea and tiredness, with improved satisfaction and consistency of bowel actions and fatigue scores. Both reduced analgesic usage. The third had improved ileostomy output and had no episodes of severe bloating, but pain scores remained high. All three worsened after drug withdrawal and requested retreatment. Three experienced abdominal pains of moderate severity for 30–60 min consistently within 5 min of each injection. No other adverse events were experienced.
Conclusions: Methylnaltrexone has a positive impact on symptoms in women with NBS, although treatment does induce transient pain following its administration. Larger studies are required to examine its efficacy and longer term safety in this patient group.

Introduction
Gut symptoms, particularly constipation and abdominal pain, are common adverse effects of opioid intake. In some patients with non-cancer-related chronic pain, chronic or frequently occurring abdominal pain that worsens with continued or escalation doses of opioids has been recognised, and the term, narcotic bowel syndrome (NBS), has been applied to such patients.\(^1\) It is probably an underrecognised condition, although attempts to define its prevalence by questionnaire studies have led to contrasting conclusions.\(^2,3\) It is a major management problem. While withdrawal of narcotics is considered the key therapeutic strategy, this is not possible in many patients due to the issues with opioid withdrawal and the relative inefficacy of non-opioid analgesia to deal with the pain.

Pathogenic mechanisms are being unravelled. For example, a recent rat model of NBS demonstrated both central and peripheral sensitisation to occur, as observed in patients with NBS.\(^4\) Visceral hypersensitivity that is likely to be one of the key mechanisms underlying the genesis of abdominal pain in NBS reduces the ability of the individual to tolerate gut luminal distension. The prolonged transit through the gut induced by narcotics leads to relative small intestinal stasis, constipation and impaired gastric emptying, all of which lead to luminal distension. Prokinetic agents have been disappointing in efficacy, and laxatives for the constipation are poorly tolerated as they often lead to further luminal distension and/or direct irritation of the enteric nervous system and subsequent aggravation of the pain. In patients with irritable bowel syndrome, where visceral hypersensitivity is also an important pathogenic factor in pain, reducing abdominal distension with dietary restriction of poorly absorbed short-chain carbohydrates (FODMAPs) is a
successful strategy in reducing the gut symptoms. A strategy to minimise luminal distension in patients with NBS seems, then, to be a reasonable strategy to reduce abdominal pain. Indeed, FODMAPs are poorly tolerated by such patients (P. R. Gibson, personal observations) but do not address the principal reason for luminal distension.

Blocking the peripheral μ-opioid receptors may provide therapeutic benefits by improving motility and transit, by reducing the constipation, and therefore, minimising luminal distension and its associated sensory input to the enteric nervous system. Methylnaltrexone bromide (Relistor (Pfizer, West Ryde, NSW, Australia)), a μ-receptor antagonist, has achieved these effects without reducing analgesic efficacy. Its use in patients with NBS, however, has not been reported.

In order to examine the hypothesis that methylnaltrexone bromide will improve gastrointestinal transit, reduce constipation and improve abdominal pain in patients with NBS, a ‘proof-of-concept’ observational study was performed in patients with NBS to examine the effect of methylnaltrexone bromide on abdominal symptoms and fatigue.

Methods

Patients

Patients with NBS were defined according to the following criteria from Grunkemeier et al.: the presence of severe to very severe abdominal pain daily of more than 3 months duration requiring more than 100 mg of morphine equivalent per day, and both the pain worsens or incompletely resolves with continued or escalation of narcotic dose, and the nature and intensity of pain are not explained by current or previous gastrointestinal diagnosis. The patients were to be aged greater than 16 years of age, able to speak and understand English, and able to give written, informed consent. Patients who weighed less than 38 kg or greater than 114 kg who had known or suspected mechanical gastrointestinal obstruction, or who had major psychoses, were excluded.

Protocol

Patients were treated with methylnaltrexone bromide in an ‘open-label’ design for 3 months, and the changes in clinically relevant end-points were documented prospectively during that 3-month period. The patients were seen twice during a 2-week run-in period, then after 2, 4, 8 and 12 weeks of therapy. The patients were reviewed 4 weeks following the withdrawal of the therapy. Other medication (apart from opiate dosage for breakthrough pain) remained stable during the study period.

Methylnaltrexone bromide was self-administered subcutaneously every other day at an initial dose of 8 mg for patients weighing 62 kg or less, and 12 mg in those weighing greater than 62 kg. If there was inadequate response after 2 weeks, the dose was increased at the same dose to daily. Compliance was assessed by diary entries, return of unused ampoules and the collection of drug from pharmacy after each study visit.

Patients were issued with diaries for the study period. This included a subjective weekly assessment of relevant end-points, as well as daily information regarding bowel habit, drug administration and side effects. Patients could also comment on tolerability of the drug.

End-points examined were (i) effect on abdominal symptoms overall, pain, bloating distension, satisfaction with bowel actions/ileostomy output, consistency of bowel actions, nausea and tiredness, as assessed using simple 10-cm visual analogue scale (VAS) of those symptoms filled out weekly; (ii) effect on fatigue as evaluated with the Functional Assessment of Chronic Illnesses Therapy-Fatigue scale administered weekly – this is a self-administered questionnaire of 13 questions using a 5-point Likert scale, and scores can range between 0 and 52, higher indicating more fatigue, and differences of three to four represent minimally important differences – (iii) subjective patient assessment of progress; (iv) global physician assessment of the status of the patient’s abdominal symptoms; (v) effect on opioid usage; and (vi) adverse events recorded by the patients in their diaries or on direct questioning at study visits.

The protocol was approved by the Eastern Health Research and Ethics Committee, which is constituted according to the National Health and Medical Research Council of Australia guidelines, and whose composition and mechanism for provision of approval are consistent with International Conference on Harmonisation, Food and Drug Administration Code of Federal Regulations. Patients gave written, informed consent prior to any study procedures being administered.

Results

Four female patients agreed to participate. The prospective reporting of abdominal symptoms and fatigue before and during therapy in three are shown in Figure 1.

Patient 1

A 58-year-old woman had a 12-year history of severe trigeminal neuralgia following failed faciomaxillary surgery. Prior to this, she had a tendency to constipation but denied any abdominal symptoms. Morphine had been used for analgesia, and its dose had increased over
the previous 6 years to 240 mg/day. She developed severe unresponsive constipation with abdominal pain. Two years prior, she had a loop ileostomy to reduce gross abdominal distension and the need for large doses of laxatives. This provided partial relief from distension, but severe chronic abdominal pain persisted. She weighed 61 kg.

She was treated with 8 mg methylnaltrexone second daily, but missed five doses over the 12 weeks due to forgetting which day to inject. There was a progressive improvement with increased volume and ease of passage of the ileostomy output, and reduced abdominal bloating and distension. Within 2 weeks of commencing methylnaltrexone, she was able to reduce the frequency of morphine use from three hourly subcutaneous injections to six hourly. These benefits were maintained throughout the 12 weeks of therapy. She described no adverse events. Physician assessment was that she benefited greatly from the therapy.

On cessation of methylnaltrexone, her symptoms deteriorated with reduced ileostomy output, greater bloating and distension, and increased pain, with morphine use regressing to three hourly injections. She wanted to recommence the drug.

**Patient 2**

A 60-year-old woman had severe gut dysmotility manifesting as long-standing severe constipation, abdominal distension, abdominal pain and slow gastric emptying. As a child, she had ‘floppy muscles’ and required callipers until 12 years of age. She also had an appendicectomy as a child and hysterectomy for menorrhagia when she was 25 years old. A colectomy and ileorectal anastomosis had been performed at the age of 45 years due to severe constipation, but continuing difficulties and pain led to an ileostomy being performed 1 year later. Two further laparotomies had been performed since then for abdominal

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**Figure 1** Response of symptoms in Patients 1–3 according to week scores on a 10-cmVAS and the summation score for the 13-question FACIT-F scale. The VAS rates 0 for ‘excellent’ and 10 for ‘really awful’, except for ‘Consistency of bowel actions’, where zero represents ‘watery’ and 10 ‘hard’. The x-axis represents time in weeks. The score at time 0 weeks is the mean of the scores during the run-in period of 2 weeks. — Pt. 1; — Pt. 2; — Pt. 3. FACIT-F, Functional Assessment of Chronic Illnesses Therapy-Fatigue; VAS, visual analogue scale.
pain and lysis of adhesions. Severe chronic abdominal pain had been managed with oral morphine for the previous 10 years, and the dose had been escalated to slow-release oral morphine 360 mg/day and parenteral pethidine 100 mg twice/day. She had poor tolerance to bolus feeding, and nutrition had been maintained through infusion of liquid feeds through a percutaneous endoscopic gastrostomy (PEG) for the last 7 years. Her current weight was 90 kg (previously more than 120 kg).

The dose of methylnaltrexone used was 12 mg. Since there was no apparent improvement in symptoms within the first 2 weeks, the drug was increased to 12 mg daily. All doses were taken. At the 6-week visit, the patient had noticed some changes with now improved stomal output that continued through the remainder of the treatment period. While abdominal bloating persisted, she described fewer days where the abdominal distension was gross. However, the abdominal pain persisted as before, and there was no change in opiate dosage. The only adverse event she described was severe abdominal pain, different from her usual pain, within 5 min of injecting methylnaltrexone. This occurred after every injection, lasting about 1 h, and neither the pattern nor severity changed during the 12 weeks’ therapy. Physician assessment was that she had significantly improved; gross distension was no longer noted, ileostomy output had changed from occurring seldom to more regularly, and pain control was not worse, although remained inadequate.

On withdrawal of methylnaltrexone, the most notable changes were that the frequency of stomal output had returned to pretreatment levels, and that abdominal pain worsened as shown by the increased frequency of pethidine use. The patient was keen to recommence therapy, despite the pain induced following the injection.

Patient 3

A 40-year-old woman had a past history of recreational narcotic abuse in her early twenties, but has been stable on regular oral methadone for several years. Prior to the use of narcotics, she had symptoms suggestive of irritable bowel syndrome. Over several years, she had developed increasing problems with constipation, abdominal distension and bloating, and severe abdominal pain that had required hospitalisation on more than one occasion for bowel clearance. The dose of methadone had been progressively increased to 280 mg/day, without ongoing benefit to her abdominal pain. She also used tramadol daily for pain. She used a variety of laxatives on a regular basis. Investigation of her gastrointestinal tract had revealed no pathology. She weighed 64 kg.

On a dose of 12 mg second daily, she described her bowel function and abdominal distension as progressively improving. After 8 weeks, bloating was markedly improved. She was no longer using laxatives. Analgesic usage changed in that she now only occasionally used tramadol (nil to three tablets/day), whereas four to six 100 mg tablets were used daily prior to therapy with methylnaltrexone. The only adverse event reported was the onset of tolerable abdominal pain within 5 min of each injection of methylnaltrexone. This pain lasted 30–60 min and did not change in character over the time course of the study. Physician assessment was that she was markedly improved without gross distension and the need for laxatives, together with improved abdominal pain.

Drug withdrawal led to a return of abdominal distension, increasing abdominal pain and discomfort, difficulty gaining any satisfaction in opening the bowels, and a return to the use of laxatives. The patient was anxious to recommence the drug.

Patient 4

This 54-year-old woman had a long-standing history of severe dysmotility of her gastrointestinal tract manifesting as long-standing severe constipation, abdominal distension, abdominal pain and slow gastric emptying. She had surgery for endometriosis 22 years previously and two subsequent laparotomies for adhesions. The constipation was refractory to therapy, and a colectomy and ileostomy were performed 10 years ago. She also had poor tolerance to bolus feeding, and infusion feeding through a PEG for the last 8 years had enabled maintenance of nutrition and avoidance of severe pain induced by food ingestion. She suffered from severe abdominal and rectal pain every day and had escalated slow-release oral morphine use to 190 mg/day, but had managed to reduce the dose only to 120 mg/day over the last 2 years in attempt to withdraw from opiates. She was using subcutaneous morphine (15 mg) intermittently (average of daily) for more severe pain. She weighed 51 kg.

This patient was not able to tolerate the study drug due to severe pain within 15 min of administration. Reducing the dose to as little as 1 mg, with subsequent stepped increase to 3 mg, failed to ameliorate the induction of greater abdominal and rectal pain, and worsening nausea and vomiting. Ileostomy output had, however, increased in association with the drug use. She withdrew from the study after 4 weeks. Her diary and VAS responses were not further analysed.

Discussion

Patients with NBS are a major management challenge for physicians. While the most effective way of improving
abdominal symptoms is believed to be cessation of opiate usage,\(^1\) this is impractical and almost impossible to achieve in the majority of patients. As the quality of life of such patients is poor, any therapy to have even a small impact on symptoms is welcome. Since a major stimulus for the induction of abdominal pain in patients with NBS who have visceral hypersensitivity is luminal distension, and since luminal distension is the result of the direct effect of opiates on gut motility, the inhibition of the gut effects of the opiates might be of therapeutic benefit. On the other hand, the promotion of gut motility might also cause an unacceptable increase in abdominal pain, defeating the main purpose of this therapeutic approach. The objective of this pilot study was to address these key issues in a few patients. Indeed, methylnaltrexone therapy was associated with subjective improvement in both the patients’ and physician’s impressions of abdominal symptoms with improvement or at least without exacerbation of pain control, but also transiently exacerbated pain.

The hypothetical way that methylnaltrexone should reduce pain is to reduce the sensory input from luminal distension by promoting peristaltic progression of contents without the irritant effect of stimulant laxatives and the distending effect of osmotic laxatives. There is no information available that might suggest methylnaltrexone changes visceral sensitivity itself. In the three patients who were able to tolerate the drug, reduction of luminal distension was achieved with improvements in the volume and/or consistency of the output from the bowel. In two patients, this was associated with a clear reduction in bloating and abdominal distension and, in the third, a lack of exacerbations of distension, most evident when the drug was ceased. The effects seemed to build over the first few weeks and persisted as long as the drug was taken.

Reasons for differences in the apparent magnitude of responses in the three patients may well lie in the relative contribution of opiates to the abdominal symptoms. The patients studied were heterogeneous in the nature of the underlying bowel condition prior to exposure to opiates. One had no evidence of functional gut problems, and one described mild symptoms consistent with irritable bowel syndrome as a teenager, but it was not until opiates were used that major bowel problems and abdominal pain developed. In contrast, the other two patients had severe motility disturbances that lie in the spectrum of pseudo-obstruction. This problem led to severe constipation and abdominal distension, and was surgically managed even before opiates were used in both. This might suggest that the opiates were only responsible for some of the current abdominal symptomatology, and therefore it might be anticipated that blocking the effects of the opiates directly on the bowel would only have partial benefit. Indeed, it was the two patients with the underlying motility disorder who did less well; one could not tolerate the abdominal pain that followed the injection, and the other had less impressive, although still positive, effects on abdominal symptoms. Such speculation that inherent motility disorders would predict less responsiveness to methylnaltrexone requires additional study.

Methylnaltrexone appeared safe in this short-term exposure. Three patients did experience more abdominal pain shortly after its administration. This pain lasted usually about 30–60 min, but did lead to the early cessation of treatment in one patient. There was no apparent change of the pain over the 12 weeks of the study. The other patients were able to tolerate this adverse effect because of greater overall benefits. The timing of the pain induction was most consistent with an acute effect of the blockade of opiate receptors and an acute change to motility patterns. The drug is rapidly absorbed after administration, and peak plasma concentrations occur within 60 min.\(^9\) Clinical trial experience in palliative care patients indicates that about one in three patients will have had a bowel action within 1 h of receiving the drug, some within 5 min.\(^10\) This indicates rapid action on the bowel consistent with the observation in the patients with NBS. Abdominal pain induced by the drug has also been reported in nearly one third of patients.\(^10\) It is possible that the acute effects of the drug might be minimised by the use of a slower release formulation, and the benefits would also be more prolonged. Patient 3 had greater benefit when the drug was used daily (the others did not try this regimen). Daily use makes more sense in patients with NBS since it would be more appropriate to have more continuous effects; the terminal half-life of methylnaltrexone is no longer than 9 h.\(^9\) This issue can only be addressed by further study.

The major focus of this study was to address the effect of methylnaltrexone on pain and bowel function. An instrument measuring fatigue was also applied since fatigue is the major complaint of these patients. Indeed, it improved concomitantly with improved bowel function and reduced abdominal distension. Whether this is a cause–effect relationship cannot be addressed in a study of this design. It would have been appropriate to apply an instrument to assess the effect on quality of life overall, but this was unfortunately not included in the study design.

Perhaps the greatest indicator of the clinical value of methylnaltrexone in patients with NBS was the desire of the three patients using it for the 12 weeks to recommence therapy after a short withdrawal period. In fact, this did occur in all three, and benefits similar to those observed during the study period continued for at least 6 months without apparent adverse effects apart from abdominal pain following the injection.
Conclusion

This proof-of-concept study has provided evidence that methylnaltrexone may be of clinically significant benefit for patients with NBS, particularly if there is not a severe underlying gut dysmotility syndrome. Larger studies of its efficacy and careful observation for long term adverse effects are warranted.

References

7 Candy B, Jones L, Goodman ML, Drake R, Tookman A. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. Cochrane Database Syst Rev 2011; (1): CD003448.
Low positive predictive value of the ABCD² score in emergency department transient ischaemic attack diagnoses: the South Western Sydney Transient Ischaemic Attack Study

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Key words
transient ischaemic attack (TIA), risk assessment, safety, stroke.

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Abstract

Background: The ABCD² stroke risk score is recommended in national guidelines for stratifying care in transient ischaemic attack (TIA) patients, based on its prediction of early stroke risk. We had become concerned about the score accuracy and its clinical value in modern TIA cohorts.

Methods: We identified emergency department-diagnosed TIA at two hospitals over 3 years (2004–2006). Cases were followed for stroke occurrence and ABCD² scores were determined from expert record review. Sensitivity, specificity and positive predictive values (PPV) of moderate–high ABCD² scores were determined.

Results: There were 827 indexed TIA diagnoses and record review was possible in 95.4%. Admitted patients had lower 30-day stroke risk (n = 0) than discharged patients (n = 7; 3.1%) (P < 0.0001). There was no significant difference in proportion of strokes between those with a low or moderate–high ABCD² score at 30 (1.2 vs 0.8%), 90 (2.0 vs 1.9%) and 365 days (2.4 vs 2.4%) respectively. At 30 days the sensitivity, specificity and PPV of a moderate–high score were 57% (95% confidence interval (CI) 25.0–84.2), 32.2% (95% CI 29.1–35.6) and 0.75% (95% CI 0.29–1.91) respectively.

Conclusions: Early stroke risk was low after an emergency diagnosis of TIA and significantly lower in admitted patients. Moderate–high ABCD² scores did not predict early stroke risk. We suggest local validation of ABCD² before its clinical use and a review of its place in national guidelines.

Introduction

The ABCD² stroke risk score was developed to identify transient ischaemic attack (TIA) patients with a high risk of early stroke requiring urgent management.¹ The 7-point unified ABCD² score (Table 1) was developed and tested against databases of TIA presentations to primary care practice, specialist clinics and emergency departments (EDs) in Oxfordshire (UK) and California (USA). In these cohorts low (<4), moderate (4–5) and high (6–7) ABCD² scores predicted 2-day stroke rates of 1.0%, 4.1% and 8.1% respectively.

At present, the ABCD² stroke risk score is recommended for use in stratifying care of TIA patients in Australian, UK and USA national guidelines,²–⁴ with moderate–high scores (≥4) to receive urgent care. Low scores are to receive relatively postponed assessment and treatment. This care stratification presumes that the score accurately predicts high early stroke risk.

Some of the databases used to validate the ABCD² score were over 10 years old and the care provided was not always urgent. The early stroke rates in the cohorts were much higher¹ than our reported experience,³ where the 30-day stroke risk was 0.66% in hospital-admitted TIA and 2.09% when TIA was discharged from the ED.

Meta-analysis of early stroke risk after TIA has indicated heterogeneity in early stroke risk,⁶ and recent individual reports indicate low stroke risk with modern urgent TIA care.⁵,⁷–¹² We were concerned that the ABCD² risk score, as derived from particular Californian and Oxfordshire databases,¹ would not be applicable to our practice. In this study, we set out to assess the value of ABCD² in a contemporary TIA cohort.

Methods

Consecutive ED diagnoses of TIA at two major hospitals (Liverpool and Bankstown) were identified from administrative datasets using International Classification...
of Diseases (ICD-9-CM) code ‘435’ over 3 years, between 1 January 2004 and 31 December 2006. The ED TIA diagnoses were made by emergency physicians. The hospitals are the largest in South Western Sydney (SWS), a large previously described metropolitan and rural area with a population of over 796,950. Each hospital had a stroke unit and a policy to admit TIA in discussion with an on-call stroke physician. The study pre-dated the publication and use of the ABCD2 score.1

If a person presented more than once with TIA during the study period only the earliest presentation, deemed index, was included in the analysis. Discharge to home from the ED or admission to hospital was identified. All available medical records were reviewed by one of four co-authors (consultant neurologist DC, stroke fellows DG and DE, and stroke database manager/biostatistician PT) to determine ABCD2 scores. Each was blinded to outcome, and uncertainties were resolved in discussion.

ABCD2 scores were dichotomised into low (<4) and moderate–high (≥4) in accordance with national guidelines.2–4 Where medical records could not be reviewed the cases were followed for stroke presentations, but were not included in the main analysis.

An administrative ‘personal identifier’ was used to identify subsequent presentations to the two study hospitals and all surrounding hospitals. Hospital datasets were searched for emergency ICD-9-CM TIA and stroke codes (431, 432.9, 433, 434, 435, 436 and 437) and primary and secondary position hospital separation ICD-10-AM codes (G45.0–4, G45.8, G45.9, I61.0–9, I62.9, I63.0–9, I64, I65.0–3, I66.0–9 and I67.0) for TIA, stroke and pre-cerebral and cerebral artery disease. Each record was then reviewed by one of four co-authors (DC, DG, DE and PT, led by DC) to determine if a diagnosis of acute stroke was present; uncertainty was resolved in discussion. Stroke presentations were extracted and SPSS statistical software, version 17.0 (SPSS, Chicago, IL, USA) was used for data analysis.

### Ethics approval

This study was approved by the South Western Sydney Area Health Service Human Research Ethics Committee (Western Zone) as a stated part of ongoing quality audit process, using de-identified administrative datasets.

### Statistical methods

We determined the cumulative risk of stroke at 2, 30, 90 and 365 days in those with low and moderate–high ABCD2 scores and those admitted to hospital or discharged from emergency (Fig. 1 and Tables 2,3). Proportions were compared using Chi-squared analyses and a P-value of <0.05 was applied to determine statistical significance. Confidence limits for sensitivity, specificity and positive predictive value (PPV) were calculated using the Wilson method, without continuity correction.14

### Results

#### Sample characteristics

There were 827 ‘first-ever’ ED diagnoses of TIA over 3 years. Medical record review was possible in 789

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Age ≥60 years</td>
<td>1</td>
</tr>
<tr>
<td>B Blood pressure &gt;140/90 at presentation</td>
<td>1</td>
</tr>
<tr>
<td>C Clinical features</td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>2</td>
</tr>
<tr>
<td>Speech impairment without weakness</td>
<td>1</td>
</tr>
<tr>
<td>D Duration</td>
<td></td>
</tr>
<tr>
<td>Greater than 60 min</td>
<td>2</td>
</tr>
<tr>
<td>10–59 min</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes</td>
<td>1</td>
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</tbody>
</table>

Two-day stroke risk: low score (<4) = 1.0%, moderate (4–5) = 4.1%, high (6–7) = 8.1%.1

![Figure 1](https://via.placeholder.com/150)
Mean age and median age were 69.6 years (standard deviation = 14.6) and 73 years (interquartile = 22) respectively and 50.2% of cases were male. Seventy-one per cent ($n = 563$) were admitted to hospital, 57.7% at Bankstown and 85.2% at Liverpool (Table 2). Duration and other ABCD² score features had been routinely recorded in the medical records.

### Cumulative stroke risk

Three (0.38%) of the 789 patients had a stroke in 2 days, seven (0.89%) in 30 days, 15 (1.90%) in 90 days and 19 (2.41%) in 1 year (Table 2). There were no stroke presentations in the 38 cases (4.6%) where records could not be obtained for review, and there were no stroke presentations in the 38 cases (4.6%) where records could not be obtained for review, and there were no stroke.

### Table 2 Characteristics and stroke rates of consecutive TIA patients (South Western Sydney TIA study) 2004–2006

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Liverpool Hospital (%)</th>
<th>Bankstown Hospital (%)</th>
<th>Discharged from ED (%)</th>
<th>Admitted to hospital (%)</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>392 (49.7)</td>
<td>397 (50.4)</td>
<td>226 (28.6)</td>
<td>563 (71.4)</td>
<td>789</td>
</tr>
<tr>
<td>Median age</td>
<td>68.5</td>
<td>76.0</td>
<td>72.0</td>
<td>73.0</td>
<td>73.0</td>
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<tr>
<td>Admitted</td>
<td>334 (85.2)</td>
<td>229 (57.7)</td>
<td>—</td>
<td>—</td>
<td>563 (71.4)</td>
</tr>
<tr>
<td>Discharged</td>
<td>58 (14.8)</td>
<td>168 (42.3)</td>
<td>—</td>
<td>—</td>
<td>226 (28.6)</td>
</tr>
<tr>
<td>ABCD² score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low &lt; 4</td>
<td>109 (27.8)</td>
<td>146 (36.8)</td>
<td>105 (46.5)</td>
<td>150 (26.6)</td>
<td>255 (32.3)</td>
</tr>
<tr>
<td>Mod–High ≥ 4</td>
<td>283 (72.2)</td>
<td>251 (63.2)</td>
<td>121 (53.5)</td>
<td>413 (73.4)</td>
<td>534 (67.7)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>268 (68.4)</td>
<td>322 (81.1)</td>
<td>162 (71.7)</td>
<td>428 (76.0)</td>
<td>590 (74.8)</td>
</tr>
<tr>
<td>Male</td>
<td>203 (51.8)</td>
<td>193 (48.6)</td>
<td>116 (51.3)</td>
<td>280 (49.7)</td>
<td>396 (50.2)</td>
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<td><strong>History</strong></td>
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<tr>
<td>Diabetes</td>
<td>87 (22.2)</td>
<td>86 (21.7)</td>
<td>40 (17.7)</td>
<td>133 (23.6)</td>
<td>173 (21.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>254 (64.8)</td>
<td>255 (64.2)</td>
<td>146 (64.6)</td>
<td>363 (64.5)</td>
<td>509 (64.5)</td>
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<td>TIA symptoms %</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Duration 11–60 min</td>
<td>103 (26.3)</td>
<td>120 (30.2)</td>
<td>85 (37.6)</td>
<td>138 (24.5)</td>
<td>223 (28.3)</td>
</tr>
<tr>
<td>Duration &gt;60 min</td>
<td>239 (64.9)</td>
<td>196 (49.4)</td>
<td>83 (36.7)</td>
<td>352 (62.5)</td>
<td>435 (53.1)</td>
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<td>Unilateral weakness</td>
<td>222 (56.6)</td>
<td>166 (41.8)</td>
<td>74 (32.7)</td>
<td>314 (55.8)</td>
<td>388 (49.2)</td>
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<tr>
<td>Changes in speech</td>
<td>68 (17.4)</td>
<td>76 (19.1)</td>
<td>43 (19.0)</td>
<td>101 (17.9)</td>
<td>144 (18.3)</td>
</tr>
<tr>
<td>Stroke presentations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 days</td>
<td>0</td>
<td>3 (0.8)</td>
<td>3 (1.3)</td>
<td>0 (0)</td>
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<td>30 days</td>
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<td>90 days</td>
<td>6 (1.5)</td>
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<td>15 (1.9)</td>
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<tr>
<td>1 year</td>
<td>6 (1.5)</td>
<td>13 (3.3)</td>
<td>11 (4.9)</td>
<td>8 (1.4)</td>
<td>19 (2.4)</td>
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ED, emergency department; TIA, transient ischaemic attack.

### Table 3 ABCD² stroke risk score and stroke events in admitted and discharged TIA patients

<table>
<thead>
<tr>
<th>ABCD² score</th>
<th>TIA patients admitted to hospital</th>
<th>TIA patients discharged from ED</th>
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<tr>
<td></td>
<td>Admitted Stroke events (%)</td>
<td>Discharged Stroke events (%)</td>
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<tr>
<td></td>
<td>2 days 30 days 90 days 1 year</td>
<td>2 days 30 days 90 days 1 year</td>
</tr>
<tr>
<td>0</td>
<td>7 0 0 0 0 0</td>
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<td>26 0 1 1 1 1</td>
</tr>
<tr>
<td>2</td>
<td>43 0 0 0 0 0</td>
<td>35 1 1 1 1 1</td>
</tr>
<tr>
<td>3</td>
<td>74 0 0 0 0 0</td>
<td>39 1 1 1 2 3</td>
</tr>
<tr>
<td>4</td>
<td>108 0 0 0 0 0</td>
<td>52 0 0 1 1 1</td>
</tr>
<tr>
<td>5</td>
<td>139 0 0 0 0 0</td>
<td>46 1 4 4 4 5</td>
</tr>
<tr>
<td>6</td>
<td>126 0 0 3 5</td>
<td>21 0 0 0 0 0</td>
</tr>
<tr>
<td>7</td>
<td>40 0 0 0 1 1</td>
<td>2 0 0 0 0 0</td>
</tr>
<tr>
<td>Low &lt; 4</td>
<td>150 0 0 1 (0.67) 1 (0.67)</td>
<td>105 2 (1.90) 3 (2.86) 4 (3.81)</td>
</tr>
<tr>
<td>Mod–High</td>
<td>413 0 0 5 (1.21) 7 (1.69)</td>
<td>121 1 (0.82) 4 (3.31) 5 (4.13)</td>
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<tr>
<td>Total</td>
<td>563 0 0 6 (1.07) 8 (1.42)</td>
<td>226 3 (1.33) 7 (3.10) 9 (3.98)</td>
</tr>
</tbody>
</table>

ED, emergency department; TIA, transient ischaemic attack.
presentations to surrounding hospitals. Of the seven strokes occurring in the first 30 days, none had atrial fibrillation on history or investigation. One had a significant carotid stenosis of 80–99%, on the symptomatic side.

Discharge versus admission

At 1 year, there were eight strokes (1.42%) among patients admitted to hospital and 11 strokes (4.87%) among patients discharged from the ED ($P = 0.004$) (Tables 2,3 and Fig. 2). Discharged patients accounted for all the strokes at 48 h ($n = 3$) ($P = 0.006$) and all strokes ($n = 7$) at 30 days ($P < 0.0001$). At 90 days, there were nine (3.98%) strokes in the discharged group and six (1.1%) in the admitted group ($P = 0.006$). Admitted patients had a significantly higher proportion of moderate–high scores ($\geq 4$) (73.4%) than discharged patients (53.5%) ($P < 0.0001$) (Tables 2,3).

Stroke risk and ABCD² scores

Overall, 255 patients (32.3%) had a low ABCD² stroke risk score ($< 4$) and 534 (67.7%) had a moderate–high score ($\geq 4$) (Fig. 1 and Table 2). There was no significant difference in stroke risk between low and moderate–high ABCD² scores. The percentage of strokes at 30 days, 90 days and 1 year for low and moderate–high scores were 1.2 and 0.8% ($P = 0.85$), 2.0 and 1.9% ($P = 0.85$) and 2.4 and 2.4% ($P = 0.94$) (Figs 1,3 and Tables 2,3) respectively.

Specificity and sensitivity of ABCD²

The sensitivity and specificity of a moderate–high ABCD² score in predicting early stroke was 57.1% (95% confidence interval (CI) 25.0–84.2) and 32.2% (95% CI 29.1–35.6) at 30 days and 66.7% (95% CI 38.7–87.0) and 32.3% (95% CI 29.0–35.7) at 90 days respectively.

Positive predictive value of ABCD²

Overall, the PPV of a moderate–high ABCD² score ($\geq 4$) was 0.75% (95% CI 0.29–1.91) at 30 days and 1.87% (95% CI 0.95–3.53) at 90 days. At 30 days, the PPV of a moderate–high score was 0% in admitted and 3.31% in discharged patients.

Discussion

After an emergency diagnosis of TIA the early stroke rate was low at 2 (0.38%), 30 (0.89%) and 90 (1.90%) days. There were no strokes among admitted patients in the first 30 days, and their stroke rates remained significantly lower than those of TIA patients discharged from the ED. Observed stroke rates were much lower than those reported for the collected cohorts used to develop and validate the unified ABCD² stroke risk score, where 2-, 30- and 90-day rates were 3.9%, 7.5% and 9.2% respectively. Four of those six combined cohorts were collected between 1981 and 1999, and the two more recently collected Oxfordshire TIA cohorts were not receiving urgent care, later confirmed in the later Early Use of Existing Preventive Strategies for Stroke (EXPRESS) study.

Stroke risk after TIA may be determined by urgency and quality of care, early use of anti-thrombotics and, the underlying stroke risk or pretest probability of the
population under study. The observed stroke rates in our SWS-TIA study are consistent with our earlier observations and other recent publications.3,7–11 The EXPRESS study reported a steep reduction in early stroke occurrence, from 10.3% at 90 days in the historic Oxfordshire cohort to 2.1% with an increased urgency of TIA clinic care.7 The SOS-TIA trial with all hours urgent care8 and an Australian study9 report 90-day stroke rates of 1.24% and 2.42% respectively. Our earlier report3 and this SWS-TIA study show that urgent and comprehensive care, implicit in stroke service admission, substantially lowers early stroke risk.

The ABCD² score did not stratify patient stroke risk in our cohort in admitted or in discharged patients. There was no significant difference in overall percentage of strokes between those with a low (<4) or a moderate–high (≥4) ABCD² score. Despite significantly lower ABCD² scores the discharged patients had significantly higher risk of early stroke than admitted patients (Table 3). We used PPV, reflecting specificity, sensitivity and prevalence, as a measure of ABCD² score performance. The PPV of a moderate–high ABCD² score at 30 days was low in the overall sample (0.75%) and low in both admitted (0%) and discharged (3.31%) patients. Lower than expected predictive values have also been reported by Saunders et al.,9 Asimos et al.13 and Sheehan et al.16

Amarenco et al.17 report that 20% of those with low ABCD² scores in the SOS-TIA study had ‘high risk disease’ in the form of atrial fibrillation, symptomatic carotid stenosis or symptomatic intracranial stenosis. The authors questioned whether a low ABCD² score should postpone urgent care13 as suggested in guidelines.

Usual caveats apply when using administrative datasets not originally intended for research purposes and the accuracy of coded TIA and stroke diagnoses need to be considered. We assessed the validity of TIA and stroke diagnostic codes and risk of misclassification in a previous study, finding that final diagnostic codes of TIA and stroke correspond closely with diagnoses made by expert medical record review.18

Our observations of low stroke rates following TIA are consistent with rates observed in other studies of modern and urgent TIA care, assessed using other methodology.3–11 Our stroke ascertainment was rigorous, over a large surrounding area. Our methodology mimicked that used in the California cohorts making up the vast majority of cases used in the development and validation of the ABCD² score.7 TIA diagnosis was determined by emergency physician assessment (not stroke physician review), stroke ascertainment was hospital-based and the determination of ABCD² factors was by expert medical record review.

Conclusion

Recent studies and our results suggest that urgent management of TIA greatly lowers early post-TIA stroke risk. In TIA patients presenting to an Australian ED the ABCD² score did not predict early stroke risk. The scores used in clinical decisions may lead clinicians to incorrectly delay management, resulting in avoidable strokes. These results have implications for guidelines and health service planning. At this stage we recommend wider validation of the ABCD² stroke risk score before use in clinical decisions and a review of its place in national guidelines.

References

5 Kehdi E, Cordato DC, Thomas PR, Beran RG, Cappelen-Smith C, Griffith NC et al. Outcomes of TIA patients following admission to hospital or discharge from ED. Med J Aust 2008; 189: 9–12.
10 Lichtman JH, Jones SB, Watanabe E, Allen NB, Wang Y, Howard VJ et al. Elderly women have lower rates of...
Factors influencing career decisions in internal medicine

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Abstract

Background: Numerous factors influence career decisions for internal medicine trainees and Fellows. There is a perception that a greater emphasis is placed on work–family balance by younger physicians.

Aims: To determine the characteristics of the modern internal medicine workforce and ascertain whether job flexibility is important to career decision-making. We hypothesised that factors which reflect flexibility would be highly influential in decision-making, especially for women and those with young children.

Methods: A questionnaire was mailed to 250 New Zealand internal medicine trainees and Fellows. It focused on factors, including job flexibility, interest and collegial support, and included demographic details which were primarily aimed at ascertaining family responsibilities.

Results: Response rate was 54%. The majority of female physicians are the main person responsible for their children (62%), and the majority of their partners work full-time (80%). This contrasts with male physicians, of whom only 4% are the main person responsible for their children. Flexibility was found to be more influential in women, those with young children, trainees and those working in outpatient-based subspecialties. However, contrary to our original hypothesis, flexibility was not reported to be highly influential in any group, with career choice being most influenced by interest and enjoyment, intellectual challenge and variety within the job.

Conclusion: It is hoped that results will inform employers and those involved with training to enable them to better cater for the needs of the workforce and also encourage trainees to consider future family commitments when making career decisions.

Introduction

There is a perception among physicians that a greater emphasis is placed on work–family balance and lifestyle...
by younger physicians (those born 1965–1980). It has been suggested that this is linked to the growing numbers of women entering medical school. Recommendations on how to accommodate this trend include improving access to part-time working and flexible training. Currently, almost half (46% in 2010) of New Zealand internal medicine trainees are women, and if these future physicians and their colleagues are highly influenced by flexibility when making career decisions, this is likely to have significant impact on the future of the internal medicine workforce.

To provide current information regarding the characteristics of the modern New Zealand internal medicine workforce and factors influencing career decisions for New Zealand internal medicine trainees and Fellows, we conducted a questionnaire-based study. We hypothesised that factors which reflect flexibility would be highly influential to career decision-making, especially for women and those with young families. We also explored how these factors differed between sex, between those with or without young families, between trainees and Fellows, and how they correlated with subspecialty choice in order to ascertain in which groups flexibility was important. The study was intended to inform trainees, employers and those involved with medical training on how to accommodate this trend including improving access to part-time working and flexible training.

Methods

This study was questionnaire based, using a questionnaire adapted from that used in a previous study but with some alterations to the grouping based on the authors’ subjective judgement and rewording to be less gender specific. The local Ethics Committee advised us that ethics approval was not deemed to be required given the nature of the study and that the study did not involve patients. The questionnaire was posted to a randomly selected cohort of 250 New Zealand internal medicine advanced trainees and Fellows aged less than 50 years. We only included those <50 years as we wished to assess the views of those more likely to have school-age children and to have made their career choices in the more recent past. This process of distributing questionnaires was anonymous with the investigators blinded to the identity of the recipients and respondents (see Acknowledgements for further details). The survey was followed by one email reminder. Responders were asked to rate (by placing a mark on a line) 21 factors as to how much influence each factor had on their career decision-making within internal medicine. Factors were designed to reflect flexibility, interest, collegial support and other areas. The distance along the line was measured to give a continuous variable rating value for each factor. Possible responses ranged from 1–9, with 1 being of ‘no influence’ and 9 being of ‘very strong influence’ on career choice. A rating of 1–3 was judged to be of ‘no influence’ on career decisions, 3–5 ‘little influence’, 5–7 ‘moderate influence’ and >7 ‘highly influential’. In addition, the questionnaire included basic demographic details, which were primarily aimed at ascertaining whether the doctor has young family and whether they were the main carer of the children, as well as space for free text comments. Questionnaire provided on request to the authors.

Results

The response rate was 54% (134 of 250 respondents). The distribution by sex, training status, relationship status, family commitments, employment status and speciality is listed in Table 1. There were more male respondents overall, but over half of advanced trainees were female.

Most internal medicine trainees and Fellows are in a long-term relationship (91%, with only 2.5% of male respondents being single), and the majority (62%) have dependent children. The majority of women physicians (62%) are in the role of primary caregiver for their children. This contrasts to male physicians where only a small minority of men (4%) are in the role of primary caregiver, with 80% stating their partner took on this responsibility. The employment status of physicians’ partners also differed with sex. Overall, 85% of women physicians’ partners were in full-time employment, versus 38% of male physicians’ partners. In those with young
children, 88% of female physicians’ partners were in full-time employment versus 22% of male physicians’ partners. For the purpose of further analysis, specialties of cardiology, respiratory and gastroenterology were grouped as ‘Interventional’ specialties, and endocrinology, rheumatology and dermatology were grouped at ‘Outpatient Based’ specialties.

Identification of factors influencing career decisions

Table 2 shows the average rating for each factor in all responders as well as different subgroups. Factors that reflected interest were most influential overall with a mean rating of 7.9 (highly influential). ‘Interest and enjoyment’, ‘intellectual challenge’ and ‘variety within job’ were the three most influential factors in all subgroups and showed the least variability. Factors that reflected flexibility and collegial support were moderately influential (mean rating 5.8 and 6.4 respectively).

Grouped factor analysis

Flexibility

Flexibility was significantly more influential in women (compared with men, 5.4 vs 4.6 $P < 0.01$), those with young children (compared with those without, 5.1 vs 4.6, $P < 0.01$) trainees (compared with Fellows, 5.5 vs 4.6 $P < 0.01$) and those working in outpatient-based specialties (compared with interventional specialties, 5.8 vs 3.8, $P < 0.01$) (Table 2). The influence of factors that reflected flexibility varied between groups but was not highly influential in any group. Table 3 shows the mean rating for grouped flexibility factors and other factors (those reflecting interest, collegial support and other) in respondents overall and in a number of subgroups. Factors that did not reflect flexibility were significantly more influential than those that did, overall, as well as in subgroups of men, women, those with and without young children, those practicing in interventional specialties and in fellows. Women with young children and those practicing in outpatient-based specialties showed a trend to favouring flexibility over non-flexibility factors, but differences did not reach statistical significance. There was no difference between flexibility and non-flexibility factors in trainees.

Factors reflecting collegial support were more influential in women (6.6 vs 6.1 $P < 0.01$), and those in the category of ‘Others’ were more influential in Fellows.

Individual factor analysis

Several the factors that reflected flexibility were more influential in women, with the greatest difference seen in the influence of ‘option for part-time work’ with women rating this as 5.4 compared with men, 3.2 ($P < 0.01$). Women were also more influenced by flexible working hours (5.8 vs 4.9, $P < 0.05$), lack of on-call duties (women 5.2, men 4.0, $P < 0.01$) and ease of re-entry after taking time off (4.8 vs 3.5 $P < 0.01$), whereas men rated financial reasons (5.0 vs 4.1, $P < 0.01$) and interventional/procedural opportunities (5.0 vs 3.6, $P < 0.01$) more highly.

The single factor ‘compatibility with family responsibility’ showed a significant difference between those with and without young children (6.2 vs 5.2, $P < 0.05$).

Interventional specialties were more influenced by ‘financial reasons’ (5.7 vs 4.6, $P < 0.01$). Those working in
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<th>Women</th>
<th>With young children</th>
<th>No young children</th>
<th>Interventional based</th>
<th>Outpatient based</th>
<th>Trainees</th>
<th>Fellows</th>
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<td>3.3</td>
<td>2.8</td>
<td>2.5</td>
<td>2.7</td>
<td>1.9</td>
<td>3.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Interventional/procedural opportunity</td>
<td>4.5</td>
<td>5.3</td>
<td>3.6</td>
<td>4.5</td>
<td>4.4</td>
<td>7.0</td>
<td>2.6</td>
<td>4.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Average or median</td>
<td>4.0</td>
<td>3.8</td>
<td>4.1</td>
<td>4.1</td>
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<td>4.8</td>
<td>3.6</td>
<td>5.7</td>
<td>4.3</td>
</tr>
<tr>
<td><em>P</em>-value</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

—, not applicable; NS, not significant (*P* > 0.05).
Table 3  Factor rating for flexibility and other factors

<table>
<thead>
<tr>
<th>Other factor</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rating</td>
<td></td>
</tr>
<tr>
<td>Flexibility</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>5.8</td>
</tr>
<tr>
<td>Women</td>
<td>5.4</td>
</tr>
<tr>
<td>Men</td>
<td>4.7</td>
</tr>
<tr>
<td>Those with young children</td>
<td>5.1</td>
</tr>
<tr>
<td>Those without young children</td>
<td>4.6</td>
</tr>
<tr>
<td>Women with young children</td>
<td>5.8</td>
</tr>
<tr>
<td>Interventional specialties</td>
<td>4.3</td>
</tr>
<tr>
<td>Outpatient-based specialties</td>
<td>5.9</td>
</tr>
<tr>
<td>Trainees</td>
<td>5.5</td>
</tr>
<tr>
<td>Fellows</td>
<td>4.6</td>
</tr>
</tbody>
</table>

NS, not significant (P ≥ 0.05).

outpatient specialties were more influenced by compatibility with family responsibilities, flexible working hours, lack of on-call duties (7.7 vs 5.2, 7.1 vs 4.7, 6.2 vs 3.7, respectively, all P < 0.01), regular working hours and option of part-time work (7.0 vs 5.9, 4.7 vs 3.2, respectively, both P < 0.05).

Individual factors that showed significant differences between trainees and Fellows were opportunities to take time off, flexible working hours, lack of on-call duties, option of part-time work, positive experiences in training (P < 0.05) and ease of re-entry after taking time off and lack of sexual harassment (P < 0.01) which were all more influential in trainees than Fellows.

Qualitative analysis

A total of 47 respondents (35%) (27 female, 20 male) made free text comments on factors influencing their career decisions.

Fourteen respondents (30%) discussed the importance of flexibility/regular hours in their career decisions. Twelve respondents mentioned the difficulty juggling work and family commitments.

• ‘I was motivated by the knowledge that I should be able to get a part-time consultant job. I’m in a strong position to negotiate due to shortages’
• ‘I liked most specialties but was not happy doing shift work. I like Monday–Friday 8-5’
• ‘There are few family-friendly subspecialties in Internal Medicine...I have seen many others opt for GP training part through specialty training rather than attempt part-time training/exams with colleagues/supervisors attitudes’.

Six respondents commented that although flexibility did not impact on their decision-making at the time of choosing their career, it is more important to them now and perhaps they should have given it more consideration.

• ‘I chose GM for interest before I had children and without thinking about how this would work, although in retrospect I could of chosen more wisely in terms of work-life balance/flexibility’
• ‘I decided to have children quite late therefore this had nothing to do with my training decision however it is now something of extreme importance to me’
• ‘Pre-children is very different to post children. I have difficulty continuing a career in my specialty in light of children’

One person commented specifically that flexibility was not an influencing factor for them.

Other factors which influenced respondents included ‘luck’ and ‘serendipity’ as well as ‘opportunities for research’/‘new developments’.

Discussion

This study examined characteristics of the New Zealand internal medical workforce as well as factors influencing career decisions in New Zealand internal medicine trainees and Fellows aged under 50 years and how these factors differed between sexes, family commitments and specialty choice. It should be noted that this study was questionnaire-based, and issues, such as validity of self-reported data and volunteer response bias, may have influenced results. Survivor bias may also be important, with physicians that are highly influenced by flexibility perhaps opting to pursue a career in general practice (as suggested by one free text comment) or other specialties.

However, we ensured anonymity to aid honest reporting and generally were given consistent responses and had a relatively good response rate for a postal questionnaire-based study of 54%.

We found that flexibility is more valued in women, those with young children, trainees and those working in an outpatient-based subspecialty. When making career decisions, female physicians were found to be more likely to be influenced by the option of part-time work, flexible working hours, lack of on-call duties and ease of re-entry after taking time off than their male colleagues. Comments made by respondents suggest flexibility and work-life balance are important and, although it may not have been highly influential at the time of making career decisions, flexibility can become more important with increasing family responsibilities. This is perhaps not surprising, given that we found the majority of female physicians are the main person responsible for their children (62%), and the majority of their partners work full-time (88%). This contrasts with male physicians, of whom only a small minority (4%) are the main person responsible for their children. There may also be a generational trend, given that trainees value flexibility more highly...
than their senior colleagues. Overall, flexibility was not more influential than factors in other categories. This may be due to the high influence of factors which reflected interest, which appears to be more of a priority at the time that career choices are first being considered (such as during medical school and early postgraduate years) rather than during later years when issues, such as family, may become more important, by which time career choice may have already been largely determined. Contrary to our original hypothesis, flexibility was not reported to be highly influential in any group, with career choice being most influenced by interest and enjoyment, intellectual challenge and variety within the job. Collegial support, including role models and mentors, was also influential and its importance should not be underestimated.

This information may be valuable to current and future New Zealand trainees, those responsible for training, and employers, in order to assist in creating a sustainable and content medical workforce. Trainees and mentors should take into consideration future family commitments when making career decisions and providing career guidance. Employers and those responsible for training should consider providing opportunities that better suit these doctors’ aspirations. Consistent with previous literature, improving access to part-time training positions and jobs and/or flexible working hours is likely to be particularly attractive to women trainees who have, or are intending to have, children. If one of the main aims is to train and retain New Zealand graduates, where remuneration rates often cannot fully compete with those offered in many overseas destinations, the New Zealand training bodies have a vital role to play in providing training and employment conditions to better suit the needs of trainees.

Acknowledgement

We thank the Royal Australasian College of Physicians, Wellington, New Zealand, for their help with this study. At the request of the investigators, the college randomly selected 250 trainees and Fellows and posted the questionnaires. The investigators were blinded to the identity of responders and non-responders in order to assure anonymity of those involved. The investigators are responsible for the conception and design of the study, the collation of results and write-up of this report.

References

Predicting failure to return to work
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Royal Australian Navy, Canberra, BC, Australian Capital Territory, Australia

Key words
Workers’ compensation, rehabilitation, return to work, data management, predicting outcomes.

Abstract
Aim: The research question is: is it possible to predict, at the time of workers’ compensation claim lodgement, which workers will have a prolonged return to work (RTW) outcome? This paper illustrates how a traditional analytic approach to the analysis of an existing large database can be insufficient to answer the research question, and suggests an alternative data management and analysis approach.

Methods: This paper retrospectively analyses 9018 workers’ compensation claims from two different workers’ compensation jurisdictions in Australia (two data sets) over a 4-month period in 2007. De-identified data, submitted at the time of claim lodgement, were compared with RTW outcomes for up to 3 months. Analysis consisted of descriptive, parametric (analysis of variance and multiple regression), survival (proportional hazards) and data mining (partitioning) analysis.

Results: No significant associations were found on parametric analysis. Multiple associations were found between the predictor variables and RTW outcome on survival analysis, with marked differences being found between some sub-groups on partitioning – where diagnosis was found to be the strongest discriminator (particularly neck and shoulder injuries). There was a consistent trend for female gender to be associated with a prolonged RTW outcome. The supplied data were not sufficient to enable the development of a predictive model.

Conclusion: If we want to predict early who will have a prolonged RTW in Australia, workers’ compensation claim forms should be redesigned, data management improved and specialised analytic techniques used.

Introduction
Can data be better managed to improve the likelihood of answering a specific research question? This paper illustrates how a traditional analytic approach to the analysis of an existing large database can be insufficient to answer the research question, and suggests an alternative data management and analysis approach.

The research question is: is it possible to predict, at the time of workers’ compensation claim lodgement, which workers will have a prolonged return-to-work (RTW) outcome?

Why is this research question important? It is known that working improves general health and well-being, with prolonged enforced absence from work being harmful.1 It is also known that greater percentage of patients with compensable injuries have poorer health outcomes than do those with similar but non-compensable injuries.2

It is also known that multiple non-medical factors influence RTW outcomes,3,4 with some of these including worker expectations,5–8 who is blamed for the accident,9 older age,6,10 psychological distress,10 job dissatisfaction,10 financial incentives,10 the local unemployment rate10 and lawyer involvement.11

It is also known that early coordinated care should improve RTW outcomes.12 Early recognition of both the predictive factors and workers at risk of a prolonged RTW outcome should therefore allow the early targeted application of resources to minimise prolonged RTW outcomes.

Methods
In 2007, de-identified claims data were obtained from two worker’s compensation sources in Australia. These data included all significant claims (with a significant claim being defined as either a claim resulting in time off work, or a claim requiring a specific amount of medical treatment costs) lodged between 01 March and 30 June 2007. This study followed each claim for 3 months from the date of notification, or until they were certified fit to return to their pre-injury duties (whichever occurred
first). Three months was chosen for follow-up, as most injured workers return to work within 1 month of their injury, with the average in 2007 being 26 days.13

One worker’s compensation source (data set A, \(n = 1377\)) was a self insurer in the state of New South Wales (NSW), involved primarily in the retail sector. In NSW a self insurer is an employer who meets certain criteria to act on behalf of the state workers’ compensation authority as a workers’ compensation insurance agent. The second source (data set B, \(n = 7641\)) was the Victorian state workers’ compensation authority (WorkSafe VIC). The intention behind using two different data sets was to improve the generalisability of any findings.

These data sets used common claim lodgement forms and medical certificates. Although more data were collected than were made available to this researcher (Table 1), both insurers confirmed that they had provided this researcher will all of their accessible (de-identified) data.

The data were analysed by descriptive analysis, parametric analysis (analysis of variance (ANOVA) for categorical predictor variables and multiple regression for continuous predictor variables), survival analysis (proportional hazard analysis) and a data mining technique (partitioning).

The response variable was ‘time from date of injury’ to ‘return to work’.

JMP Version 7.0.2 (SAS Institute, Cary, NC, USA) was used for the analysis.

ANOVA and multiple regression analysis were used as these forms of analysis are commonly used in the literature to develop predictive models. Additional analytic techniques were used as the author considered it unlikely for both systems and statistical reasons that ANOVA and multiple regression analysis would provide useful information.

From a systems perspective ANOVA and multiple regression analysis work best where there is a linear cause and effect relationship that is constant over time (allowing the future to be predicted from analysis of the past). The sequential relationship between well worker, injured worker, injured worker going off work, and subsequent durable RTW is, however, a complex, dynamic and interrelated relationship. The progression from one stage to the next is also not always on the basis of rational logic, and cannot be analysed in the same way as for a closed system.

It is also highly likely that the data being analysed do not meet the assumptions underpinning the statistical techniques of ANOVA and multiple regression analysis (including having a linear relationship between variables, independence of variables, constant variance of variables and normal distribution).

Proportional hazard analysis was selected as this is a regression method used for modelling survival times of categorical data. RTW is essentially a measure of survival of those injured workers who remain off work following an injury.

Partitioning (also referred to as Decision Trees) is a form of analysis used in data mining, and is used to split the data into the most diverse subgroups. Generally the first split is the best split, with each subsequent split having a smaller and less representative population with which to work. Partitioning can discover patterns by identifying which groups within the analysed sample are different.

The level of statistical significance for this study was set at 0.05. When proportional hazard (Cox regression) analysis was performed hazard ratios of greater than 2.0 or less than 0.5 were set as the level at which apparent associations were not rejected. When a 95% confidence interval includes one, apparent associations between the variable being tested and the return-to-work outcome were rejected.

Power was set to have an 80% probability of being able to distinguish between a difference in groups of 0.5 standard deviation (equating to a return-to-work outcome difference off approximately 26 days for each data set). This required a sample size of at least 65.

**Results**

Table 1 summarises the findings of the descriptive analysis.

Analysis of the data using parametric techniques failed to identify any statistically significant associations in data set A. The one exception was the time from date of injury to insurer notification (\(R^2 0.965\)), which probably represented a large outlier effect of a small number of claims. Multiple regression analysis of Data Set B calculated \(R^2\) of 0.375, with this effect being lost when time to insurer notification was excluded as a predictor variable.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data set A</th>
<th>Data set B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population size (count)</td>
<td>1442</td>
<td>9077</td>
</tr>
<tr>
<td>Median age</td>
<td>33 years</td>
<td>43 years</td>
</tr>
<tr>
<td>Percentage male</td>
<td>41.0%</td>
<td>67.5%</td>
</tr>
<tr>
<td>Percentage no lost time</td>
<td>5.52%</td>
<td>7.01%</td>
</tr>
<tr>
<td>Median income</td>
<td>$622</td>
<td>$642</td>
</tr>
<tr>
<td>Median workplace size</td>
<td>150</td>
<td>52</td>
</tr>
<tr>
<td>Median days to endpoint</td>
<td>25 days</td>
<td>76 days</td>
</tr>
<tr>
<td>SD days to endpoint</td>
<td>55.5 days</td>
<td>52.8 days</td>
</tr>
<tr>
<td>Missing data</td>
<td>65</td>
<td>1406</td>
</tr>
<tr>
<td>Analysable</td>
<td>1377</td>
<td>7671</td>
</tr>
</tbody>
</table>

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There was a consistent trend for female gender to be associated with a prolonged return-to-work outcome. Although statistical significance was not reached, qualitatively females had a longer time to endpoint than males in data set A. A similar trend was found in data set B, with the mean return-to-work outcomes being 80 days (female) and 66 days (male).

No association was found between Occupation, Type of Employment, Diagnosis, Bodily Location of injury, Mechanism of Injury, or Industry and RTW outcome in either data set.

Survival analysis found injuries involving the neck and shoulders, or shoulder, and the mechanisms of injury of being hit by or hitting objects and falls to be associated with a prolonged RTW outcome.

There was also a trend for injuries involving a mechanism of injury of being hit by or hitting objects and falls to be associated with a shortened RTW outcome.

Injuries involving the face, not elsewhere classified, or mouth, and the mechanisms of injury of lifting, muscular stress (no object), and posture/steeping/kneeling/sitting/repetitive movement were associated with a prolonged RTW outcome.

There was a trend for the mechanism of injury repetitive movement with low muscle loading to be associated with a prolonged RTW outcome.

On partitioning analysis of data set A two combinations of subgroups were associated with short RTW outcomes, having means of 17 days (days to notification <50 with certain body locations and income <$254.35) and 20 days (days to notification ≥50 with income <$241.03 or days to notification <107 and certain body locations).

For data set B found the groupings associated with the shortest RTW outcomes had means of to 29 days (various bodily locations and mechanisms of injury with age <32 and income <$559) and 34 days (various bodily locations and mechanisms of injury with age ≥32 and income <$168).

The groupings with the longest RTW outcomes in data set A had a mean 104 days (days to notification ≥50 with income ≥$241.03 and certain body locations). The grouping with the longest RTW outcomes in data set B had a mean of 94 days (various bodily locations with age ≥32).

The strongest discriminator on partitioning analysis in both data sets was diagnosis. The diagnoses repeatedly associated with prolonged RTW outcomes were neck and shoulder injuries. Other discriminators associated with longer RTW outcomes include (longer) time to notification of injury (higher) income and older age in data set A, and occupation, days to notification, bodily location of injury and age in data set B.

In data set A (but not B) advancing age was associated with either a shortened or prolonged return-to-work outcome on proportional hazards analysis and partitioning (dependent upon which other predictor variables age was grouped with), with no associations found between age and RTW outcome on ANOVA or multiple regression.

Discussion

This study failed to demonstrate any significant associations between the predictor variables and the response variable of RTW outcome on parametric (regression and ANOVA) or survival analysis (proportional hazards). The latter form of analysis did, however, demonstrate a consistent trend for females having longer RTW outcomes. Both survival and partitioning analysis identified differences between sub-groups.

The findings of this study are, however, generally consistent with what is known in the literature, and illustrate the difficulty in untangling any underlying predictive relationships. When viewed from the perspective of the biopsychosocial model of injury the findings of this study make intuitive sense. It might be expected that non-specific (medically less plausible) injuries would do poorly. Injuries that are not readily explainable on the basis of their mechanism of injury would also be expected to do poorly.

There are multiple reasons why this study failed to identify any statistically significant associations, including poor quality data, data organisation, collected data being unavailable for analysis, and importantly, failure to meet the underlying assumptions for regression analysis.

The power of this study was also severely limited by the number of subcategories (and thus small sub-group populations). This significantly restricted the number of sub-groups available for meaningful statistical analysis. For example data set A had 612 diagnoses, 61 bodily locations of injury and 30 mechanisms of injury. Data set B had 92 diagnoses, 76 bodily locations and 46 mechanisms of injury.

The major strengths of this paper are the large sample size, the cross-jurisdictional origins of the data and the analytic methodology (employing parametric and non-parametric statistical analysis, combined with data mining techniques). Associations that were common to both data sets suggest that these findings are much more likely to be generalisable.

There are several limitations to the work. It is retrospective and some of the data collected at the time of claim lodgement were not accessible for analysis. Also, some variables suggested by the literature to be
associated with prolonged return-to-work outcomes were not collected at the time of claim lodgement in the two workers’ compensations systems under study. The conservative statistical approach taken (including restricting sub-groups to $n$ of at least 65) increased the likelihood of any demonstrated associations as being real, but markedly limited the ability to find associations (as many subgroups had populations of less than 65). This was considered to be appropriate to avoid erroneous associations, given the multiple variables examined. This, however, did result in many subgroups being too small to allow meaningful analysis.

Other limitations to this work include the lack of a control group, the poor quality of some of the data (including data inputting errors, missing data and the potential for misclassification), the inability to access some of the collected data and the relatively short follow-up time. In addition, some subgroups were too small for meaningful analysis.

Many of the shortcomings of this work could be solved if the work could be performed prospectively, with the information collected specifically designed for this purpose. Then through a combination of better data management (including cleaning of data, collapsing of categories, eliminating ambiguity and overlap of definitions, and improved accessibility), expanding the questions asked at the time of claim lodgement (to include potentially predictive data identified by the literature) and utilising different analytic tools (applying data mining techniques before developing regression models) it may be possible to improve markedly the predictability of return-to-work outcomes at the time of claim lodgement.

This would require the development of a specific questionnaire that focuses on RTW outcome prediction rather than administrative claims management. Such a questionnaire would require an expanded question bank (to capture some of the additional variables identified in the literature as possible predictors) with fewer subcategories and elimination of definitional overlap/ambiguity (as is currently seen between the variables Diagnosis, Bodily Location of Injury and Mechanism of Injury). This study could then be repeated with there being a high likelihood that it would generate a predictive model that could be subsequently tested in a prospective manner.

**Conclusion**

This paper illustrates the old adage: ‘rubbish in, rubbish out’. When we are creating a database we need to consider the intended purpose of the database. A database created to track an administrative process will not automatically work for predictive modelling.

This paper suggests a methodology for further researchers to develop a robust predictive model for RTW outcomes.

**References**

Natural history of severe eosinophilia with uncertain aetiology and proposals on a practical approach to its management

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Key words: eosinophilia, hypereosinophilia, idiopathic, unknown, aetiology.

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Abstract

Background: Eosinophilia is commonly encountered during clinical practice. Some can be attributed to well-defined causes while others cannot. Optimal management of hypereosinophilia with unknown aetiology is uncertain as the natural history is not well described.

Methods: We retrospectively studied patients with hypereosinophilia (>5 × 10⁹/L) and described the characteristics, natural history and treatment of those with eosinophilia of uncertain aetiology.

Results: There were 141 patients with hypereosinophilia: 87 with well-defined causes, 54 with uncertain aetiology. The latter was managed as hypereosinophilic syndrome (HES) (n = 5), idiopathic hypereosinophilia (IH) (n = 11), presumptive helminthic infection (n = 11) and reactive eosinophilia (n = 5), while 22 were insufficiently investigated and did not have definite working diagnoses. Their median age and peak eosinophil count were 64 (22 to 94) years and 10.0 (5.2–33.9) × 10⁹/L respectively. Forty-six per cent had symptoms attributable to eosinophilia, with the HES and insufficiently investigated groups having the highest (100%) and lowest (27%) percentages respectively. HES and IH patients were most extensively investigated. All 14 HES or IH patients who received steroids responded. All presumptive helminthic infection patients received mebendazole: nine responded, and two had unassessable responses. For the remaining patients, seven received steroids and all responded; one received mebendazole but defaulted; 19 were not treated: 11 resolved spontaneously. No non-HES patients developed eosinophilia-related organ dysfunction. No mortality was caused by hypereosinophilia.

Conclusions: Patients with hypereosinophilia of uncertain aetiology can be empirically managed according to working diagnoses derived from history taking, examination and selective investigations. Most patients have benign short-term outcomes, but longer monitoring is required to assess long-term outcomes from untreated hypereosinophilia.

Introduction

Eosinophilia is often encountered during daily clinical practice. The underlying causes vary from atopy, medications, helminthic infection (HI) to more serious conditions like malignancies, vasculitis and myeloproliferative neoplasms (MPN).

Eosinophilia may obviously be the primary process of a haematological neoplasm or secondary to an established disease. Treatment can be directed towards the underlying causes of eosinophilia for such patients. However, eosinophilia may also present as the sole abnormality in an otherwise healthy person with no obvious signs and symptoms to suggest an underlying cause. The extent of investigations and the management of such patients are often variable and physician dependent. Some patients have no conclusive diagnoses in spite of extensive investigations, while others are not thoroughly investigated because they refuse extensive tests or these are deemed unnecessary by their physicians. The natural history of eosinophilia among patients with uncertain aetiology has not been well described and might have contributed to such variations in management.

We retrospectively reviewed the demographics, clinical manifestations, investigations and management of patients with severe eosinophilia (>5 × 10⁹/L) of uncertain aetiology who were seen at a single large tertiary institution. These patients, including those with presumptive hypereosinophilic syndrome (HES) and idiopathic hypereosinophilia (IH), were included regardless of the extent of investigations done.
We arrived at some conclusions on the natural history of severe eosinophilia with uncertain causes. We also suggested a realistic approach to the management of such conditions, especially within the constraints of limited investigations due to limited resources or patients’ choices, which are situations not infrequently encountered during daily practice.

**Methods**

A list of inpatients and outpatients with at least one eosinophil count of \(>5 \times 10^9/L\), who were seen at our institution over a 5-year period from January 2003 to December 2007, was electronically generated. The eosinophil counts of all selected patients were reviewed from the time when they first attended our institute or other affiliated institutes where electronic medical records were accessible. This enabled us to determine as accurately as possible the first day when their eosinophil counts rose above \(5 \times 10^9/L\).

To exclude spurious results, patients with only one documented high eosinophil count with no further follow up were excluded after we had verified that this was true at other affiliated institutes. However, this could not be done for those who were followed up at non-affiliated institutes or clinics.

Case notes of the selected patients were retrospectively reviewed for information on their demographics, relevant past medical history, clinical manifestations, investigations, evidence of end-organ involvement secondary to eosinophilia, physicians’ diagnoses, treatment, treatment responses, durability of responses, progress of eosinophilia, mortality and follow-up status. For each patient, the underlying cause of eosinophilia was also determined and agreed upon by two of the authors (Ang and Linn) in the light of the available information. These authors’ diagnoses were reached independently of the physicians’ diagnoses stated in the case notes.

Patients with eosinophilia of uncertain aetiology as assessed by their physicians (stated in the case notes) were further analysed in an attempt to determine their characteristics and the natural history of their eosinophilia.

World Health Organization (WHO)\(^1\) defines HES as at least 6 months of persistent eosinophilia \((\geq 1.5 \times 10^9/L)\) for which no underlying causes can be found and which is associated with signs of organ dysfunction. IH refers to similar cases of eosinophilia without associated organ dysfunction.\(^1\) Because HES and IH are diagnoses of exclusion and are of uncertain aetiology, patients who were thought to have these by their physicians were also included in our analysis.

Follow-up data were analysed up to February 2009. All statistical analyses were done using SPSS (version 13.0, SPSS, Chicago, IL, USA).

**Results**

There were 141 patients who had at least one eosinophil count of \(>5 \times 10^9/L\) during the study period. In 62\% \((n = 87)\) of these patients, the severe eosinophilia could be attributed to definite primary or secondary causes, such as MPN, leukaemias, lymphomas, non-haematological malignancies, vasculitis, autoimmune diseases, medications, proven HIs, atopy, Kimura disease, eosinophilic pneumonia and fasciitis. The remaining 54 patients (38\%) were not given any definitive diagnoses by their physicians and were managed based on the presumptive diagnoses detailed in Tables 1 (first row) and 2 (first column). The authors’ assessment of the working diagnoses concurred with those of the physicians in 48 (89\%) of the patients.

The following results were based on the analyses of these 54 patients who did not have definite aetiologies for their hypereosinophilia.

**Table 1** Frequencies (%) of the various types of investigations within each physician’s working diagnoses group

<table>
<thead>
<tr>
<th></th>
<th>HES ((n = 5))</th>
<th>Idiopathic hypereosinophilia ((n = 11))</th>
<th>Presumptive helminthic infection ((n = 11))</th>
<th>Reactive eosinophilia or inconclusive working diagnoses ((n = 27))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool microscopy</td>
<td>80%</td>
<td>45%</td>
<td>73%</td>
<td>30%</td>
</tr>
<tr>
<td>ANCA screening</td>
<td>100%</td>
<td>73%</td>
<td>45%</td>
<td>26%</td>
</tr>
<tr>
<td>Autoimmune screening</td>
<td>100%</td>
<td>73%</td>
<td>64%</td>
<td>30%</td>
</tr>
<tr>
<td>CT scan</td>
<td>60%</td>
<td>73%</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Bone marrow studies</td>
<td>80%</td>
<td>82%</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>80%</td>
<td>82%</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>TCR clonality</td>
<td>None</td>
<td>18%</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>FIP1L1-PDGFRA(^\dagger)</td>
<td>40%</td>
<td>45%</td>
<td>18%</td>
<td>4%</td>
</tr>
</tbody>
</table>

\(^\dagger\)Polymerase chain reaction for FIP1L1-PDGFRA was only available from March 2004 onwards. ANCA, antineutrophilic cytoplasmic antibody; CT, computed tomography; HES, hypereosinophilic syndrome; TCR, T-cell receptor.
Demographics and relevant medical history

The patients’ median age was 64 (22 to 94) years, with a male:female ratio of 1.8:1. They comprised of 65% Chinese, 11% Malays, 19% Indians and 5% other ethnicity (Thais and Indonesians). Sixty-five per cent were inpatients, while the rest were outpatients. They had median peak eosinophil counts of 10.0 (5.2–33.9) × 10^9/L, and median immunoglobulin E levels of 2990 (20–67 800) IU/mL (normal range 18–100 IU/mL).

Among the 51 patients whose creatinine levels were known, two were mildly raised to <200 μmol/L, nine had chronic renal failure with creatinine >200 μmol/L, six had end-stage renal failure on haemodialysis (n = 3) or peritoneal dialysis (n = 3). Some patients had a background history of atopy (n = 13) or rheumatological diseases (n = 2) which were deemed not to have caused the severe eosinophilia.

Frequency and type of symptoms

Overall, 46% of the patients presented with symptoms which were attributable to eosinophilia. All patients presumed to have HES were symptomatic with proven gastrointestinal tract (GIT) (n = 2), cardiac (n = 2) and/or neuromuscular involvement (n = 2). About half of the patients thought to have HI and IH were symptomatic, while only about a quarter of patients who were insufficiently investigated were symptomatic.

Investigations

Blood cell indices did not show any evidence of primary clonal diseases for severe eosinophilia in all patients. A wide range of investigations was done, but the extent of investigations showed great variation among patients. Stool microscopy for ova/cyst/parasites, autoimmune screening and antineutrophilic cytoplasmic antibody (ANCA) screening were the three most common investigations carried out. Only 12 patients underwent thorough investigations with bone marrow studies, computed tomography (CT) scans, autoimmune screening and ANCA screening, many of whom were eventually thought to have HES (n = 3) or IH (n = 6). The types and frequencies of investigations done according to the working diagnoses of the physicians were shown in Table 1.

Treatment, progress of eosinophilia and patients’ outcome

Table 2 reflected the treatment given, treatment responses and durability of responses according to working diagnoses. A response was taken as a decrease in eosinophil count to <1.5 × 10^9/L on at least two consecutive occasions, and a patient was considered cured if he maintained his response without treatment for at least 1 month. An eosinophil count of below 1.5 × 10^9/L instead of the normal value of 0.5 × 10^9/L was taken as a response because target organ damage associated with mild eosinophilia (0.5–1.5 × 10^9/L) is rare.

Overall, 61% of the patients received some form of appropriate empirical treatment. Patients who were insufficiently investigated and had no conclusive working diagnoses were least likely to receive treatment. Seventy-six per cent of the patients had resolution of their eosinophilia with or without treatment. The durability of responses of the patients at a median follow up of 15 months is summarised in Table 2.

The overall median duration to resolution of eosinophilia was 55 days. The individual median duration to resolution of eosinophilia for the various groups of patients was as follows: presumptive HES and IH – 77 days; presumptive HI – 25 days; presumptive reactive eosinophilia – 27 days; insufficiently investigated and no conclusive working diagnoses – 168 days.

The overall mortality rate was 11% (n = 6, including three who died before resolution of eosinophilia), but none was due to hyper eosinophilia or other undiagnosed serious aetiologies. Except for patients with presumptive HES, none developed end-organ involvement or dysfunction as a result of eosinophilia at a median follow up of 15 months.

Discussion

We focused on patients with severe eosinophilia because their eosinophil counts would most likely remain significantly elevated with a higher likelihood of associations with organ damage, even with mild fluctuations from time to time.

A significant proportion of our patients had hyper eosinophilia that could not be attributed to well-defined aetiologies. This finding was quite similar to the other studies (34–36%), including one of which excluded HES and presumptive IH from the group with unknown aetiology. If we had excluded such patients (n = 16), our percentage of patients with unknown aetiology would become lower at 27%, which was still quite substantial. This difference might be explained by the different selection criteria: the other study studied patients who were admitted for problems relating to any degree of eosinophilia, while we had included all inpatients and outpatients with severe eosinophilia.

Our patients were mainly middle aged, and there was a slight male preponderance. Of interest, 17 of the patients had renal impairment. Renal failure had been...
reported to be associated with eosinophilia, some of which had been attributed to haemodialysis. Only three of our patients with renal impairment were on haemodialysis. Therefore, renal dysfunction independent of the effects of haemodialysis could have contributed to hypereosinophilia, and the underlying pathogenesis remained to be established.

Only nearly half of our patients were symptomatic from the eosinophilia, despite having such high eosinophil counts. Due to disease definition, all five patients with presumptive HES were symptomatic with involvement of the GIT, heart and/or neuromuscular system as shown on biopsy or imaging. This was consistent with the findings of a National Institute of Health study which found that the cardiovascular and nervous systems were most severely affected in patients with IH. On the other hand, much lower proportions of patients with other working diagnoses, especially those without conclusive diagnoses, were symptomatic. These differences might be due to symptomatic patients being more likely to undergo investigations than asymptomatic ones.

It is sometimes difficult to decide on the necessity and the extent of investigations among hypereosinophilia patients. Non-invasive, less expensive and more widely known tests were performed more frequently for our patients. Only 56% of all presumptive HES and IH patients in our study received more thorough investigations with bone marrow studies, CT scan, autoimmune screening and ANCA screening. In spite of not being fully investigated, none of them developed serious diseases, such as lymphoma at a median follow up of 37 months. Ideally, complete investigations need to be done for all patients with persistent eosinophilia of unknown aetiology before HES or IH can be diagnosed. This may not always be possible during daily practice due to cost concerns, patients’ preferences or unavailability of special tests in some institutes. Patients who are...
initially thought to have HES in spite of incomplete investigations due to these reasons should still be empirically managed as for HES. Those who do not respond to empirical treatment should be persuaded to undergo complete investigations or have their blood samples sent to another centre for the specialised tests. Therefore, selective investigations and appropriate management after detailed clinical assessments, rather than fully investigating all patients regardless of the working diagnoses, would probably be the most sensible approach. This was further supported by our observation that with such a selective approach, there was agreement in the conclusions reached between the physicians and the authors for most patients, even though the authors had additional knowledge on the patients’ subsequent clinical courses. There was no mortality or morbidity due to eosinophilia or other serious undiagnosed aetiologies among our patients.

Patients thought to have IH and HES were most likely to be treated soon after presentation to control their symptoms or organ dysfunction, even though by WHO definition, HES should be diagnosed only when there was persistent eosinophilia of \( \geq 1.5 \times 10^9/L \) beyond 6 months. However, in the presence of organ dysfunction or symptoms, observing the eosinophilia for longer periods without treatment may be detrimental. As observed among our patients, most HES and some IH were not self-limiting and required continuous treatment. Patients with untreated IH must have long-term monitoring for end-organ dysfunction if eosinophilia was persistent. On the other hand, it might be possible for some who were initially treated to be tailed off therapy so as to minimise the side-effects.

Empirical mebendazole resulted in the resolution of eosinophilia in all assessable patients with presumptive HI. Hence, empirical treatment of patients at risk or with symptoms of HI can be considered before carrying out further investigations even if stool microscopy is not diagnostic. They should be followed up for resolution of the eosinophilia after treatment. The median duration to resolution of eosinophilia among patients with reactive eosinophilia (27 days) and presumptive HI (25 days) in our study could potentially be used as a guide to determine the time frame after which further investigations should be carried out for patients who were initially thought to have reactive eosinophilia or presumptive HI.

Our study’s limitations were its retrospective nature, short overall median follow up and significant proportion of patients who defaulted. Larger prospective observational studies with longer follow up will more accurately reflect the natural history of patients with hypereosinophilia of uncertain aetiology. Despite these deficiencies, we were able to derive some conclusions from this study. We propose the following practical approach when encountering a patient with hypereosinophilia:

1. Before deciding on the necessity, type and extent of investigations, detailed history taking and physical examination should be carried out for all patients to determine the working diagnoses and presence of eosinophilia-related organ dysfunction.

2. Patients with risks of exposure or symptoms suggestive of HI can be given empirical antihelminthic treatment before extensive investigations. These patients, together with those who are thought to have reactive eosinophilia and who are initially minimally investigated must be monitored. Further investigations should be considered when eosinophilia does not resolve after about 1 month despite resolution of the original infection or other stimulus.

3. Patients with severe eosinophilia and end-organ dysfunction not attributable to other causes should be managed as for HES and be promptly started on treatment (with steroids) rather than being observed for persistent eosinophilia beyond 6 months because it may not always be possible to diagnose HES only after thorough investigations. In the presence of end-organ dysfunction, FIP1L1-PDGFRA should preferably be done at presentation for these patients, because clonal eosinophilia with this mutation responds well to low dose imatinib rather than steroids. However, if this test cannot be done soon after presentation, patients may have to be empirically managed as for HES after exclusion of other causes from available clinical information and limited test results. Because HES largely responds well to steroids, failure to do so will warrant full investigations (including FIP1L1-PDG1RA) to exclude other more serious aetiologies.

4. Patients with asymptomatic IH may not need treatment but will need close monitoring for end-organ involvement. Patients who are symptomatic may be given a trial of steroids which may be subsequently decreased or weaned off to minimise side-effects. Patients with symptoms who do not respond well to steroids and those who have persistent eosinophilia of \( >1.5 \times 10^9/L \) even if asymptomatic should be considered for complete investigations (including FIP1L1-PDG1RA), if these have not been done earlier.

**Conclusion**

Selective investigations and appropriate empirical treatment based on clinicians’ assessments are the most rational approaches when encountering patients with hypereosinophilia. These patients should be monitored closely for the progress of the eosinophilia, and further
investigations should be carried out if the hypereosinophilia persists. Although no major end-organ damage is seen among our patients, longer prospective follow up of such patients will be necessary to confirm this observation.

Acknowledgements

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References


Prevalence and determinants of QT interval prolongation in medical inpatients

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Key words

QT interval, torsades de pointes, arrhythmia, epidemiology.

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Abstract

Background: QT interval prolongation carries an increased risk of torsade de pointes and death.

Aim: We sought to determine the prevalence of QT prolongation in medical inpatients and to identify determinants of this condition.

Methods: We enrolled consecutive patients who were admitted to the internal medicine ward and who had an electrocardiogram performed within 24 h of admission. We collected information on baseline patient characteristics and the use of QT-prolonging drugs. Two blinded readers manually measured the QT intervals. QT intervals were corrected for heart rate using the traditional Bazett formula and the linear regression-based Framingham formula. We used logistic regression to identify patient characteristics and drugs that were independently associated with QTc prolongation.

Results: Of 537 inpatients, 22.3% had a prolonged QTc based on the Bazett formula. The adjusted odds for QTc prolongation based on the Bazett correction were significantly higher in patients who had liver disease (OR 2.9, 95% CI: 1.5–5.6), hypokalaemia (OR 3.3, 95% CI: 1.9–5.6) and who were taking QT-prolonging drug at admission (OR 1.7, 95% CI: 1.1–2.6). Overall, 50.8% of patients with QTc prolongation received additional QT-prolonging drugs during hospitalisation.

Conclusions: The prevalence of QTc prolongation was high among medical inpatients but depended on the method used to correct for heart rate. The use of QT-prolonging drugs, hypokalaemia and liver disease increased the risk of QTc prolongation. Many patients with QTc prolongation received additional QT-prolonging drugs during hospitalisation, further increasing the risk of torsade de pointes and death.
Introduction

QT interval prolongation is a congenital or acquired condition that is associated with an increased risk of torsade de pointes ventricular tachycardia, coronary heart disease, and cardiovascular and overall mortality.\(^1\)\(^-\)\(^3\) Risk factors for acquired prolongation of the QT interval and torsade de pointes include electrolyte disorders, bradycardia, organic heart disease, subarachnoid haemorrhage, starvation, HIV infection and genetic susceptibility.\(^4\)\(^-\)\(^7\) The use of drugs known to prolong the QT interval or to interfere with the metabolism of QT-prolonging drugs is another common risk factor.\(^4\)\(^-\)\(^8\) In a population-based study of about 5 million of adult outpatients, 22.8% of patients filled prescriptions for at least one QT-prolonging drug during a twelve-month period.\(^9\)

The prevalence and risk factors associated with a prolonged QTc interval have been studied in selected populations, such as patients with myocardial infarction, subarachnoid haemorrhage and alcoholic liver disease, in drug safety studies, and in healthy individuals.\(^10\)\(^-\)\(^13\) However, little is known about the prevalence and determinants of QT interval prolongation in unselected medical inpatients. Medical inpatients represent a large patient group, are typically elderly and polymorbid, and receive multiple drug treatments. Therefore, medical inpatients may be at particular risk for QT prolongation. The goal of this study was to determine the prevalence of QT prolongation in unselected medical inpatients and to identify clinical patient factors and drugs that are associated with QT interval prolongation.

Materials and methods

Patient identification and eligibility

We screened consecutive patients hospitalised in the division of general internal medicine of a Swiss teaching hospital from 1 January to 31 March 2009. All patients who had an electrocardiogram (ECG) performed within the first 24 h of admission were potentially eligible for this study. We excluded patients who were hospitalised for more than 48 h before admission to the medical ward. We also excluded patients with atrial fibrillation, bigeminy, wide QRS complex (>120 ms) or unidentifiable T waves on the baseline ECG because the QT interval cannot be reliably measured under such conditions.\(^14\) Our Ethics Committee approved this study.

Measurements of the QT interval

Two trained readers, blinded to the clinical data, manually measured the RR and QT intervals using the first printed 12-lead ECG available within 24 h of admission. The QT interval was measured on a single beat from the beginning of the QRS complex to the end of the T wave in lead V2 based on the tangent method, with the aid of calipers.\(^13\) The lead V2 was chosen because it usually provides the closest approximation of the longest QT.
If the end of the T wave in lead V2 could not be clearly identified, the lead with the most well-defined T wave end was chosen. We then averaged the RR and QT intervals obtained by the two readers and corrected the QT intervals for heart rate using Bazett’s formula ($QTc = QT/\sqrt{RR}$). This formula was chosen because it is widely used in clinical practice and prolonged QTc intervals based on this formula are associated with an increased risk of torsade de pointes and sudden death. However, because the Bazett correction tends to produce overlong QTc values at faster heart rates, we also used the linear regression-based Framingham formula to adjust for heart rate ($QTc = QT + 0.154 \times (1 - RR)$). QT intervals corrected with this formula were found to have a negligible correlation with heart rate as opposed to Bazett’s formula. Based on current recommendations, we defined QTc prolongation as a QTc of >450 ms in men and >460 ms in women. A QTc interval above 500 ms in either sex is significantly associated with a higher risk for torsade de pointes.

**Statistical analyses**

We assessed the interrater reliability for RR and QT measurements between the two readers using the intraclass correlation coefficient. We explored differences in baseline characteristics between patients with and without a prolonged QTc interval based on the Bazett correction using Wilcoxon rank-sum tests for continuous variables and chi-square tests (or Fisher’s exact tests) for categorical variables. We used two-sided $P$-values of <0.05 to define statistical significance.

We used backward stepwise logistic regression to identify baseline patient characteristics that were independently associated with a prolonged QTc interval based on the Bazett correction. We used $P$-values of ≥0.2 as a criterion for variable elimination and $P$-values of <0.15 as a criterion for variable addition. We considered the following variables in the multivariable model: age ≥65 years, sex, coronary artery disease, systolic dysfunction, liver disease, hypokalaemia, elevated serum creatinine and use of at least one QT-prolonging drug from Lists 1–3 at the time of admission.

In sensitivity analyses, we used the same logistic regression approach to investigate whether patient characteristics and the use of QT-prolonging drugs were independently associated with a prolonged QTc interval based on the Framingham correction. Because the association between QT-prolonging drugs from List 1 and the occurrence of torsade de pointes is best documented, we also repeated the analyses, including the use of at least one QT-prolonging drug from List 1 only in the logistic regression model.

**Results**

Of the 902 patients screened, 777 had an ECG performed at the time of admission and met the inclusion criteria (Fig. 1). Of these, we excluded 38 because they were hospitalised for more than 48 h before transfer to the medical ward, 197 with atrial fibrillation, bundle branch block, or both, three in whom T waves could not be identified and two who had bigeminy. The final study sample comprised 537 patients. The interrater agreement for RR and QT interval measurements between the two readers was excellent, with intraclass correlation coefficients of 0.99 and 0.95 respectively. Overall, 120 patients (22.3%) had a prolonged QTc interval based on the Bazett correction. A severe QTc prolongation >500 ms was present in 14 patients only (2.6%). When the QT interval was corrected using the Framingham formula, 34 patients (6.3%) had a prolonged QTc interval and four (0.8%) had severe QTc prolongation >500 ms.

**Comparison of patient baseline characteristics according to QTc interval**

In general, patients with and without QTc interval prolongation based on the Bazett correction had similar baseline characteristics (Table 1). However, patients with QTc prolongation at admission were significantly more likely to have liver disease (17.5% vs 7.4%; $P = 0.001$), hypokalaemia (26.7% vs 10.8%; $P < 0.001$) or to take

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**Figure 1** Selection of study sample. ECG, electrocardiogram.
Table 1 Baseline patient characteristics according to QTc interval at admission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 537)</th>
<th>Patients with prolonged QTc† (n = 120)</th>
<th>Patients without prolonged QTc† (n = 417)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>66.9</td>
<td>67.5</td>
<td>66.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Male sex</td>
<td>52.0</td>
<td>55.0</td>
<td>51.1</td>
<td>0.45</td>
</tr>
<tr>
<td>Principal discharge diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia and other infectious diseases</td>
<td>29.1</td>
<td>30.0</td>
<td>28.8</td>
<td></td>
</tr>
<tr>
<td>Cardiac diseases</td>
<td>11.9</td>
<td>10.0</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal and hepatic diseases</td>
<td>9.3</td>
<td>14.2</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>8.4</td>
<td>6.7</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>8.8</td>
<td>8.3</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>32.6</td>
<td>30.8</td>
<td>33.1</td>
<td></td>
</tr>
<tr>
<td>History of a prolonged QT interval</td>
<td>1.1</td>
<td>2.5</td>
<td>0.7</td>
<td>0.13</td>
</tr>
<tr>
<td>History of torsade de pointes</td>
<td>0.2</td>
<td>0.8</td>
<td>0</td>
<td>0.22</td>
</tr>
<tr>
<td>History of cardiac arrest</td>
<td>0.4</td>
<td>0.8</td>
<td>0.2</td>
<td>0.40</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>21.2</td>
<td>20.0</td>
<td>21.6</td>
<td>0.71</td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction‡</td>
<td>11.4</td>
<td>10.8</td>
<td>11.5</td>
<td>0.84</td>
</tr>
<tr>
<td>Liver disease§</td>
<td>9.7</td>
<td>17.5</td>
<td>7.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate &gt;85 b.p.m.</td>
<td>43.6</td>
<td>50.8</td>
<td>41.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypokalaemia (&lt;3.5 mmol/L)</td>
<td>14.3</td>
<td>26.7</td>
<td>10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypomagnesaemia (&lt;0.6 mmol/L)‡‡</td>
<td>9.3</td>
<td>8.0</td>
<td>9.4</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Elevated serum creatinine†</td>
<td>46.4</td>
<td>50.0</td>
<td>45.3</td>
<td>0.37</td>
</tr>
<tr>
<td>Use of drugs that may prolong QT interval‡‡</td>
<td></td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>None</td>
<td>66.5</td>
<td>56.7</td>
<td>69.3</td>
<td>0.01</td>
</tr>
<tr>
<td>≥2</td>
<td>24.8</td>
<td>28.3</td>
<td>23.7</td>
<td>0.30</td>
</tr>
<tr>
<td>Use of ≥1 drug that may prolong QT interval‡‡</td>
<td>33.5</td>
<td>43.3</td>
<td>30.7</td>
<td>0.01</td>
</tr>
<tr>
<td>From List 1</td>
<td>10.2</td>
<td>17.5</td>
<td>8.2</td>
<td>0.003</td>
</tr>
<tr>
<td>From List 2</td>
<td>12.7</td>
<td>12.5</td>
<td>12.7</td>
<td>0.95</td>
</tr>
<tr>
<td>From List 3</td>
<td>10.6</td>
<td>13.3</td>
<td>9.8</td>
<td>0.27</td>
</tr>
</tbody>
</table>

†Defined as a QTc interval ≥450 ms in men and ≥460 ms in women using the Bazett correction. ‡Defined as a left ventricular ejection fraction ≤50%. §Defined as a diagnosis of liver cirrhosis, active viral hepatitis, acute hepatitis or hepatic failure; 32 of 52 patients (62%) with liver disease had also a history of alcohol abuse. ‡‡Any medication at admission from http://www.qtdrugs.org Lists 1–3. In alphabetical order: alfuzosin (n = 2), amitriptyline (n = 3), atazanavir (n = 4), azithromycin (n = 5), chloral hydrate (n = 3), chloroquine (n = 1), ciprofloxacin (n = 8), citalopram (n = 44), clarithromycin (n = 5), clomipramine (n = 3), clozapine (n = 2), domperidone (n = 19), flecaïnide (n = 1), fluconazole (n = 2), fluoxetine (n = 7), galantamine (n = 2), haloperidol (n = 5), indapamide (n = 4), levofloxacin (n = 5), lithium (n = 6), methadone (n = 7), moxifloxacin (n = 4), ondansetron (n = 3), paroxetine (n = 9), quetiapine (n = 25), quindine (n = 1), risperidone (n = 11), sertraline (n = 8), sotalol (n = 2), tizanidine (n = 3), trimethoprim/sulphamethoxazole (n = 1), verapamil (n = 11) and voriconazole (n = 1).

least one drug with the potential to prolong the QT interval (43.3% vs 30.7%; P = 0.01). The proportion of patients who had hypomagnesaemia was similar among patients with and without QTc interval prolongation.

Inpatient processes and outcomes of care according to QTc interval

A substantial proportion of patients received at least one additional drug known to prolong the QT interval (51%). The prescription rate was similar in patients with and without prolonged QTc interval based on the Bazett correction (50.8% vs 51.1%; P = 0.96) (Table 2). A somewhat higher proportion of patients with QTc prolongation received at least one drug that may prolong the QT interval at the time of hospital discharge than patients without QTc prolongation, but the difference failed to achieve statistical significance (49.1% vs 39.5%; P = 0.07). Overall, a somewhat higher proportion of patients with QTc prolongation received QT-prolonging drugs at any time than patients without QTc prolongation (75.8% vs 66.4%; P = 0.051).

Overall 47 patients (8.8%) died during the hospital stay (Table 2), with no significant difference between patients with and without QTc prolongation based on the Bazett correction. The mortality rates of patients with and
without severe QTc prolongation (>500 ms) were similar (7.1% vs 8.8%; P > 0.99). None of the deaths was sudden or could be attributed to arrhythmia. Only one patient who was enrolled in a methadone substitution programme and who had a prolonged QTc of 478 ms based on the Bazett correction (but a normal QTc (446 ms) based on the Framingham correction) at the time of admission had a nonfatal episode of torsade de pointes during hospitalisation. The length of hospital stay did not differ between patients with and without QTc prolongation.

Independent predictors of QTc interval prolongation

After adjustment for clinical patient factors and the use of QT-prolonging drugs at baseline (Table 3), the odds of QTc interval prolongation based on the Bazett correction were significantly higher in patients who had liver disease (OR 2.9, 95% CI: 1.5–5.6), hypokalaemia (OR 3.3, 95% CI: 1.9–5.6) or who used at least one QT-prolonging drug at baseline (OR 1.7, 95% CI: 1.1–2.6). The same factors, liver disease (OR 4.5, 95% CI: 1.7–12.1), hypokalaemia (OR 4.1, 95% CI: 1.8–9.4) or use of at least one QT-prolonging drug (OR 2.2, 95% CI: 1.1–4.6), were significantly associated with QTc prolongation when the Framingham correction was applied. When we restricted our analyses to the use of at least one drug from List 1 only, the magnitude of risk for this variable increased substantially using both the Bazett (OR 2.1, 95% CI: 1.1–3.8) and the Framingham correction (OR 3.9, 95% CI: 1.7–9.0), while the risks for liver disease and hypokalaemia remained unchanged.

Discussion

Our results demonstrate that a substantial proportion of medical inpatients (22.3%) had a prolonged QTc interval at the time of admission based on Bazett’s heart rate correction method. Three clinical factors, the use of at least one QT-prolonging drug at admission, use of at least one QT-prolonging drug at admission, use of at least one QT-prolonging drug at admission, use of at least one QT-prolonging drug at admission, use of at least one QT-prolonging drug at admission, use of at least one QT-prolonging drug at admission.

Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 537) Per cent or median (IQR)</th>
<th>Patients with prolonged QTc† (n = 120)</th>
<th>Patients without prolonged QTc† (n = 417)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processes of care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addition of ≥1 drug that may prolong QT interval during the hospital stay‡</td>
<td>51.0</td>
<td>50.8</td>
<td>51.1</td>
<td>0.96</td>
</tr>
<tr>
<td>Discharge from the hospital with ≥1 drug that may prolong QT interval‡</td>
<td>41.6</td>
<td>49.1</td>
<td>39.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Outcomes of care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>8.8</td>
<td>8.3</td>
<td>8.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Cardiopulmonary resuscitation due to torsade de pointes</td>
<td>0.2</td>
<td>0.8</td>
<td>0</td>
<td>0.22</td>
</tr>
<tr>
<td>Length of hospital stay, days§</td>
<td>11 (7–20)</td>
<td>12 (8–21)</td>
<td>11 (7–18)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

†Defined as a QTc interval ≥450 ms in men and ≥460 ms in women using the Bazett correction. ‡Any medication from http://www.qtdrugs.org Lists 1–3. §After exclusion of 47 patients who died in the hospital. IQR, interquartile range.

Table 3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted OR for QTc prolongation‡</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Bazett correction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>1.5</td>
<td>0.9–2.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.4</td>
<td>0.9–2.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Liver disease</td>
<td>2.9</td>
<td>1.5–5.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>3.3</td>
<td>1.9–5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use ≥1 drug that may prolong QT interval§</td>
<td>1.7</td>
<td>1.1–2.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Framingham correction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>2.2</td>
<td>0.9–5.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.0</td>
<td>0.9–4.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.2</td>
<td>1.0–5.1</td>
<td>0.06</td>
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<tr>
<td>Liver disease</td>
<td>4.5</td>
<td>1.7–12.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>4.1</td>
<td>1.8–9.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Use ≥1 drug that may prolong QT interval§</td>
<td>2.2</td>
<td>1.1–4.6</td>
<td>0.04</td>
</tr>
</tbody>
</table>

†Defined as a QTc interval ≥450 ms in men and ≥460 ms in women. §The following variables were included in the logistic regression model: age ≥65 years, sex, coronary artery disease, left ventricular systolic dysfunction (ejection fraction ≤50%), liver disease, hypokalaemia (<3.5 mmol/L), elevated serum creatinine (>106 µmol/L for men and >80 µmol/L for women) and use ≥1 drug at admission that may prolong QT interval. §Any medication at admission from http://www.qtdrugs.org Lists 1–3.
hypokalaemia and liver disease were independently associated with QTc prolongation, regardless of the heart rate correction method that was applied. Importantly, more than half of patients with QTc prolongation at the time of admission had at least one additional QT-prolonging drug prescribed during hospitalisation or were discharged with such a drug.

Our findings are consistent with the results from a cross-sectional study in which 25% of 258 general medical inpatients had a QTc interval of >450 ms based on the Bazett correction. The prevalence of severe QTc prolongation >500 ms, which confers a two- to threefold risk for torsade de pointes, was 3.5% in this study. In a retrospective analysis of 1558 adult patients admitted to the emergency department, 35% of patients had a Bazett-corrected QTc prolongation, defined as a QTc of >450 ms for men and >460 ms for women, and 8% had severe QTc prolongation. The higher prevalence of QTc prolongation observed in that study may be explained by the high prevalence of patients with structural heart disease (39%). In contrast to our work, both studies also included patients with a wide QRS interval or atrial fibrillation, factors known to interfere with the accurate measurement of the QT interval.

Bazett’s formula is the most widely used method to correct QT intervals for heart rate. Prolonged QTc intervals >440 to 470 ms based on the Bazett formula have been associated with long-term overall and cardiovascular mortality in middle-aged and elderly populations and patients with coronary heart disease. Severe QTc prolongation >500 ms based on the Bazett formula is also associated with a significantly increased risk of torsade de pointes and sudden cardiac death. However, there is a growing body of evidence demonstrating that the Bazett formula undercorrects the QT interval at heart rates faster than 85 b.p.m., as it is commonly found in hospitalised patients. Therefore, the American Heart Association and other professional societies recommend the use of linear regression-based methods, such as the Framingham method, to correct the QT interval for heart rate. QT intervals corrected with the Framingham method were found to be less sensitive to heart rate as opposed to Bazett’s formula. Using the Framingham correction formula, the prevalence of QTc prolongation was 6.3% only in our study. The higher prevalence of QTc prolongation based on the Bazett formula (22.3%) can be explained by the high proportion of patients (43.6%) who had a baseline heart rate >85 b.p.m. in our sample. Future studies should examine which correction formula most accurately and efficiently identifies patients with QTc prolongation who are at risk of clinically relevant outcomes, such as torsade de pointes.

Our results demonstrate that 33.5% of patients were taking at least one drug with the potential to prolong the QT interval at the time of admission and that the prescription of such a drug independently doubled the risk of QTc prolongation. Moreover, half of patients who had a prolonged QT at the time of admission received at least one additional QT-prolonging drug during the hospital stay or were discharged with such a drug. Given the potential of QT-prolonging drugs to induce fatal torsade de pointes, the widespread use of QT-prolonging drugs among medical inpatients is noteworthy. Clinicians should exercise caution in prescribing potentially QT-prolonging medications in hospitalised patients. The use of computerised physician order entry systems may help reduce QT-prolonging drug combinations. If the prescription of such drugs cannot be avoided, the QTc interval should be closely monitored and prompt therapeutic action taken if the QTc interval exceeds 500 ms. Therapeutic options include the removal of the offending drug and substitution of electrolytes if necessary. The clinical significance of a QTc prolongation below 500 ms and whether therapeutic measures below this threshold have the potential to reduce the risk of torsade de pointes remains uncertain.

We found that the presence of hypokalaemia at the time of admission independently triples the risk of QTc prolongation. The association between hypokalaemia and QTc prolongation has previously been described in psychiatric inpatients and the general population. Because hypokalaemia may further increase the risk of drug-induced torsade de pointes, low serum potassium levels should be promptly corrected.

Our results also showed an independent association between the presence of liver disease and QTc prolongation. In a prior case–control study, patients with alcoholic liver disease had a significantly increased risk of QTc. Whether QT interval prolongation is related to the presence of liver disease per se or alcohol toxicity remains uncertain.

Given the high prevalence of hypokalaemia, liver disease and treatment with QT-prolonging drugs, and the association of these factors with QTc prolongation, medical inpatients patients with any of these conditions should have an assessment of the QTc interval. Prior studies demonstrated that clinicians not only experience significant difficulties to recognise a prolonged QTc but also have substantial knowledge deficits regarding QT-prolonging medications. Both factors may contribute to the inadequate physician documentation of QT intervals. Thus, the implementation of educational measures to increase physicians’ knowledge regarding risk factors and detection of QTc prolongation may be necessary.
Our study has several limitations. First, we could not examine the effect of hypocalcaemia on QTc prolongation because this electrolyte was not routinely measured in our study sample. Although case reports indicated a potential association between hypocalcaemia and QTc prolongation and torsade de pointes, this association appears to be less certain than for other electrolyte abnormalities, such as hypokalaemia. Second, we had no information on the QTc interval over the course of the hospital stay or at the time of discharge. Thus, we could not link treatments, such as potassium supplementation, to changes in the QTc interval duration. Finally, given the low incidence of torsade de pointes during the hospital stay, we could not examine the association between QTc prolongation at the time of admission, treatments (e.g., surveillance in a telemetry unit), and the occurrence of fatal and nonfatal torsade de pointes.

**Conclusion**

The prevalence of QTc prolongation was high among medical inpatients but depended substantially on the method used to correct for heart rate. The use of QT-prolonging drugs at admission, hypokalaemia and liver disease were independently associated with a prolonged QTc interval. More than half of patients with QTc prolongation at admission received additional QT-prolonging drugs during the hospital stay, further increasing the risk of torsade de pointes and cardiac death.

**References**


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BRIEF COMMUNICATION

Coccidioidomycosis in returned Australian travellers

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Key words
Coccidioidomycosis, Coccidioides, meningitis, pneumonia, travellers, fungal infection.

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A previously healthy 33-year-old Caucasian man presented to Nambour Hospital, Queensland with a 2-day history of severe frontal headache associated with photophobia, fevers, rigors and neck stiffness. Two weeks prior, he had presented to his general practitioner with symptoms of a lower respiratory tract infection and had received 7 days of oral amoxicillin-clavulanic acid with clinical resolution of symptoms. There was no significant

Abstract
Coccidioidomycosis is a fungal infection caused by Coccidioides species. The disease has wide clinical presentation and a distinct geographical distribution. We describe two cases of coccidioidomycosis in returned Australian travellers who presented to Nambour Hospital. Knowledge of the international geographical distribution of endemic fungal infections and their clinical manifestations can assist in earlier diagnosis and appropriate management.

Funding: None.
Conflict of interest: None.
medical history, and he took no regular medications. He had travelled to the United States 6 months prior to this presentation, including travel to San Francisco, Arizona and the Mexican border.

On examination, the patient was febrile with a temperature of 38.6°C. There was clinical evidence of photophobia and nuchal rigidity. No neurological signs including papilloedema were evident. Respiratory examination revealed a few inspiratory crepitations at the left lung base.

Initial full blood examination showed mild peripheral blood leucocytosis $13.3 \times 10^9/L$ (4.0–11.0 $\times 10^9$) with neutrophil predominance, $8.61 \times 10^9$ (2.0–8.0 $\times 10^9$). His computed tomography (CT) brain and chest X-ray were normal. Cerebrospinal fluid (CSF) showed a total white blood cell (WBC) of $1017 \times 10^6/L$ ($<5 \times 10^6$), polymorphonuclear cells 61%, mononuclear cells (MONOs) 37% and eosinophils 2%. The red blood cell count was $22 \times 10^6$ ($<5 \times 10^6/L$), glucose (GLUC) 1.6 mmol/L (2.8–4.0) and protein (PROT) 1300 mg/L (150–500). Gram stain was reported as Gram-negative bacilli.

Ceftriaxone was initiated for presumptive treatment of *Haemophilus influenzae* meningitis. *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae* polymerase chain reaction (PCR) results in CSF, and routine bacterial cultures were negative. The initial Gram stain finding was later recognised as a likely artefact. Fevers and headaches persisted despite ceftriaxone, prompting a change to meropenem and benzylpenicillin to cover for other organisms that cause bacterial meningitis. A magnetic resonance imaging/magnetic resonance venography of brain was normal. Repeat CSF demonstrated persistence of inflammatory picture, with an elevated WBC of 1730, with predominantly MONOs. Gram stain was negative; the GLUC was 0.7 and PROT 1400. Stains for acid fast bacilli were negative, as were serological testing for *Cryptococcus* and PCR testing for enteroviral, *Herpes simplex* virus 1 and 2, and *Mycobacterium tuberculosis*. It was not possible to perform a 16s RNA on the CSF sample because of the presence of inhibitors. CSF culture was again negative. Flow cytometry of the CSF did not detect a lymphoid monoclonal population. Human immunodeficiency virus (HIV) antibody and mycoplasma serology were negative, as was the serum cryptococcal antigen. Peripheral blood lymphocyte subsets were normal. Histoplasma serology for *Histoplasma capsulatum* yeast, performed at Sullivan Nicolaides Pathology, Brisbane using the complement fixation method, was positive with a reciprocal titre of 16.

A CT of the chest performed 2 weeks after the initial presentation demonstrated a cavitating lesion in his left lower lobe (Fig. 1). A CT-guided fine-needle aspiration (FNA) biopsy of the lesion was performed, and the patient was commenced on intravenous liposomal amphotericin 5 mg/kg to cover for presumed fungal meningitis. Fungal growth was seen in day 2, and subcultures were sent to Associate Professor David Ellis, Women’s and Children’s hospital in Adelaide. The isolate was identified to be *Coccidioides immitis* using the exoantigen technique. Amphotericin was changed to oral fluconazole 400 mg twice daily. *Coccidioides* serology performed at Westmead Hospital Laboratory, Sydney by immunodiffusion method subsequently came back positive. A repeat CSF performed 2 weeks after treatment showed improvement in WBCs, GLUC and PROT levels. He was discharged home and on review in clinic 3 months later continues to improve.

The second case was a 71-year-old man who presented to hospital with a 5-day history of pleuritic chest pain and exertional dyspnoea. He had returned 11 days earlier from the United States where he spent 16 days in Sacramento, Los Angeles and Seattle. His past medical history included gastro-oesophageal reflux disease and transient ischaemic attack.

On examination, he was afebrile and haemodynamically stable. Oxygen saturations were 95% on room air. Physical examination was unremarkable.

Full blood examination showed a mild neutrophilia. Electrolytes and liver function tests were normal. A CT pulmonary angiogram showed no evidence of pulmonary embolism but identified an area of focal consolidation in left lower lobe. He was discharged home with oral amoxicillin-clavulanic acid with a presumptive diagnosis of a lower respiratory tract infection.
Two months later, he presented to a respiratory physician with ongoing symptoms of cough, weight loss and night sweats. A repeat CT chest demonstrated localised pleural effusion on the left lower lobe associated with consolidation. A FNA biopsy of the lung lesion and pleurocentesis was performed. Histopathology revealed spherules with internal endospores consistent with *Coccidioides* (Fig. 2). Cultures were negative. *Coccidioides* serology performed at Westmead Hospital laboratory, Sydney by immunodiffusion method was positive. He was commenced on fluconazole 200 mg daily. Three months after treatment, his symptoms have resolved with resolution of the effusion and infiltrates on his chest X-ray, and fluconazole was ceased.

*Coccidioidomycosis*, also known as Valley fever, results from inhaling of *Coccidioides* species, most commonly *Coccidioides immitis* or *Coccidioides posadasii*. The disease has a distinct geographical distribution in the South Western United States, including parts of California, Nevada, Arizona, New Mexico and Texas. Areas of highest endemicity include the southern San Joaquin Valley of California and New Mexico.

Approximately two thirds of the patients with coccidioidomycosis are asymptomatic or have a very mild disease. Symptoms consistent with community acquired pneumonia are the most common form of presentation. Chest X-ray in patients with pulmonary infection may show diffuse or nodular infiltrates and sometimes hilar adenopathy, with or without pleural effusions.

Less than 5% of patients present with disseminated disease, which is associated with significant morbidity, and mortality. Factors associated with higher risk of dissemination include being a male gender, advanced HIV/acquired immune deficiency syndrome, transplant recipient, third-trimester pregnancy, standardised complement fixation antibody titre greater than or equal to 1:32, patients on immunosuppressive therapy, and those of Filipino or African ethnicity. Patients receiving tumour necrosis factor inhibiting treatments for diseases such as rheumatoid arthritis also have an increased risk of dissemination.

Meningitis is the most devastating form of coccidioidomycosis, with 100% fatality rate if untreated within 2 years. Common symptoms include headache, nausea, vomiting, photophobia, nuchal rigidity and altered sensorium. CSF often shows an elevated white cell count with lymphocytic pleocytosis, low GLUC and elevated PROT levels. Hydrocephalus is the most frequent complication and further increases the risk of death.

Diagnosis of coccidioidomycosis can be established by isolating the organism from clinical specimens. The fungus grows on most media cultures as early as 2 days after inoculation, although often more than 5 days or longer is required. Direct examination of tissue specimen may reveal mature spherules with endospores, which are pathognomic. Immunoglobulin M (IgM)-specific coccidioidal antibody was detected by immunodiffusion method performed at Westmead Hospital Laboratory in both cases. The immunodiffusion test for coccidioidomycosis is a qualitative screening test for the detection of precipitating antibodies. The principal antigen used is coccidioidin, a soluble filtrate of mycelial-phase broth cultures. The test usually becomes positive 4 weeks after initial infection and remains positive throughout the clinically active disease. Only a third of patients with meningitis culture *Coccidioides* from CSF. CSF enzyme-linked immunosorbent assay IgG and IgM are infrequently positive.

Laboratory-associated infections have been reported in healthy immunocompetent individuals after exposure to airborne conidia. Laboratory staff at Nambour Hospital handled the cultures with extreme care because of high clinical suspicion of diomorphic fungi. Manipulations of cultures were performed in a class II biological safety cabinet, and culture plates were sealed to avoid inadvertent exposure.

**Figure 2** Histopathology of lung tissue from patient 2 showing thick-walled spherules consisting of endospores.
Treatment of uncomplicated pneumonia is controversial with no controlled trial to support its role, and many authorities recommend regular follow-up without treatment. Immunosuppressed, pregnant patients and those belonging to higher risk ethnic group warrant antifungal therapy. Other patients who may benefit from treatment include those who have more a severe form of illness, such as extensive lung infiltrates or pleural effusions, systemic symptoms with intense night sweats, or weight loss. Oral azole therapy at dosages of 200–400 mg per day is recommended for 3–6 months, with follow-up imaging to ensure resolution of infection. Because of the presence of persisting radiological changes and systemic symptoms, the second patient was treated with antifungal therapy.

Treatment of meningitis is with oral fluconazole therapy. Relapse rate has been reported to be 75% within a year if treatment is ceased, therefore, lifelong therapy is indicated. Other azoles such as itraconazole and voriconazole have also been used. Intrathecal amphotericin can be considered for severe meningitis or those not responding to azole therapy. Hydrocephalus requires shunting in addition to antifungal therapy.

Our first case demonstrates difficulties associated with diagnosing meningitis caused by Coccidioides infection. Diagnosis was confounded by the presence of artefact on Gram stain suggestive of Gram-negative bacilli and low titre positive Histoplasma serology. Histoplasma serology has shown to cross react with other fungal infections including Blastomyces, Paracoccidioides, aspergillosis, Coccidioides, as well as candidiasis and cryptococcosis.

These cases demonstrate the importance of taking a travel history and having an awareness of the geographical distribution of endemic fungal infections in patients with pneumonia and meningitis.

Acknowledgements

The authors thank Associate Professor David Ellis, Women’s and Children Hospital, Adelaide and Dr Tim McNamara, General Pathologist, Nambour General Hospital.

References

Case of syndrome of headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL) with focal slowing on electroencephalogram

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Key words
headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL), migraine, pseudomigraine, electroencephalogram.

Abstract
We describe a case of headache and neurological deficits with cerebrospinal fluid (CSF) lymphocytosis in a patient presenting with a 3-week history of recurrent severe headaches associated with negative sensory symptoms and dysphasia. The patient had no cardiovascular risk factors and no family history of migraines. Neurological examination was unremarkable. Cerebral magnetic resonance imaging was unremarkable. CSF analysis revealed lymphocytosis (leucocytes 84 × 10⁶/L, 100% lymphocytes). Extensive laboratory investigations of CSF and serum did not reveal an infectious, autoimmune or metabolic cause. Visual evoked potentials were normal. Awake electroencephalogram revealed intermittent 3–5 Hz generalised slowing and frontal intermittent rhythmic delta activity, without epileptiform discharges. Repeat CSF analysis showed marked reduction of the total leucocyte count and remained negative for infectious aetiology. Propranolol was commenced, and no recurrence of headache or neurological symptoms was observed at follow-up. An extensive literature review on the topic is discussed.

An 18-year-old woman with no significant past medical history was admitted into hospital following a 3-week history of recurrent episodes of severe headache associated with negative sensory symptoms without weakness. The patient had no cardiovascular risk factors and no family history of migraines. The sensory symptoms were characterised by acute numbness that began in the left leg and subsequently involved the whole of the left side before spreading to involve the entire contralateral side. A severe generalised headache occurred in close temporality of the sensory symptoms and was associated with nausea, vomiting and expressive dysphasia. There were no associated visual symptoms or photophobia. Symptoms recurred after intervals of 1–7 days and typically resolved within 8 h. The patient was asymptomatic between attacks. There was no preceding viral illness. Neurological examination between episodes was unremarkable. Gadolinium-enhanced cerebral magnetic resonance imaging (MRI), including angiography and venography sequences, was unremarkable.

Routine laboratory studies including thyroid function tests, C-reactive protein and erythrocyte sedimentation rate were unremarkable. Peripheral lymphocyte subset analysis and flow cytometry were normal. Serologic tests for antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, hepatitis B and C, cytomegalovirus, Epstein–Barr virus, flavivirus, mycoplasma, syphilis, rickettsia, and toxoplasma were unremarkable. Cerebrospinal fluid (CSF) analysis revealed lymphocytosis (leucocytes 84 × 10⁶/L, 100% lymphocytes), glucose level 3.2 mmol/L, protein level 0.74 g/L and xanthochromia index <0.001, and was negative for oligoclonal bands (see Table 1). Bacterial and fungal cultures and polymerase chain reaction for neurotropic viruses of CSF specimens also proved negative. Intravenous aciclovir and benzylpenicillin were only given during the initial 12 h. Another similar headache episode recurred 5 days later, and the patient was diagnosed as headache and neurological deficits with CSF lymphocytosis (HaNDL) syndrome. Antimicrobials were ceased, and propranolol was started at an initial dose of 20 mg twice per day.

Visual evoked potentials (VEPs) were within normal limits. Awake and drowsy electroencephalography (EEG) on day 2 showed intermittent 3–5 Hz generalised slowing and frontal intermittent rhythmic delta activity, without epileptiform discharges despite provocation procedures (see Fig. 1). The initial EEG abnormalities persisted on a repeat study 2 weeks later. Repeat CSF analysis 1 month later showed marked reduction of the total leucocyte count.
count but persistent lymphocytosis (leucocytes $9 \times 10^6/L$, 100% lymphocytes) with normal protein and glucose, and remained negative for infectious aetiology (see Table 1). No recurrence of headache or neurological symptoms was observed at follow-up 12 weeks after presentation.

The HaNDL syndrome, previously known as migraine with cerebrospinal pleocytosis or pseudomigraine with lymphocytic pleocytosis, was first described in 1981.1 The diagnostic criteria for HaNDL (see Table 2) is described in the second edition of the International Classification of Headache Disorders.2 To our knowledge, this is the second case of HaNDL to be described in Australia,3 suggesting that it is underrecognised.

In 1997, Gomez-Aranda et al.4 described the largest case series to date on HaNDL comprising 50 patients. The age of onset was between 14 and 39 years, with a male predominance (68%), and 26% of patients had a personal history of migraine. One quarter had a preceding viral-like illness up to 3 weeks prior. The clinical picture described consisted of 1–12 episodes of moderate-to-severe bilateral or hemicranial headache (mean duration, 19 h) accompanied by changing variable neurological deficits (range 5 min to 3 days; mean duration, 5 h) and occasionally with leucocytosis and fever. Sensory symptoms were most common (78% of episodes), followed by aphasia (60%) or motor deficits (56%), whereas visual symptoms were uncommon (12%). CSF lymphocytosis ranged from 10 to 760 (mean $11006_174 \times 10^6$ cells/L with uniformly negative aetiological results. Elevated CSF total protein (range 0.2–2.5 g/L, mean $11006_0.03 \, \text{g/L}$) occurred in 96% of cases, and oligoclonal bands were not found. All patients had normal neuroradiological studies, except for transient, focal, decreased radionuclide uptake in brain single-photon emission computed tomography on the corresponding side in three patients. Typically patients are asymptomatic between episodes and undergo a self-limiting course with complete recovery within 2 months, including normalisation of CSF leucocytosis on repeat testing.4–13

With regard to MRI, no abnormalities have been found on diffusion-weighted imaging9,11,13,14 however, subtle perfusion-weighted images abnormalities have been recently noted9,11,14 Potentiation12 and habituation14 of VEP amplitude have been conflictingly documented. Focal non-epileptiform abnormalities such as intermit-tent theta to delta range slowing on EEG have also been described.5,7,8,14

### Table 1 Cumulative results of cerebrospinal fluid analysis

<table>
<thead>
<tr>
<th>CSF analysis</th>
<th>On admission</th>
<th>1 month later</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/L)</td>
<td>0.74</td>
<td>0.26</td>
<td>&lt;0.45</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>3.2</td>
<td>3.0</td>
<td>2.2–5.5</td>
</tr>
<tr>
<td>Xanthochromia index</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total leucocytes ($\times 10^6/L$)</td>
<td>84</td>
<td>9</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Neutrophils ($\times 10^6/L$)</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Mononuclears ($\times 10^6/L$)</td>
<td>84</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Eosinophils ($\times 10^6/L$)</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Erythrocytes ($\times 10^6/L$)</td>
<td>16</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Cytology</td>
<td>—</td>
<td></td>
<td>Reactive lymphoid cells, no malignant cells</td>
</tr>
<tr>
<td>Gram stain and culture</td>
<td>Negative</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>Negative</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>Cryptococcal antigen</td>
<td>Negative</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>Viral PCR of mumps, HSV1, HSV2, CMV, VZV, enterovirus, HHV6</td>
<td>Negative</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis PCR and culture</td>
<td>—</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>Quantiferon gold</td>
<td>—</td>
<td>Negative</td>
<td>—</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; CSF, cerebrospinal fluid; HHV6, human herpes virus 6; HSV, herpes simplex virus; PCR, polymerase chain reaction; VZV, varicella zoster virus; —, not applicable.

### Table 2 Diagnostic criteria for syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis according to the International Classification of Headache Disorders, 2nd edition

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Episodes of moderate or severe headache lasting hours before resolving fully and fulfilling C and D</td>
<td>Cerebrospinal fluid (CSF) pleocytosis with lymphocytic predominance ($&gt;15 \times 10^6$ cells/L) and normal neuroimaging, CSF culture and other tests for aetiology</td>
</tr>
<tr>
<td>B Episodes of headache are accompanied by or shortly follow transient neurological deficits and commence in close temporal relation to the development of CSF pleocytosis</td>
<td></td>
</tr>
<tr>
<td>C Episodes of headache and neurological deficits recur over &lt;3 months</td>
<td></td>
</tr>
<tr>
<td>D Episodic headache and neurological deficits recur over 3 months</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Electroencephalogram at day 2 showing bilateral frontal intermittent rhythmic delta activity. ECG, electroencephalogram.
The pathogenesis of HaNDL is poorly understood, but most authors believe it is due to an underlying inflammatory disorder of the central nervous system (CNS). It is postulated that viruses or autoimmune disease activate the immune system, thereby producing antibodies that would induce an aseptic inflammation of the leptomeningeal vasculature causing CSF pleocytosis and the neurological symptoms possibly through a cortical spreading depression-like mechanism. No causative genes have been identified in HaNDL. Chapman et al. did not identify mutations in CACNA1A gene in their series despite the similarities with familial hemiplegic migraine (FHM).

The major differential diagnoses of HaNDL are migraine disorders such as migraine with aura or FHM that can also present with recurrent headache with auras, reversible neurological deficits and CSF lymphocytosis. This was excluded in our patient with the absence of both aura and family history of hemiplegic migraine. Other important differentials for the clinical syndrome include meningoencephalitis, Mollaret’s meningitis, acute stroke, neoplastic arachnoiditis, reversible posterior leukoencephalopathy syndrome and CNS vasculitis. These differentials were excluded on the basis of clinical history and examination, serum autoantibodies, CSF, and neuroimaging findings.

In conclusion, HaNDL should be considered when evaluating a patient with headache in the company of neurological features and is essentially a diagnosis of exclusion. Useful features that point to HaNDL are recurrent episodes of neurological dysfunction plus CSF pleocytosis with normal neuroimaging. The identification of this uncommon syndrome is also important in order to avoid unnecessary treatment, such as thrombolysis or prolonged antimicrobials.

References

Oral administration of arsenic trioxide in the treatment of acute promyelocytic leukaemia and accelerated phase chronic myeloid leukaemia: an Australian single-centre study

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Key words
oral arsenic trioxide, acute promyelocytic leukaemia.

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Abstract
Experience in the treatment of patients with acute promyelocytic leukaemia (APL) and accelerated phase chronic myeloid leukaemia with orally administered arsenic trioxide (ATO) in our institution since 1999 has demonstrated that bioavailability of oral ATO is comparable with intravenous administration, and similar outcomes are produced in treatment of APL. Oral administration was well tolerated, with good compliance, in patients not requiring hospitalisation for postinduction treatment and was particularly convenient for patients living considerable distances from our institution. Orally administered ATO can be considered a practicable option in management of APL.

Arsenic trioxide (ATO) is a potent therapeutic agent for treatment of acute promyelocytic leukaemia (APL). Complete remission (CR) is induced by ATO in almost all patients with newly presenting or relapsed APL,1,2 apart from the relatively small minority who die early, usually from haemorrhage or sepsis. Relapse does not occur in the majority who achieve CR,1,2 but is less common when treatment with ATO is combined with all-trans retinoic acid (ATRA).3 ATO is typically administered by intravenous (IV) infusion over 2–3 h in a dose of the order of 10 mg daily, first in initial treatment until CR or for up to 60 days, and then in reported series for 4 weeks of one to three courses in consolidation therapy,1–3 followed by one to four maintenance therapy cycles of 4-week duration,2,3 or for 10-day courses monthly for 6 months.4 Such protracted daily IV infusions for consolidation and maintenance therapy produce significant logistic problems for patients who do not require hospitalisation, especially those living considerable distances from a centre that administers IV ATO. The numerous IV infusions also incur appreciable hospital operational costs.

Capacity of oral administration of ATO to provide a home-based alternative to IV administration in terms of tolerance, compliance and bioavailability has been evaluated at our institution since 1999 in patients where IV administration was not a prerogative for treatment. Use of oral ATO is described in this report for treatment of relapsed APL, and particularly for inclusion of ATO in consolidation therapy of patients who lived considerable distances from our own and other treatment centres and were not participating in prospective trials that mandated IV ATO administration. Oral ATO was also trialled in two patients with accelerated phase chronic myeloid leukaemia (APCML) uncontrolled by conventional agents prior to availability of imatinib and provided considerable additional data on bioavailability of oral ATO.

Details of nine patients treated with oral ATO are shown in Table 1. ATO solution was prepared initially in the Pharmacy Department of St Vincent’s Hospital, as described in the British Pharmacopoeia.4 ATO obtained from Sigma Chemical Company (99.9% pure) was dissolved in 1 mol/L pharmaceutical grade NaOH, and the pH adjusted to 7.0 with 1 mol/L pharmaceutical grade HCl. The ATO concentration was then adjusted to 1 mg/mL with distilled water, and the solution sterilised by 0.22 μm pore-size filtration. ATO solution was subsequently obtained as 10 mg in 10 mL vials, initially from Ophthalmic Laboratories, Sydney, and then from Pharmalab, Sydney, Australia. ATO was administered orally after mixture with 100-mL tap water, and by IV administration in 500-mL normal saline over 2 h. Oral ATO was administered in conjunction with oral ATRA 45 mg/m²/day in view of the superior outcomes reported for combined therapy. Treatment with ATO was carried out with
informed consent, as approved by the Human Research Ethics Committee of St Vincent’s Hospital.

All APL patients had the \( t(15;17)(q22;q21) \) translocation. Patient APL1 was in fourth relapse with central nervous system (CNS) disease, and patient APL2 was in second relapse following prior inductions of molecular remission (MR), defined by negativity for PML-RAR\( a \) by reverse transcriptase–polymerase chain reaction (RT-PCR), with ATRA and chemotherapy. Patients with relapsed APL have an inferior prognosis than \textit{de novo} APL in view of higher incidence of relapse post reinduction of CR.1,2

Oral ATO 5 mg bd was substituted for IV ATO to avert daily IV infusions during protracted treatment of CNS relapse in patient APL1 in combination with ATRA and intrathecal methotrexate and cytarabine. MR was achieved, but remission was brief because of fatal systemic relapse 4 months later.

Oral ATO 5 mg bd was employed in consolidation treatment after induction of MR in the other six patients. In two of these patients, it provided the only opportunity to include ATO in treatment. Four patients lived considerable distances from our institution, and two had developed severe anxiety reactions to hospital attendances for IV therapy. One patient had a trial of 7.5-mg oral ATO bd but reverted to 5 mg bd because of mild nausea. Fatal relapse occurred in APL patient 3, and relapse at the molecular level occurred after 24 months in patient APL2. Patient APL2 was then treated with 4 weeks of home-based oral ATO and ATRA that resulted in induction of MR at bone marrow assessment 3 weeks post-treatment. Three subsequent low level relapses detected only by RT-PCR in this patient over a 9-year period were treated in the same manner with reinduction of MR. Five of the seven APL patients are alive, and APL patients 4–7 remain in continuous MR for 17 months to 9 years (median 104 months).

APCML in the two patients treated with oral ATO had the \( t(9;22)(q34;q11) \) translocation. Accelerated phase was manifested in both by a falling haemoglobin and an increasing white cell count, circulating blast cell count and spleen size, and also in the platelet count in patient APCML2 despite maximum tolerated doses of available therapeutic agents. Oral ATO therapy was considered because of its capacity to produce substantial cytoreductive activity in the chronic phase of the disorder.3

Cytoreductive capacity of ATO was evaluated by administration of 10-mg IV ATO daily for 8 days in APCML patient 1, and 10-mg IV ATO daily for 13 days in addition to ongoing treatment with hydroxyurea (HU) and 6-thioguanine (6TG) in the other. A decrease to nadir values after 14 days in patients APCML1 and 2 occurred in WCC from 60 to 13 and 23 to \( 1.2 \times 10^9/L \), circulating

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender/age</th>
<th>APL status</th>
<th>Prior therapy</th>
<th>Indication</th>
<th>Period of oral ATO treatment</th>
<th>Oral ATO dose (mg)</th>
<th>Total days</th>
<th>Median blood As (m mol/L)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>APL 1</td>
<td>F/32</td>
<td>R4</td>
<td>CNS relapse</td>
<td>CNS relapse</td>
<td>5/12/2000-23/3/2001</td>
<td>5 bd</td>
<td>40/12</td>
<td>0.6</td>
<td>CNS CR, subsequent fatal systemic R</td>
</tr>
<tr>
<td>APL 2</td>
<td>M/47</td>
<td>R2</td>
<td>CNS relapse</td>
<td>CNS relapse</td>
<td>11/7/2002-present</td>
<td>5 bd</td>
<td>75/12</td>
<td>0.3</td>
<td>CNS CR, subsequent fatal systemic R</td>
</tr>
<tr>
<td>APL 3</td>
<td>M/75</td>
<td>CR1</td>
<td>Induction for three</td>
<td>CNS relapse</td>
<td>12/2000-12/2002</td>
<td>5 bd</td>
<td>48/12</td>
<td>0.7</td>
<td>CNS CR, subsequent molecular remission</td>
</tr>
<tr>
<td>APL 4</td>
<td>F/67</td>
<td>CR1</td>
<td>Induction for three</td>
<td>CNS relapse</td>
<td>6/10/2000-8/14/2000</td>
<td>5 bd</td>
<td>54/22</td>
<td>1.1</td>
<td>CNS CR, subsequent molecular remission</td>
</tr>
<tr>
<td>APL 5</td>
<td>F/69</td>
<td>CR1</td>
<td>Induction for three</td>
<td>CNS relapse</td>
<td>21/12/2000-2/20/2002</td>
<td>5 bd</td>
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<td>0.8</td>
<td>CNS CR, subsequent molecular remission</td>
</tr>
<tr>
<td>APL 6</td>
<td>F/69</td>
<td>CR1</td>
<td>Induction for three</td>
<td>CNS relapse</td>
<td>24/11/2000-24/2/2001</td>
<td>5 bd</td>
<td>60/25</td>
<td>0.8</td>
<td>CNS CR, subsequent molecular remission</td>
</tr>
<tr>
<td>APL 7</td>
<td>F/69</td>
<td>CR1</td>
<td>Induction for three</td>
<td>CNS relapse</td>
<td>15/10/1999-9/8/2000</td>
<td>5 bd</td>
<td>90/31</td>
<td>1.1</td>
<td>CNS CR, subsequent molecular remission</td>
</tr>
<tr>
<td>APCML 1</td>
<td>F/58</td>
<td>CR1</td>
<td>Induction for three</td>
<td>CNS relapse</td>
<td>18/11/1999-29/3/2000</td>
<td>5 mane</td>
<td>90/31</td>
<td>1.6</td>
<td>CNS CR, subsequent molecular remission</td>
</tr>
<tr>
<td>APCML 2</td>
<td>F/69</td>
<td>CR1</td>
<td>Induction for three</td>
<td>CNS relapse</td>
<td>21/12/2000-20/4/2010</td>
<td>5 bd</td>
<td>60/31</td>
<td>0.8</td>
<td>CNS CR, subsequent molecular remission</td>
</tr>
<tr>
<td>APCML 1</td>
<td>F/58</td>
<td>CR1</td>
<td>Induction for three</td>
<td>CNS relapse</td>
<td>15/10/1999-9/8/2000</td>
<td>5 bd</td>
<td>90/31</td>
<td>1.1</td>
<td>CNS CR, subsequent molecular remission</td>
</tr>
<tr>
<td>APCML 2</td>
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<td>CNS relapse</td>
<td>21/12/2000-2/20/2002</td>
<td>5 bd</td>
<td>42/20</td>
<td>0.8</td>
<td>CNS CR, subsequent molecular remission</td>
</tr>
</tbody>
</table>
blasts from 5.0 to 0.3 and 4.0 to 0 × 10⁹/L, and in spleen lower border by 3 and 5 cm respectively. Duration of response was only 14–18 days, indicating that ongoing ATO administration was required to maintain a cytoreductive effect as in chronic phase disease. Oral ATO was then initiated to provide convenient home-based treatment, as both patients lived considerable distances from our institution. Both had preceding nausea and constitutional symptoms that contributed to intolerance of 5-mg ATO bd in contrast with the patients with APL. Both tolerated 5-mg ATO daily, which in combination with doses of HU and 6TG that were previously ineffective, resulted in stable suppression of WCC and splenomegaly. Treatment with ATO was terminated at development of blast crisis.

Monitoring for toxicity during home-based oral ATO administration was performed by weekly assessment of the electrocardiogram, full blood examination, serum electrolytes, creatinine and liver function tests, either by the local medical practitioner or during return visits to our institution for further supplies of ATO. The QTc interval increased by 18–30 ms in five patients but did not exceed 500 ms, and no arrhythmic or other abnormal events were detected. Elevation of gamma glutamyl transferase or transaminases of up to 2 × ULN occurred in two patients and to 2–3 × ULN in one other but normalised 1–2 weeks after ATO was ceased. A similarly reversible depression of the neutrophil count to 1–1.5 × 10⁹/L occurred in three patients, resulting in an overall toxicity profile resembling that reported during IV administration of ATO.

Bioavailability of oral ATO could be expected to impact on therapeutic efficacy relative to the same daily dose delivered by IV administration. Several pharmacokinetic studies have reported the arsenic (As) assimilated after a dose of IV or orally administered ATO is relatively rapidly cleared from plasma to be essentially undetectable after 22 h, thereby rendering plasma levels unsuitable at that time for assessment of As assimilation compared with the greater levels in whole blood because of more sustained retention of assimilated As in erythrocytes. Assimilation of oral compared with IV-administered ATO was consequently assessed in our patients by comparison of blood As levels during oral and IV administration. Blood for assay was taken during IV treatment immediately prior to IV infusion and during oral administration immediately before the morning dose of ATO. Levels of As were determined by graphite crucible vaporisation and atomic absorption spectroscopy.

Levels obtained during IV and oral ATO administration in five patients are shown in Figure 1 and indicate development of steady state As concentrations over time with overlap of As levels during oral and IV administration in the three patients receiving 10 mg per day by either route. Despite some variability in sequentially assessed As levels, median values during IV versus oral ATO treatment were 0.8 and 0.6, 1.0 and 1.3, and 2.0 and 2.6 μM in APL patients 1, 2 and 3 respectively. Under steady-state conditions, the rate at which As is assimilated into blood is equal to the rate at which it is eliminated from blood. Assimilation of orally administered ATO is dependent on bioavailability through the oral route, and represents the proportion of the administered dose absorbed by the gut that is not extracted by first pass hepatic processes. The rate of elimination of As from blood after oral or IV administration is the same at comparable steady-state As blood levels, indicating the development of comparable steady-state blood As levels at the same daily dose in these patients is consistent with comparable bioavailability of ATO following oral and IV administration.

A relationship between As blood level and oral ATO dose was suggested in APL patient 2 by a median level of 2.2 μmol/L at 7.5 mg bd compared with 1.3 μmol/L at 5 mg bd. Median levels on 5 mg ATO orally daily in the two patients with APCML were 0.8 μM compared with approximately 50% greater levels of 1.1 and 1.2 μmol/L on 10-mg ATO IV, consistent with an increase in blood As level with increased ATO dose, although further studies are required for confirmation. No trend to accumulation of As in blood occurred during continuous oral administration for up to 56 days. Median blood As levels in APL patients receiving oral administration of 5 mg bd ranged from 0.6 to 2.6 μmol/L, with the highest level in the only patient with a subnormal creatinine clearance of 1.05 mL/min (N1.5–2.5), presumably reflecting the major role of renal excretion in elimination of As.

The present 955 days experience with oral ATO treatment provides the most detailed assessment of As blood levels during extended periods of treatment yet to be reported, and indicated oral administration can deliver a daily dose of ATO with bioavailability comparable with IV administration. Oral administration was capable of delivering doses of ATO of the order appropriate for therapy of APL with acceptable tolerance and compliance. The object of this report has been to describe an examination of the potential of oral administration to serve as a practical substitute for IV administration of ATO in treatment regimens in which ATO represented an appropriate component. A detailed analysis of treatment outcomes is not statistically feasible in this relatively small and heterogeneous cohort of patients in which some had active disease or were receiving consolidation therapy, and some had either relapsed or newly presenting APL. Therapeutic efficacy of an orally administered ATO-based regimen was, however, demonstrated by reinduction of MR in
two patients with multiply-relapsed disease, where the coadministered ATRA is typically not associated with capacity to induce MR in contrast with the capacity of ATO to do so when administered as a single agent. The finding of a high rate of MR induction, as well as sustained MR in the majority of these patients, is in keeping with beneficial outcomes reported elsewhere for oral ATO therapy in relapsed APL, treated, as in the present study, in combination with other therapeutic agents. Oral administration can permit home-based treatment that is especially convenient for patients who live considerable distances from the treating institution. Orally administered ATO can thus be considered a practicable option in the management of APL.

References


5 Forkner CE, Scott TFM. Arsenic as a therapeutic agent in chronic myelogenous leukaemia. JAMA 1933; 97: 3–5.

Familial Mediterranean fever (FMF) typically presents in childhood or early in adulthood and is associated with a relapsing history of sporadic, paroxysmal attacks of fever and serosal inflammation. Here, we present an atypical case of FMF, with a late onset of attacks and delayed diagnosis associated with a variant in the MEFV gene that has been described as producing a highly variable clinical phenotype.

A 65-year-old man of Italian origin presented with a 5-day history of dyspnoea and 2 weeks of epigastric discomfort. He was an ex-smoker of 30 pack-years and worked in the construction industry. There were no known exposures to either asbestos or to tuberculosis.

At age 38, he had experienced an episode of fever, arthralgia and chest pain lasting 4 days that had resolved spontaneously. At 63 years of age, he developed fever, arthralgia and chest pain lasting 4 days that had resolved. Clinical examination revealed a large left-sided pleural effusion that was confirmed on chest radiograph (Fig. 1a). There was no fever, pericardial rub or lymphadenopathy, and no evidence of active arthritis. Renal function and urinalysis were unremarkable. Pleurocentesis revealed an exudate. Gram stain, culture, mycobacterial cultures and cytology were negative. Subsequent computed tomography examination of the chest demonstrated bilateral pleural effusions with a moderate pericardial effusion (see Fig. 1b).

No pulmonary parenchymal abnormality was identified, and there was no hilar or mediastinal lymphadenopathy. A video-assisted thoracoscopic pleural biopsy revealed focal lymphoplasmacytic inflammation consistent with active fibrosing pleuritis. There was no evidence of granulomatous inflammation, malignancy or rheumatoid nodules. Serological testing for autoimmune and connective tissue diseases was negative.

Molecular testing for familial Mediterranean fever (FMF) revealed three base substitutions within the MEFV gene: c.442G>C (p.E148Q), c.1105C>T (p.P369S) and c.1223G>A (p.R408Q). The patient was commenced on colchicine and to date has had no recurrence of symptoms.

FMF is characterised by sporadic, paroxysmal attacks of fever and serosal inflammation and has been described primarily in populations surrounding the Mediterranean basin. It is inherited as an autosomal recessive trait. Ninety per cent of patients experience their first attack prior to the age of 20. Diagnosis is based on a combination of clinical features, response to colchicine and genetic testing demonstrating abnormalities within the MEFV gene. Untreated disease can lead to chronic polyarteritis with involvement of the heart, kidneys, liver and central nervous system.
to the development of AA amyloidosis with subsequent proteinuria and chronic renal failure. Treatment with colchicine has been shown to be effective in reducing acute attacks as well as in preventing or delaying progression of amyloidosis.4

Since the cloning of the MEFV gene in 1997, up to 40 variants have been identified in patients with FMF, with the M694V, V726A, M680I and E148Q variants the most frequently identified.5 While some variants have been associated with more severe manifestations (particularly M694V), incomplete penetrance and varying expression of the disease suggest that other factors may contribute to the development of clinical illness.6 Both the E148Q and the P369S/R408Q variants (identified in our patient) have been demonstrated to produce variable clinical phenotypes.7,8 A recent study from the United States described a cohort of patients with P369S/R408Q variants that also had a variable response to colchicine. Not all patients in this cohort fulfilled the clinical criteria for FMF, whereas our patient did. The more frequently identified E148Q variant has also been shown to have high rates of asymptomatic carriage in populations where FMF is prevalent, leading some authors to question its association with clinical episodes.5,9 In contrast, other reports have suggested an association between the E148Q variant and both acute attacks and the development of amyloidosis.7,11,12 The role of colchicine for patients with this variant is also unclear, although most authors recommend treatment for symptomatic patients in order to prevent attacks.5,7

This case is unusual and highlights some of the difficulties related to the diagnosis and treatment of FMF. The patient’s late onset of initial symptoms and extended attack-free intervals differ significantly from the classical description of the disease. This presentation raises the possibility that FMF may be underdiagnosed in those who present late or without the classic relapsing history. Genetic testing for FMF should therefore be considered in patients who present with serositis and fever, if other more common causes are excluded. Careful consideration of both clinical features and the results of genetic testing is required to confirm the diagnosis. In general, patients with symptomatic attacks should be offered a trial of colchicine prophylaxis given the potential long-term complications of the disease.

References


Importance of screening for renal disease among the human immunodeficiency virus-infected patient population

Assessment of tenofovir disoproxil fumarate (TDF)-related nephrotoxicity has become the single commonest reason for the referral of human immunodeficiency virus (HIV)-infected patients to renal specialists in many centres. Although there is concern about the renal effects of TDF, they are seen in only a minority of patients (1–2%). However, these adverse effects are important as they may be profound, particularly the Fanconi syndrome. TDF has added importance to the screening and management of renal disease amongst the HIV-infected population, which is at particular risk of kidney disease. In fact, despite the use of antiretrovirals, the prevalence of kidney disease among the HIV-infected cohort has increased.

We discuss a case of Fanconi syndrome and chronic renal impairment; we then review the importance of screening for renal disease and discuss the implications of the use of TDF on this background of increased renal risk.

A 17-year-old boy was referred for evaluation of renal impairment in April 2010. He also described leg pain and weakness; he was using a walking stick to mobilise. He resided in a rural area and attended follow-up infrequently. His renal function was normal 4 years earlier. He had perinatally acquired HIV. The current antivirals included tenofovir/emtricitabine and lopinavir/ritonavir. He had an undetectable HIV viral load and a stable CD4 T-cell count.

At the initial review, his serum creatinine was 150 µmol/L, estimated glomerular filtration rate (eGFR) 52 mL/min/1.73 m². He had all the features of the Fanconi syndrome including hypophosphataemia, glycosuria, aminoaciduria and proteinuria (1.93 g/day). He was hypokalaemic and acidotic, and had beta-2 microglobulinuria. The renal biopsy demonstrated pronounced proximal tubular abnormalities. He had reduced bone mineral densitometry and osteomalacia.

TDF was ceased, and he switched to an alternative antiretroviral regimen. He was placed on supplements to correct the biochemical abnormalities as well as vitamin D and calcitriol. His leg pain and weakness resolved, and he was able to mobilise independently within 1 month, however, the renal impairment persisted. Tubular dysfunction had resolved 2 months after cessation of TDF.

This case highlights the importance of vigilant screening and management of renal complications among the HIV-infected cohort. His infrequent attendance at follow-up and rural location made this challenging. His nonattendance and lack of regular screening tests contributed to the delayed diagnosis. It is prudent to reconsider the use of TDF in situations where optimal monitoring is not possible.

Overall, renal disease has become a particular issue among patients infected with HIV, with increasing prevalence. A suggested algorithm for the screening and management of renal disease in the HIV-infected population is shown in Figure 1.

Patients on TDF should be screened at least every 6 months for eGFR, serum phosphate, proteinuria and glycosuria. Risk factors for nephrotoxicity include glomerular filtration rate <90 mL/min/m², use of renally excreted medications, comorbidities (e.g. diabetes and hypertension) and use of some protease inhibitors.

References:

Nephrotoxicity may develop in patients without risk factors, so it is important that all patients be screened; 3 monthly testing in the initial year is prudent, as well as increased vigilance long-term.5

References


Prolonged adefovir therapy associated Fanconi syndrome and interstitial nephritis in hepatitis B

Fanconi syndrome results from generalised dysfunction of the proximal renal tubule leading to impaired reabsorption of amino acids, glucose, uric acid and phosphate. The chronic renal loss of phosphate and the inadequate synthesis of 1,25(OH)2 vitamin D together produce phosphate depletion and failure to mineralise bone properly.1 The symptoms include fatigue, muscle weakness, bone pain, fracture and bone deformity. Patients may have
hypophosphataemia, glycosuria with normal glucose level, aminoaciduria, hypouricaemia and hypokalaemia.

We report two cases of Fanconi syndrome, both patients have hepatitis B and have been taking adefovir for more than 3 years.

Two middle-aged male patients presented to our hospital for investigation of generalised bone pain, muscle weakness and limitation of movement even at rest. Dual energy X-ray absorptiometry and X-rays revealed diffused decrease in bone density. Kidney biopsy confirmed interstitial nephritis in both. Laboratory investigation results on admission are included in Table 1. Both patients were treated with calcitriol (3 μg/day) and prednisone (15 mg/day).

Fanconi syndrome secondary to prolonged adefovir treatment at a conventional dose of 10 mg per day has been recently reported.2–4 Both our patients have been on adefovir for more than 3 years. They had typical symptoms of Fanconi syndrome, including muscle weakness, bone pain and low bone mineral density. Adefovir was therefore ceased, and entecavir was commenced instead. In order to correct the calcium/phosphate metabolism, we started both patients on high-dose calcitriol. After the initial treatment, the serum phosphate level was increased but was still below the normal range. However, with the calcitriol treatment alone, the proteinuria failed to improve, and the patients’ symptoms were only slightly relieved.

As suggested by several studies,5,6 after discontinuation of adefovir and commencement of neutral phosphate and calcitriol, the patient’s symptoms should resolve, and hypophosphataemia could correct. Calcitriol may be necessary to correct hypophosphataemia in some patients. However, hypophosphataemia persists in some patients.

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**Table 1** Laboratory results of two patients on admission/after treatment

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td></td>
<td></td>
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<tr>
<td>Phosphate</td>
<td>0.64/1.14 (0.8–1.45 mmol/L)</td>
<td>0.37/0.82 (0.8–1.45 mmol/L)</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.06/2.44 (2.15–2.55 mmol/L)</td>
<td>2.08/2.22 (2.15–2.55 mmol/L)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>420/302 (40–150 U/L)</td>
<td>317/366 (40–150 U/L)</td>
</tr>
<tr>
<td>PTH</td>
<td>6.0 (1.1–7.3 pmol/l)</td>
<td>2.6 (1.1–7.3 pmol/l)</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.71 (3.6–5.8 mmol/L)</td>
<td>3.69 (3.6–5.8 mmol/L)</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.07 (3.6–5.8 mmol/L)</td>
<td>5.0 (3.6–5.8 mmol/L)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>120 (120–141 umol/L)</td>
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</tr>
<tr>
<td>Creatinine</td>
<td>87 (44–115 μmol/L)</td>
<td>98 (44–115 μmol/L)</td>
</tr>
<tr>
<td>25(OH)D3</td>
<td>48.7 (47.7–144 mmol/L)</td>
<td>19 (47.7–144 mmol/L)</td>
</tr>
<tr>
<td>1,25(OH)D3</td>
<td>55.85 (39–193 mmol/L)</td>
<td>41 (39–193 mmol/L)</td>
</tr>
<tr>
<td>Phosphorus reabsorption rate</td>
<td>76.4/93.6 (84–96%)</td>
<td>72.5/83.5 (84–96%)</td>
</tr>
<tr>
<td>Creatinine clearance rate</td>
<td>87.6/100.24 (80–120 mL/min)</td>
<td>81/98 (80–120 mL/min)</td>
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<tr>
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<tr>
<td>Calcium</td>
<td>3.28/4.16 (150–250 mg/24 h)</td>
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<tr>
<td>Glucose</td>
<td>3.0/0.16 (0–0.25 g/24 h)</td>
<td>2.6/0.13 (0–0.25 g/24 h)</td>
</tr>
<tr>
<td>Protein</td>
<td>1.2/0.56 (30–150 mg/24 h)</td>
<td>1.96/0.22 (30–150 mg/24 h)</td>
</tr>
<tr>
<td>Aminoacid</td>
<td>Diffusely positive12/18</td>
<td>Diffusely positive16/18</td>
</tr>
<tr>
<td>Tubular acidification function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.4 (4.5–6.5)</td>
<td>7.1 (4.5–6.5)</td>
</tr>
<tr>
<td>HCO3</td>
<td>16.1 (0–12.44 mmol/L)</td>
<td>14.2 (0–12.44 mmol/L)</td>
</tr>
<tr>
<td>Titratable acid</td>
<td>11.1 (9.57–150 mmol/L)</td>
<td>0.31 (9.57–150 mmol/L)</td>
</tr>
<tr>
<td>NH₄⁺</td>
<td>11.3 (25.84–200 mmol/L)</td>
<td>10.5 (25.84–200 mmol/L)</td>
</tr>
<tr>
<td>BMId (g/cm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.566/0.761 (0.63–0.851)</td>
<td>0.608/0.851 (0.63–0.851)</td>
</tr>
<tr>
<td>L2-L4 spine</td>
<td>0.841/0.870 (0.791/0.901)</td>
<td>0.729/1.051 (0.791/0.901)</td>
</tr>
<tr>
<td>Whole body</td>
<td>0.873/0.882 (0.838/0.914)</td>
<td>0.838/0.914 (0.838/0.914)</td>
</tr>
<tr>
<td>Kidney biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomeruli with no significant change. Tubular epithelial cells with granular-vacuolar degeneration, multifocal atrophy, epithelial cells became flat with small focal brush border off.</td>
<td>Glomeruli with no significant change. Renal tubular epithelial cells with mild hydropic degeneration, individual lumen with protein casts. Interstitial with multifocal fibrosis, moderate-to-severe mononuclear cell infiltration, thickness of small artery wall.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| BMD, bone mineral density; PTH, parathyroid hormone.
patients despite phosphate and calcitrol treatment. Besides hypophosphataemia, these patients had proteinuria and renal dysfunction. Renal biopsy was performed, and interstitial nephritis was found. In the absence of other therapy, we attributed this to long-term adefovir treatment consistent with previous reports. Prednisone was started at the dose of 15 mg/day for 4–6 months. Both patients had significant symptomatic improvement compared with when they were only treated with calcitriol. Proteinuria, glucosuria, and renal function all improved, and the serum phosphate level returned to normal level. Unexpectedly, the bone mineral density also increased. Both patients can now mobilise without pain. Because of the relatively short period of treatment, we remain uncertain whether this treatment changes the long-term prognosis in such patients with adefovir-induced Fanconi syndrome.

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References

General correspondence

‘The association between time to disposition plan in the emergency department and in-hospital mortality of general medical patients’

Mitra1 points out an important issue when pleading not to stare blind at performance indicators, especially if they have not been validated by evidence, and not to ‘forget’ to deliver good quality care.

However, one could argue the importance of the influence of the time to disposition plan (TDP) on in-hospital mortality because it only increases in-hospital mortality in case of a prolonged emergency department (ED) length of stay (LOS). This might mean that it is not the rapid setting of a disposition plan but rather the boarding of the patient in the ED that leads to increased mortality. It would be interesting to know if the ED LOS or even more so the boarding time in the ED (time between disposition plan and actual admission of the patient) did not contribute to the increased mortality more than the TDP did. The data provided in table 2 suggest that ED LOS was an independent variable on in-hospital mortality, as were both TDP <4 h and TDP ≥4 h. Also, no data are provided on the influence of ED LOS when TDP is ≥4 h.

Longer ED LOS have been shown to result in significantly higher inpatient mortality, in-hospital LOS and readmission rates in several populations,2–4 suggesting that reducing ED LOS might contribute to patient safety and better quality of care.

One of the many ways to reduce ED LOS is by rapid patient assessment and implementation of a disposition plan. However, this will only reduce ED LOS if the disposition plan is executed in an evenly rapid and efficient way. To achieve this, the complete patient flow process through the ED and through the hospital needs to be evaluated and adapted if necessary, as suggested by the Institute of Healthcare Improvement.5 Multidisciplinary agreements should be made with hospitalists on when and under which conditions the patient can be admitted, proper handover protocols should be developed, and
proper initial care for admitted patients (still boarding in the ED or being admitted to the wards) should be organised. Viccellio et al. found that moving up patients to the hallway of the hospital ward resulted in reduced mortality and intensive care unit admissions as compared with moving the patients to standard beds, even if ED LOS was longer for the patients who were sent to the hallway.6 Although their findings need to be confirmed by studies in other centres, they suggest that ‘shared boarding’, that is, boarding both on the ward as in the ED, might be better for patient safety.6

In conclusion, arbitrary TDP targets are tempting for measuring performance, but they have no use if they are not linked to indicators measuring the execution of the disposition plan.

References


Reply

We thank Heerinckx for his comments and reinforcing the message that prolonged emergency department (ED) length of stay (LOS) is associated with adverse patient outcomes.1 We also agree that while time to disposition plans (TDP) are tempting to measure, they are a poor reflection of ED performance and yet to be reliably associated with patient safety. Whether longer ED LOS contributes to higher mortality, more than rushed disposition, cannot be answered from retrospective reviews and prospective studies are required to answer this question.

In figure 1 of our manuscript, we had shown that the highest mortality rates were observed in the setting of short TDP compounded by longer LOS, and it is important that evidence-based health policy is directed at avoiding both.2 In the setting of long TDP, the association of ED LOS with mortality was relatively small, suggesting that complete assessment and management by clinicians trained in acute care may be an important safeguard. Previous reports have highlighted the myth of ED waiting times and ED assessment times as the cause for prolonged ED LOS.3 Accordingly, any policy that inhibits complete and appropriate assessment, management and handover of an acutely ill patient should be avoided.

The importance of evidence-based policy cannot be overstated and has been previously highlighted.4,5 We do, however, appreciate that without evidence, policymakers must fall back on intuition, ideology and conventional wisdom with the risk that these ‘experimental’ policies go seriously astray given the complexities and interdependencies of our society and economy, and the unpredictability of people’s reaction to change.6 Well-resourced continuing evaluation, keeping open the options of refinement and change, are essential in this setting.
As stated by Heerinckx and others, access block and ED overcrowding represent hospital-wide dysfunction. Appropriate health policies are required targeting deficiencies in these processes, that is, the ‘execution of the disposition plan’ and timely transfer of patients to the wards following complete ED assessment, management and handover.

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The DiaSorin Liaison method has not underestimated serum 25-OH-vitamin D levels or misclassified patients with vitamin D deficiency in the Australian population

The assumption of Lai et al.1 that their liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay is a nominal gold standard for measurement of 25-OH-vitamin D is flawed. Their conclusion that vitamin D deficiency is overdiagnosed by the DiaSorin Liaison method when compared with their LC-MS/MS method shows lack of understanding of technical and biological issues when assessing vitamin D deficiency in a general population.

First, their paper makes no reference to how their LC-MS/MS method correlates to the US National Institute of Standards and Technology (NIST) LC-MS/MS candidate reference method and NIST standards for 25-OH-vitamin D. External quality assurance studies2 using the NIST LC-MS/MS candidate reference method and NIST standards demonstrated that routine LC-MS/MS methods as a group were overestimating 25-OH-vitamin D by 11.2%. This is consistent with overestimation of 25-OH-vitamin D by the LC-MS/MS method of Lai et al.1 invalidating important study conclusions. Overestimation in the Lai et al.1 method could be due to lack of standardisation of their LC-MS/MS method against the NIST reference method as well as potentially confounding metabolites (e.g. epimers and isobars) in a now ‘out of date’ LC-MS/MS method.2–4

In 2010, Binkley et al.,3 using liquid chromatography (LC) with ultraviolet detection (LC-UV) calibrated against the NIST standards, demonstrated reasonable agreement between their HPLC method and results from four laboratories using the DiaSorin Liaison. Variations in results were due only to random error between the two methods. These observations also support our conclusion that the LC-MS/MS method of Lai et al.1 is overestimating 25-OH-vitamin D.

25-OH-vitamin D LC-MS/MS assays are not always the gold standard. Nonstandardised LC-MS/MS methods are equally guilty of overestimating serum 25-OH-vitamin D levels.

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Variability in vitamin D assays impairs clinical assessment of vitamin D status

We read with interest the article by Lai et al.1 that reported variability in serum 25-hydroxy-vitamin D (25(OH)D) results analysed using different methods. The authors reported that compared with the liquid chromatography-tandem mass spectrometry (LCMS/MS) as a gold standard, the Diasorin Liaison method overestimated substantially the percentage of people with vitamin D deficiency. However, the authors failed to report the performance of their LCMS/MS in any external quality assurance program (EQA). While 25(OH)D results from immunoassays could be variable, results from LCMS/MS users could also be vastly different. In the last Australian-based EQA (Royal College of Pathologists of Australasia Chemical Pathology Quality Assurance Program), for a target 25(OH)D of 43 nmol/L (sample 36-12), laboratories using mass spectrometry reported results from <27 to 43 nmol/L. The LCMS/MS methodology is technically demanding, and currently, the calibrators are not standardised universally, although the recent introduction of the vitamin D standard reference material (SRM 972 and SRM 2972) by the National Institute of Standards and Technology (NIST) and the availability of EQA have reduced interlaboratory variability in 25(OH)D measurements.

In addition, while LCMS/MS is probably the most important advance in 25(OH)D methodology, the LCMS/MS methods for 25(OH)D measurement are not perfect yet. It has recently been revealed that LCMS/MS methods can be interfered by 25(OH)D metabolites, such as C-3 epimer of 25-hydroxy vitamin D [3-epi-25(OH)D]2–5 and the biological significance of the metabolites remains unclear. In the October 2011 cycle of the UK-based EQA (the Vitamin D External Quality Assessment Scheme), laboratories using LCMS/MS, the proposed ‘gold standard’ for 25(OH)D analysis overestimated substantially the 25(OH)D concentration in a specimen containing 3-epi-25(OH)D, while most laboratories using immunoassays did not. For sample 405 that contained approximately equal amounts of 25(OH)D3 and 3-epi-25(OH)D3 (51 nmol/L each), 99% (109/115) of the LCMS/MS users failed to separate out the 3-epimer that coelutes with 25(OH)D3 and resulted a much higher method median of 109 nmol/L as 25(OH)D3. This may be one reason behind the positive bias in some LCMS/MS methods compared with the NIST reference method5 that is able to separate the 3-epimer. In the study by Lai et al.,1 it was unclear whether their LCMS/MS method was able to separate 3-epi-25(OH)D3, as this was not discussed by the authors. This is important because 3-epi-25(OH)D, thought to be only in neonates,2 is now commonly found in adults.3,4 Lensmeyer et al.4 showed that 212 of 214 specimens from people age ranging from neonate to over 80 years had detectable 3-epi-25(OH)D3. At 25(OH)D3 values of 50–55 nmol/L (20–22 ng/mL), the ratio of 3-epi-25(OH)D3 to 25(OH)D3 varied from 2% to 8.5%.

In summary, all the methods for vitamin D-testing, including those using LCMS/MS and immunoassay methodologies, are in a state of rapid change and improving for both accuracy and precision. In 2011, many immunoassays for 25(OH)D, including Diasorin Liaison, have been reformulated or restandardised. The clinical significance of studies that fail to report the performance of their 25(OH)D methods in an EQA is dampened and possibly more so when the ability of the 25(OH)D method to separate 3-epi-25(OH)D is also not considered.

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Reply

High variability in the measurement of vitamin D levels is the key clinical issue

We are pleased that our paper1 has generated the discussion in the *Journal*,2,3 further highlighting the issues with measurement of vitamin D status. In light of recent publications of high prevalence of vitamin D deficiency in Australia,4 it is important that clinicians are aware of the scope of the problems in measurement of vitamin D status.

All of the laboratories measuring 25(OH)D for this study1 participated in DEQAS, the external quality assurance programmes for the measurement of 25(OH)D at the time of the study measurements. The Diasorin Liaison measurements were completed in November 2007 and the liquid chromatography-dual mass spectrometry (LC-MS/MS) in October 2008. The National Institute of Standards and Technology (NIST) standard 972 for measurement of 25(OH)D was released on 8 July 2009. Thus, at the time that the samples were tested, none of the labs was calibrating against the NIST standard.

Overestimation has been previously reported for LC-MS/MS5 and underestimation for Liaison5 – although prior to the development of a standard reference material (SRM), this was relative (to the all-laboratory trimmed mean) rather than absolute (compared with an SRM). LC-MS/MS assays are reported to be generally reliable and accurate6 in comparison with the wide variability reported for results from immunoassays.7 What is perhaps notable in our findings is one of the Liaison assays underestimated compared with the other Liaison assay. For this and other reasons, we refer to LC-MS/MS as the ‘nominal’ gold standard rather than assuming that one measure gives a ‘correct’ measure of vitamin D status. Our analysis focuses upon the agreement between assays, using Bland–Altman plots and Deming regression that do not assume a gold standard.

For the clinician, the key message is not which assay is underestimating or overestimating but that there is *high variability* in the estimation according to the assay used and the laboratory in which the testing is undertaken. The original NIST 972 SRM was unsuitable for immunoassays, limiting calibration against the SRM across the full range of 25(OH)D concentration. It is thus fortunate that a new SRM has recently been developed specifically for use with the LC-MS/MS in conjunction with a reference measurement protocol (RMP) that should resolve these issues and allow for accurate and reliable 25(OH)D measurement.

None of the assays used in this study evaluated the concentration of the C3-epimer or the isobars of 25(OH)D – these are recently recognised problems in 25(OH)D measurement. It is possible that the LC-MS/MS assay used here overestimated 25(OH)D because of the inclusion of the C3-epimer, although this is usually at very low levels in adult samples. The Liaison assay does not detect C3-epimer but may cross-react with other vitamin D metabolites, for example, 24,25(OH)D7. Fortunately, the new SRM and RMP allow quantification of the C3-epimer, while recently developed LC-MS/MS assays also quantify isobars,8 facilitating future research into the functional significance of these metabolites.

The automated Liaison assays are subject to variability in the kits supplied;7 LC-MS/MS assays are highly user-dependent. Hence, it is imperative that a rigorous RMP with a SRM is available to ensure standardisation of 25(OH)D measurement across assays and laboratories. It is only when standardised and calibrated methods are used that estimates of the prevalence of vitamin D deficiency in Australia can be made reliably; clinicians can then both detect and manage vitamin D deficiency in...
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their patients with some confidence in the results of the testing ordered.

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