INTERNAL MEDICINE JOURNAL


Avant Getting Started in Private Practice Program

Take the pressure off your first years in private practice.

Comprehensive protection plus 4 years of savings>

As Australia’s leading MEPO, only Avant can give you this industry-leading offer on Practitioner Indemnity Insurance. When you sign up as a new private practitioner you can take advantage of substantial savings along with full membership benefits, backed by the defence of Australia’s largest specialist medical-legal team. Just one of the many advantages you receive with Avant.

YEAR 1/ 80% DISCOUNT
YEAR 2/ 60% DISCOUNT
YEAR 3/ 40% DISCOUNT
YEAR 4/ 20% DISCOUNT

JOIN NOW > 1800 128 268  avant.org.au/newprivatepractice

Biosimilars: how similar?

Clinical potential of gene therapy

Antimicrobial prescribing patterns in private hospitals

Medical practitioners and patients’ advanced care plans

Acute poisoning: fatalities and hospitalisations

Dabigatran tolerance
Editor-in-Chief
Jeff Szer, Melbourne

Continuing Education
Deputy Editor-in-Chief
Zoltan Endre, Sydney

Deputy Editor-in-Chief
Paul Bridgman, Christchurch

Subspecialty Editors
Cardiology
Paul Bridgman, Christchurch
Andrew McGavigan, Adelaide
(Deputy Editor)

Clinical Genetics
Les Sheffield, Melbourne

Clinical Pharmacology
Jenny Martin, Brisbane
Yvonne Bonomo, Melbourne
(Addiction Medicine)

Continuing Education
( Clinical Perspectives)
Christopher Pokorny, Sydney

Emergency Medicine
John Vinen, Sydney

Endocrinology
Mark McLean, Sydney
Morton Burt, Adelaide

Ethics
Paul Komesaroff, Melbourne

Gastroenterology
Anne Duggan, Newcastle

Geriatric Medicine
Leon Flicker, Perth

General Haematology
Peter Browett, Auckland

Haemostasis/Thrombosis
Claire McIntock, Auckland

Immunology and Allergy
Marianne Empson, Auckland

Infectious Diseases
David Murdoch, Christchurch

Intensive Care
Michael O’Leary, Sydney

Internal Medicine
Ian Scott, Brisbane

Nephrology
Zoltan Endre, Sydney

Neurology
David Blacker, Perth

Nuclear Medicine
Frederick A. Khafagi, Brisbane

Occupational and Environmental Medicine; Health Economics; Editorials Editor
Des Gorman, Auckland

Oncology
Damien Thomson, Brisbane

Palliative Medicine
Janet Hardy, Brisbane

Public Health Medicine
Mark Ferson, Sydney

Respiratory Medicine
Matthew Naughton, Melbourne

Rheumatology
Peter Youssif, Sydney

Sexual Health Medicine
Darren Russell, Cairns

Honorary Advisory Board
Peter Doherty, Melbourne
Kar Neng Lai, Hong Kong
Richard Larkins, Melbourne
Sir Gustav Nossal, Melbourne
Lawrie W. Powell, Brisbane
Nicholas Saunders, Newcastle
John Shine, Sydney
Chorh Chuan Tan, Singapore
Sir David Weatherall, Oxford
Judith Whitworth, Canberra

Editorial Ombudsman
Graham Macdonald, Sydney

Manager
Virginia Savickis, Sydney

Editorial Office Administrator
Lorelie Willoughby, Sydney

Previous Editors-in-Chief
Internal Medicine Journal
The Australian and New Zealand Journal of Medicine
The Australasian Annals of Medicine
Ronald Winton (1957–1970)
Mervyn Archdall (1952–1956)
Did you know you can access *Internal Medicine Journal* online through the Royal Australasian College of Physicians’ website?

Go to [www.racp.edu.au](http://www.racp.edu.au)

- Find ‘member services’ in the middle navigation bar
- Click Access to Journals
- Select IMJ and then enter username or member identification number (MIN) number & password

= FREE access to all IMJ current and digitised backfile content to volume one, 1971

Wiley-Blackwell is proud to publish in partnership with a majority of medical Colleges in Australia and New Zealand.

In accessing your journal online through your College website, you now also have access to these College titles published by Wiley-Blackwell:

For more information on these journals, go to [www.wiley.com/go/healthprofessionalanz](http://www.wiley.com/go/healthprofessionalanz)

**Access your College journal online**

[The Royal Australasian College of Physicians](http://www.racp.edu.au)
Let your partners in research energize your career.

Drawing on our expertise and relationships in the healthcare industry, Wiley-Blackwell invites you to join Wiley Healthcare Jobs, the definitive job site for healthcare professionals.

- **FIND** premium jobs from the most respected names in healthcare
- **ATTRACT** hundreds of healthcare-industry recruiters and employers
- **CREATE** job alerts that match your criteria
- **OBTAIN** expert career advice and candidate resources

Register and upload your resume/CV now to begin your job search!

Part of Wiley Job Network

wileyhealthcarejobs.com
aims and scope
The Internal Medicine Journal, formerly known as the Australian and New Zealand Journal of Medicine, is the official journal of the Adult Medicine Division of The Royal Australasian College of Physicians (RACP). Its purpose is to publish high-quality internationally competitive peer-reviewed original medical research, both laboratory and clinical, relating to the study and research of human disease. Papers will be considered from all areas of medical practice and science. The Journal also has a major role in continuing medical education and publishes review articles relevant to physician education. Except where otherwise stated, articles are peer reviewed.

abstracting and indexing
This journal is indexed by Abstracts on Hygiene and Communicable Diseases, AgBiotech News and Information, AIDS Abstracts, Australian Medical Index, BIOSIS, Biological Abstracts (BIOSIS), Biomedical Reference (EBSCO), Cambridge Scientific Abstracts, Chemical Abstracts Service, Current Contents/Clinical Medicine (an ISI product), Current Opinion in Biotechnology, Environmental Sciences and Pollution Management, Health and Safety Science Abstracts (Online version), Helminthological Abstracts, InPharma Weekly, International Pharmaceutical Abstracts (IPA), Journals @ Ovid, MEDLINE, Nutrition Abstracts and Reviews, Pharmacoeconomics and Outcomes News, Reactions Weekly, Science Citation Index, SCOPUS, Tropical Diseases Bulletin, Vitis-Viticulture and Oenology Abstracts (Online Edition), World Agricultural Economics and Rural Sociology Abstracts, and CINAHL.

address for editorial correspondence
Editor-in-Chief, Internal Medicine Journal, The Royal Australasian College of Physicians, 145 Macquarie Street, Sydney, NSW 2000, Australia (tel: +61 2 9256 5431; fax: +61 2 9252 3310). For enquiries regarding ScholarOne Manuscripts (formerly known as ManuscriptCentral) submissions please email ManuscriptCentral@racp.edu.au (e.g. IMJ-0000-2013). General enquiries should be directed to Virginia Savickis, the Editorial Office, Internal Medicine Journal, using imj@racp.edu.au
Comments on published papers are welcomed. Authors are offered right of reply (no more than 500 words) at the discretion of the Editor and discussion will not be entered into. Given the current pressures on editorial space, however, invited comments are restricted to one reply.

disclaimer
The Publisher, RACP and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher, RACP and Editors, neither does the publication of advertisements constitute any endorsement by the Publisher, RACP and Editors of the products advertised.

Copyright © 2014 Royal Australasian College of Physicians.

For submission instructions, subscription and all other information visit www.wileyonlinelibrary.com/journal/imj

This journal is available online at Wiley Online Library. Visit www.onlinelibrary.wiley.com to search the articles and register for table of contents and email alerts.

Wiley’s Corporate Citizenship initiative seeks to address the environmental, social, economic, and ethical challenges faced in our business and which are important to our diverse stakeholder groups. We have made a long-term commitment to standardise and improve our efforts around the world to reduce our carbon footprint. Follow our progress at www.wiley.com/go/citizenship

Access to this journal is available free online within institutions in the developing world through the HINARI initiative with the WHO. For information, visit www.healthinternetwork.org

ISSN 1444-0903 (Print)
ISSN 1445-5994 (Online)
Visit the Author Services website at http://authorservices.wiley.com to:

- Track your article from production to publication with optional e-alerts at key stages
- Nominate up to 10 colleagues to receive FREE online access to your article
- Find author guidelines by journal
- Save 25% discount on Wiley books
- Get access to resources, FAQs and tips on article preparation, submission, artwork, copyright, offprints, etc.
- Receive free online access to your article when it is published online

http://authorservices.wiley.com
Editorial
213 Chronic kidney disease and the ageing population
M. Tonelli and M. Riella

Review
218 Biosimilars: how similar?
V. Strand and B. Cronstein

Clinical Perspectives
224 Clinical potential of gene therapy: towards meeting the demand
J. L. Macpherson and J. E. J. Rasko

Original Articles
234 Medical practitioners’ knowledge and self-reported practices of substitute decision making and implementation of advance care plans
C. Cartwright, J. Montgomery, J. Rhee, N. Zwar and A. Banbury

240 Using periodic point-prevalence surveys to assess appropriateness of antimicrobial prescribing in Australian private hospitals
M. O. Cotta, M. S. Robertson, L. M. Upjohn, C. Marshall, D. Liew and K. L. Buisng

246 Deteriorating patients managed with end-of-life care following Medical Emergency Team calls
J. Orosz, M. Bailey, M. Bohensky, M. Gold, S. Zalstein and D. Pilcher

254 Early hyperglycaemia and the early-term death in patients with spontaneous intracerebral haemorrhage: a meta-analysis
X. Tan, J. He, L. Li, G. Yang, H. Liu, S. Tang and Y. Wang

261 Adherence and outcomes of patients prescribed dabigatran (Pradaxa) in routine clinical practice

266 Metformin usage in type 2 diabetes mellitus: are safety guidelines adhered to?
W. Huang, R. L. Castelino and G. M. Peterson

273 Fatalities and hospitalisations due to acute poisoning among New Zealand adults
R. Peiris-John, B. Kool and S. Ameratunga

281 Examining patients’ preferences for participation in clinical decision-making: the experience in a Latin American chronic obstructive pulmonary disease and cancer outpatient population
P. Jordan, S. Quadrelli, M. Heres, L. Belli, N. Ruhl and H. Colt

Brief Communications
287 Hepatosplenic T-cell lymphoma, immunosuppressive agents and biologicals: what are the risks?
March 2014, Volume 44, Issue 3

291 Long-term outcomes in patients with restrictive filling following ST-segment elevation myocardial infarction

295 Left atrial appendage occlusion with the Watchman device in a patient with paroxysmal atrial fibrillation and intolerance of all forms of anticoagulation due to hereditary haemorrhagic telangiectasia
R. Spina and B. Gunalingam

298 Method for improving the quality of discharge summaries written by a general medical team
P. Russell, U. Hewage and C. Thompson

Personal Viewpoint
302 General medicine advanced training: lessons from the John Hunter training programme
D. Jackel, J. Attia and R. Pickles

Letters to the Editor

Clinical-scientific notes

306 Lymphangioma: an unusual cause for a non-functioning adrenal mass
E. Blanchard, P. Brenner, W. Delprado and K. Samaras

307 Recurrence of Carney complex atrial myxoma causing embolic stroke

309 Ventricular fibrillation storm in a young man with early repolarisation abnormality: the role of isoprenaline and quinidine
A. Voskoboinik, A. J. McLellan and P. M. Kistler

General correspondence

312 Professionalism, patient-centred care and revalidation
G. Gabb

312 Author reply
G. Phelps and S. Dalton
WILEY ONLINE LIBRARY
Access this journal and thousands of other essential resources.

Featuring a clean and easy-to-use interface, this online service delivers intuitive navigation, enhanced discoverability, expanded functionalities, and a range of personalization and alerting options.

Sign up for content alerts and RSS feeds, access full-text, learn more about the journal, find related content, export citations, and click through to references.
Youth, which is forgiven everything, forgives itself nothing; age, which forgives itself everything, is forgiven nothing.

George Bernard Shaw

The proportion of older people in the general population is steadily increasing worldwide, with the most rapid growth in low and middle-income countries. This demographic change is to be celebrated, because it is the consequence of socio-economic development and better life expectancy. However, population ageing also has important implications for society – in diverse areas including health systems, labour markets, public policy, social programmes and family dynamics. A successful response to the ageing population will require capitalising on the opportunities that this transition offers, as well as effectively addressing its challenges.

Chronic kidney disease (CKD) is an important public health problem that is characterised by poor health outcomes and very high healthcare costs. CKD is a major risk multiplier in patients with diabetes, hypertension, heart disease and stroke – all of which are key causes of death and disability in older people. Since the prevalence of CKD is higher in older people, the health impact of population ageing will depend in part on how the kidney community responds.

March 13, 2014 will mark the celebration of the 9th World Kidney Day (WKD), an annual event jointly sponsored by the International Society of Nephrology and the International Federation of Kidney Foundations. Since its inception in 2006, WKD has become the most successful effort to raise awareness among policy makers and the general public about the importance of kidney disease. The topic for WKD 2014 is ‘CKD in older people’. This article reviews the key links between kidney function, age, health and illness – and discusses the implications of the ageing population for the care of people with CKD.

Epidemiology of ageing

The key drivers of population ageing are socio-economic development and increasing prosperity – which result in lower perinatal, infant and childhood mortality; lower risk of death in early adulthood due to accidents and unsafe living conditions; and improving survival of middle-aged and older people due to chronic disease. The resulting increases in life expectancy (together with the lower birth rates that typically accompany socio-economic development) mean that older people account for a larger proportion of the general population. The extent of the resulting changes in population characteristics can be startling, especially for developing countries (Fig. 1).

In contrast to the situation even two generations ago, people can expect to live for many years after the usual retirement age. For example, UK men and women aged 65 years in 2030 can expect to live until age 88 and 91 years respectively. Predicted life expectancy for today’s children is controversial, but experts estimate that 50% of UK children born in 2007 will live to at least 103 years. Although it is clear that people are living longer, it is uncertain how much of the increased life expectancy will translate into years of good health. These demographic changes have dramatic potential implications for conditions such as CKD, for which the prevalence increases with age.

CKD is common in older people and its prevalence increases in parallel with age

It has been known for decades that estimated glomerular filtration rate (eGFR) declines in parallel with age. The prevalence of CKD among females in the Chinese general population increases from 7.4% among those aged 18–39 years to 18.0% and 24.2% among those aged 60–69 and 70 years respectively. Relative increases in the prevalence of CKD with age are equally striking for populations in the U.S, Canada and Europe, although there are between-country differences in the absolute prevalence.

At older ages, an increased proportion of prevalent CKD cases has low eGFR alone (as compared to albuminuria alone, or both low eGFR and albuminuria). Although this might suggest that many older people with CKD can expect lower rates of kidney function loss, available data are inconclusive – and current knowledge does
not allow clinicians to reliably distinguish between those whose CKD will and will not progress.

As for other age groups, the incidence of dialysis-dependent kidney failure has steadily increased among older people over the past few decades: in the United States, a 57% age-adjusted increase in the number of incident octogenarians and nonagenarians was noted between 1996 and 2003 alone.\(^1\) Despite this increase, patients aged >80 years are still less likely to initiate dialysis than those aged 75–79 years – although a large recent study suggested that the risk of developing very low eGFR (<15 mL/min/1.73 m\(^2\)) is similar for older and younger adults.\(^2\) It is uncertain whether this discrepancy is due to between-age differences in the true rate of progressive kidney function loss, the risk of death due to competing causes, patient views about dialysis or physician practices.\(^2,\)\(^1\) Regardless of the explanation, the ageing population will likely lead to continued increases in the number of older people with severe CKD.

**CKD is harmful but treatable if patients at risk are identified**

Like younger people, older people with advanced CKD are at increased risk of death, kidney failure, myocardial infarction and stroke compared to otherwise similar people with normal or mildly reduced eGFR.\(^1\)\(^4,\)\(^1\)\(^5\)

Although death is by far the most common of these adverse outcomes, this does not mean that older patients with clinically relevant CKD cannot benefit from timely specialist referral.
With appropriate management, patients with advanced CKD (regardless of age) may benefit from slower loss of kidney function (potentially preventing kidney failure), better control of metabolic consequences such as acidosis, anaemia and hyperphosphataemia, lower risk of cardiovascular events and (for those who are interested in renal replacement) a more informed choice of renal replacement modality, including timely creation of vascular access.\textsuperscript{16} The ageing population will likely lead to continued increases in the number of older people who might require such referral, which should be considered in assessments of future nephrology workforce capacity.

Dialysis can benefit older people with kidney failure

In developed countries, the default management strategy for older people with kidney failure appears to have shifted from conservative management to initiation of dialysis.\textsuperscript{17} On average, life expectancy after initiation of dialysis is relatively short for older patients: median survival among incident US dialysis patients aged 80–84 years is 16 months – and is only 12 months among those aged 85–89 years.\textsuperscript{11} At the same time, these median statistics reflect a bimodal distribution of survival time in older dialysis patients; although a large proportion die within 6 months of commencing dialysis, a substantial minority may live for years. This heterogeneity in mortality appears to be driven by differences in baseline comorbidity. For example, analyses of a small UK cohort of people with advanced kidney failure suggested that initiation of dialysis was not associated with increased survival for those aged ≥75 and with two or more comorbidities.\textsuperscript{18,19} Similarly, the presence of two to three comorbid conditions in US dialysis patients aged ≥65 years was associated with substantially increased mortality compared to those in better health.\textsuperscript{11} When functional status is lower at baseline, initiation of dialysis often signals the onset of further declines; among 3702 nursing home residents initiating dialysis, 58% had died and 87% had experienced additional loss of function at 1 year.\textsuperscript{20} Although available data have limitations, quality of life appears reasonable among selected older dialysis patients – and can remain stable despite moderate or high levels of comorbidity.\textsuperscript{21,22}

These data suggest that dialysis is an appropriate treatment option for well-informed older patients with kidney failure – especially for those with good baseline quality of life. On the other hand, the very poor outcomes experienced in those with more comorbidity or lower functional status at baseline clearly demonstrate that dialysis does not improve clinical outcomes for all older people with kidney failure – and that good clinical judgment and careful communication will be increasingly required as the general population continues to age.

Kidney transplantation can also benefit older people with kidney failure

It is generally accepted that older age alone does not preclude kidney transplantation in otherwise suitable candidates. However, older patients with kidney failure are more likely to have absolute and relative contraindications to transplantation, and are less likely to be placed on the kidney transplantation waiting list. Unsurprisingly, patient and graft 5-year survival probabilities are lower among US kidney transplant patients aged ≥65 years as compared to those aged 35–49 years (patient: 67.2% vs 89.6%; graft: 60.9% vs 75.4% respectively).\textsuperscript{21} In addition, older people who are potential kidney transplant patients face several potential disadvantages compared to their younger counterparts (Box 1).

Nonetheless, transplantation appears to reduce mortality among patients of all ages. For example, among those aged 74 years, receiving a deceased donor transplant was associated with a hazard ratio of mortality of 0.67 (95% confidence interval 0.53, 0.86) as compared to remaining on dialysis.\textsuperscript{22} Use of expanded criteria deceased donors\textsuperscript{23,26} as well as more liberal use of older living donors\textsuperscript{27} appear to reduce mortality among older people with kidney failure, as compared to similar patients who remain on the transplant waiting list (Box 2). These latter two strategies are especially appealing for use in developing countries, where growth in the prevalence of older people has been most pronounced. However, because transplant surgery itself temporarily increases the risk of death, the mortality benefits associated with kidney transplantation (regardless of donor type) are restricted to those with reasonable baseline life expectancy and without dramatically increased perioperative risk.\textsuperscript{28}

\begin{boxedenv}
\begin{itemize}
\item Organ shortage
\item Paucity of live donors
\item Organ allocation policies that appropriately weight likelihood of benefit from transplantation as well as chronological age
\item Ensuring appropriate referral of potentially suitable older patients for transplantation assessment
\item Ethical concerns about offering a kidney to an older patient versus a younger one
\item Optimal immunosuppressive regimen
\end{itemize}
Adapted from Mohanlal and Weir.\textsuperscript{24}
\end{boxedenv}
Research needs

Although much is known about chronic kidney disease in older populations, a great deal remains to be learned. Many trials of therapies for CKD have excluded older patients – and most do not provide guidance on how to manage comorbidities that often accompany CKD but may lead to competing therapeutic priorities. More information is needed on how to identify accurately people who will progress to kidney failure – and among these, the subset that can expect reasonable life expectancy and quality of life if they opt for dialysis treatment. Future studies should test new ways to communicate information about the risks and benefits of dialysis (as compared to conservative management), to facilitate informed patient decisions. Above all, we need more studies that demonstrate how to optimise quality of life and manage symptoms in elderly people with CKD – including those who have chosen conservative management.

The way forward

The ageing of the general population means that older people now account for a much greater proportion of patients with or at risk for kidney disease and kidney failure. The tremendous clinical heterogeneity within this population indicates the need for more discerning management. Chronological age alone will not be sufficient as the basis for clinical decisions, and a more nuanced approach is required – based on the comorbidities, functional status, quality of life and preferences of each individual patient. Clinicians can be reassured that dialysis and kidney transplantation can increase life expectancy – and will allow reasonable quality of life in selected older people with kidney failure. Perhaps more importantly, clinicians, patients and their families can be comforted by the knowledge that timely specialist evaluation can help to improve outcomes and reduce symptoms in older people with advanced kidney disease – whether they have selected conservative management or dialysis as their treatment plan.

Acknowledgements

M. Tonelli was supported by a Government of Canada research chair in the optimal care of people with chronic kidney disease.

Received 11 December 2013; accepted 7 January 2014.

doi:10.1111/imj.12367

M. Tonelli1 and M. Riella2

1University of Alberta, Alberta, Canada and 2Catholic University of Parana, Curitiba, Brazil

Box 2: Meeting the growing demand for kidney transplantation in older CKD patients

- Preferential transplantation of organs from older donors to older patients
- Enlarge the donor pool by accepting expanded criteria donors: ≥60 years or ≥50 years with any of the following two conditions: history of hypertension, serum creatinine ≥1.5 mg/dL or death due to cerebrovascular accident.
- ‘Old for old’: preferentially using kidneys from older living donors for older patients
- Transplanting two marginal kidneys instead of one

Adapted from Mohanlal and Weir. 24

References

12 Hemmelgarn BR, James MT, Manns BJ, O’Hare AM, Muntner P, Ravani P et al. Rates of treated and untreated kidney
Biosimilars: how similar?
V. Strand¹ and B. Cronstein²

¹Biopharmaceutical Consultant, Portola Valley, California and ²Divisions of Translational Medicine and Rheumatology, NYU School of Medicine, New York, USA

Key words
biosimilar, intended copy, monoclonal antibody, biosimilar regulation.

Abstract
As patents expire on biological agents for the treatment of rheumatic diseases, we have the opportunity to develop non-proprietary biologic agents, biosimilars. The development and approval of these agents present novel challenges to both pharma and regulatory agencies although there is great promise of high quality, less expensive biologic agents for the treatment of rheumatic diseases. Here, we review the definitions of biosimilars, the regulatory challenges to approval of these agents and the record of approvals of biosimilars to date.

Introduction
As rheumatologists, we have keenly experienced the benefit biologic therapies have brought to our therapeutic armamentarium. As monoclonal antibodies (mAbs) and soluble receptors (cepts) against cytokines, cell surface antigens and co-stimulation signals, they represent the ‘most complicated’ of biologic agents in terms of development of biosimilars. Several, including the tumour necrosis factor inhibitors (TNFis) have also shown dramatic efficacy in treatment of psoriasis and inflammatory bowel disease, and many of these products share similarities with mAbs used in oncology.¹-⁴

Now that the first biosimilar in rheumatology to infliximab (Remicade; Janssen Biotech, Horsham, PA, USA), Remsima (Celltrion, Incheon, South Korea) or Inflectra (Hospira, Lake Forest, IL, USA), has received a positive recommendation for marketing approval from the European Medicines Agency (EMA), a ‘road map’ is available to understand better the development of mAb and soluble receptor biosimilars.⁵ Regulatory review was based on data derived from two large randomised controlled trials (RCT): one phase 2 in Ankylosing Spondylitis (AS): PLANETAS in 250 patients⁶ and one phase 3 in Rheumatoid Arthritis (RA): PLANETRA in 600 patients.⁷

Biosimilarity was demonstrated for efficacy, pharmacodynamics (PD), pharmacokinetics (PK) and immunogenicity with ‘comparable’ safety. Extrapolation to all indications for which Infliximab is currently approved for marketing in European (EU) countries was recommended and marketing approval granted by the European Commission on 10 Sept 2013.⁸ It is expected that an application submission will occur soon in the United States, which will be important to compare in terms of expectations of and decisions made by EMA. Based on published data from the above RCT, it can be expected that a ‘bridging study’ against a US produced version of Infliximab would be required by the Food and Drug Administration (FDA). Speculation also includes the potential need for additional RCT to support extrapolation to other approved US indications for Infliximab. Finally, it will be of great interest to determine which regulatory agency decisions, EMA or FDA, will be considered most relevant to Australian (and Canadian) authorities – in part, these may be determined by patent positions.

Economic rationale
Although their impact on rheumatic diseases has been remarkable, the cost of biologic therapies imposes a significant financial burden on patients and third party payors. With sales for the top three TNFis exceeding $20 billion in 2012, ranging from $10–30 000 per patient per
year, this burden restricts their use to patients in wealthier countries. As patents are expiring on the first generation of biologic therapies, it is not surprising that there is considerable interest in development of effective biosimilar agents. Nonetheless, the expected decline in cost of biologic therapies following the introduction of biosimilars will not approach price reductions (often = 90%) associated with generic small molecule drugs.

**Definition of a biosimilar**

Recently the World Health Organization defined a biosimilar as a ‘... biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.’ 

Rigorous testing and licensing requirements for biosimilars have been developed by EMA and FDA, and biosimilars should be developed in accordance with these requirements. Both agencies developed these review processes to minimise any clinically meaningful differences between the biosimilar and the reference product.

A number of agents has previously been approved for treatment of rheumatologic conditions as ‘biosimilars’ in a number of countries but, in fact, are ‘intended copies’ or ‘non-comparable biologics’. Although these products met local regulatory requirements, they have not been shown to meet criteria for biosimilars and typically have not been rigorously compared to the innovator product preclinically or clinically.

**EU regulations and biosimilar precedent**

EMA has regulated biosimilars since 2004 when the European Commission adopted a new directive laying out the legal ground for approval of biosimilars: that the biosimilar must be sufficiently similar to the reference product (already licensed in the EU) to be used in the same clinical indication at the same dose; requiring additional clinical trials but likely more abbreviated where the risk of failure is less, as the target and mechanism of action are well demonstrated. Nonetheless, it is recognised that small changes may impact clinical efficacy and/or safety and much depends on the reference product and selected clinical indication. Comparability to the reference product must be demonstrated in terms of quality, safety and efficacy. This legislation resulted in approval of two somatropins: human growth hormones (HGH), five biosimilar erythropoietins and seven filgrastims: granulocyte colony stimulating factors (G-CSF) between 2006 and 2010. In contrast, approval of several proposed agents were denied: interferon alpha (determined as not biosimilar) and insulin (more effective than the reference product).

Recognising that mAbs and soluble receptors present unique challenges over and above hormones and growth factors, EMA issued two recent Guidelines specific to mAbs: ‘On similar biological medicinal products containing mAbs – non-clinical and clinical issues’ and ‘Immunogenicity assessment of mAbs intended for in vivo clinical use’ in October 2010, adopted in May 2012 and considered in effect in December 2012. These followed a previous Guideline which discussed ‘Procedural advice for users of the centralised procedure for similar biological medicinal products applications’, November 2011. Three revisions of guidelines issued in 2005–2006: ‘Draft guideline on similar biological medicinal products’, ‘Draft guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: quality issues’ and ‘non-clinical and clinical issues’ were issued in May 2013, April 2012 and June 2013 for comments by October 2013, November 2012 and November 2013 respectively. Altogether, these documents outline the regulatory pathway for defining comparable quality, safety and efficacy between a biosimilar and an innovator mAb.

**US regulations and biosimilar precedent**

In contrast, US FDA did not have a legal mandate to regulate biosimilars until passage of the Biologics Price Competition and Innovation Act (BPCI Act) of 2009 as part of the ‘ObamaCare’ legislation in March 2010. It defined a biosimilar to be a ‘biologic product highly similar to the reference product . . . With no clinically meaningful differences . . . in terms of the safety, purity and potency of product . . . must utilise the same mechanism of action for the conditions of use prescribed . . . same route of administration, dosage form, strength . . . and proposed conditions of use as the reference product . . . expected to produce the same clinical result in any given patient . . . ’ It further states that the same clinical result must be obtained in any given patient, back and forth, with no reduced risks of switching or alteration. A ‘higher hurdle’, specific to the United States, defines a product as interchangeable, meaning that the pharmacist can substitute it without knowledge of the prescribing healthcare provider (HCP). This expanded scope defined biologic agents as any α amino polymer with a specific sequence >40 amino acids, with exception of chemically synthesised polypeptides <100 amino acids, and created a new abbreviated licensure path: section 351(k) of the Public Health Services Act (PHS Act) for a Biologic License Application (BLA) route for approval, analogous to the 505(b)(2) mechanism for generic pharmaceuticals. The product under review for a 351(k) application must be evaluated against a biologic...
agent licensed in the United States under an original 351(a) application. Recognising patent issues and to preserve exclusivity, a biosimilar application may not be submitted until 4 years and may not be approved until 12 years after approval of the reference product. This legislation also established a new paradigm for sponsor-FDA interactions, defined by Prescription Drug User Fee Act 5 (PDUFA 5).

Thus, no biosimilars were approved in the United States until recently. An exception, Omnitrope (Sandoz; Novartis, Basel, Switzerland), a biosimilar of somatropin (HGH) gained approval as a drug before the biosimilar regulations were established. In August 2012 Neutroval (Teva Pharmaceuticals, Petah Tikva, Israel), tbo-filgrastim received approval under this new BLA route, but is not expected to be marketed in the United States until November 2013.21

After a series of open public meetings and a New England Journal of Medicine article discussing regulation of biosimilars,22 FDA issued a series of three Draft Guidance Documents for Industry in April 2012. These included: ‘Scientific Considerations and Quality Considerations in demonstrating biosimilarity to a reference protein product and Questions and Answers regarding Implementation of the BPCI Act of 2009’. Scientific Considerations23 indicate that FDA would rely upon a stepwise approach to support a demonstration of biosimilarity – ‘to evaluate the extent to which there is residual uncertainty to be addressed by additional animal and clinical studies’. Multiple factors will be considered as part of the assessment, including but not limited to a product’s complexity, formulation and stability as well as the usefulness of biochemical and functional characterisations. Incorporation of these factors will be ‘risk based’, affected by knowledge regarding the product characteristics, and analysis and testing will be determined on a product-specific basis. ‘Quality considerations’24 include the type, nature and extent of any differences between the proposed biosimilar and the reference product; and potential effect of these differences on its safety, purity and potency. Recognising the large advances in analytical and manufacturing technology, use of ‘Quality by Design’ approaches may facilitate what are described as ‘fingerprint-like’ analyses. These may provide appropriate bases for more selective and targeted approaches to subsequent animal and/or clinical studies, and identical lots must be used for determination of biosimilarity. Questions and Answers25 outline that analytical studies and at least one clinical PK study, and, if appropriate, at least one PD study intended to support demonstration of biosimilarity must include an adequate comparison directly to the US licensed reference product. A bridging study with a US licensed product may be acceptable; and a sponsor may apply for fewer than all clinical indications and/or routes of administration currently approved for the reference product. Data are expected to support ‘extrapolation’ to other clinical indications, and formulations may differ if they do not result in clinically meaningful differences in safety, purity or potency.

In April 2013, FDA issued a fourth ‘Draft Guidance: Formal meetings between FDA and Biosimilar sponsors/applicants’.26 A Biosimilar Initial Advisory Meeting is defined to indicate whether licensure under 351(k) pathway is feasible; followed by four types of Biosimilar Product Development Meetings. Type 1 is necessary for an otherwise stalled programme to proceed; Type 2 to discuss a specific issue such as study design or endpoints designed to obtain targeted advice regarding an ongoing programme; Type 3 for in-depth review and advice regarding an ongoing programme and Type 4 to discuss the format and content of a biosimilar product application or supplement. Clearly, FDA is indicating their willingness to provide guidance throughout a biosimilar development programme.

Differences between FDA and EMA regulations

Certain obvious and other more subtle differences exist between published guidance and guidelines of FDA and EMA. Both advocate step-wise approaches in demonstrating biosimilarity. Regarding PK studies, FDA specifies ‘Comparative human studies’ versus ‘Single dose, comparative human studies’ by EMA, and PD studies: ‘Comparative human studies, where clinically relevant measures are available’ versus ‘Combine with PK studies where a clinically relevant PD endpoint is available’, suggesting FDA requirements may be more stringent. Nonetheless, PK and PD may be assessed as parallel endpoints in RCT. Both agencies require pre-clinical evaluation of PK and PD where relevant.

An obvious question is whether (RCT) will be required for demonstration of biosimilarity. FDA requires ‘At least one, adequately powered equivalence trial’ versus EMA: ‘Highly sensitive, dose-comparative PD studies may be sufficient . . . Otherwise, at least one, adequately powered equivalence trial’. Regarding immunogenicity, FDA specifies that: ‘At least two comparative trials, one pre- and one postmarketing’ versus ‘Must be assessed during the safety trial’ by EMA. FDA and EMA both agree that ‘At least one, adequately powered equivalence trial’ must demonstrate highly similar safety, and both agencies recommend that the clinical data required to demonstrate comparability of the biosimilar be generated with product from the final manufacturing process, representing the quality of the batches intended to be commercialised.
Although EMA guidelines have emphasised that the biosimilar clinical development programme and RCT may be more abbreviated, both regulatory agencies indicate that proof of clinical similarity requires demonstration of equivalence within strict pre-defined margins rather than non-inferiority. And proof of efficacy requires commonly accepted clinical endpoints, especially as there are no data to support accelerated approval of a biosimilar based on surrogate endpoints.27 Design of these RCT will be based on data from the reference product and that a stringent statistical definition be selected to preserve 50–75% of the effect size for non-inferiority (according to what is clinically meaningful, typically >70–75%), and that the lower limit of the 95% confidence interval of the difference between the biosimilar and the reference product does not cross the margin. Such statistical determinations require that the reference product has been well demonstrated in RCT as efficacious versus placebo, and the size of the trial(s) depends on how small a difference in efficacy to exclude. A challenge remains in adequately powering an RCT to demonstrate a comparable safety profile.

The FDA draft Guidance documents state that the ‘clinical programme must include a clinical study or studies (including an assessment of immunogenicity and PK or PD) sufficient to demonstrate safety, purity and potency in one or more appropriate conditions of use’. Thus, it is clear that at least one active comparator trial will be required, likely more to support ‘extrapolation’ to other indications.

Although EMA specifies that ‘intended changes to improve efficacy are not compatible with the biosimilarity approach’... the guidance continues later to say: ‘Differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be explained, but may not preclude biosimilarity’.18

Finally, the US law makes a distinction between ‘biosimilar’ and ‘highly similar’. If a product is considered to be highly similar, it will be substitutable without knowledge of the HCP, and a specific paediatric study is not required. Nonetheless, demonstration of ‘high similarity’ will likely require cross-over studies with switching, as were necessary for approval of abatacept administered subcutaneously versus intravenously, despite it being the same product, differing only in formulation and route of administration.28–30 A distinction of ‘highly similar’ by EMA does not exist as substitution will be regulated by the individual member countries, and EMA specifies that a brand name and batch number be recorded for any biologic medicinal product. Despite the above wording, legislatures in a variety of US states and Canada are considering or have passed laws prohibiting such substitution without knowledge of the HCP.31

For a majority of the above points, FDA and EMA appear to be offering similar guidance, and most of their outlined expectations regarding approval of biosimilars appear comparable. Now that a biosimilar mAb has been approved in the EU, speculation may be made as to potential differences in how FDA will regulate this product. As the RCT performed to date to demonstrate non-inferiority were against an ex-US-produced infliximab, a bridging study to a US-produced product can be expected. Further, it is unclear how FDA will consider extrapolation to other clinical indications, particularly inflammatory bowel disease and psoriasis, based on trials performed exclusively in arthritides. Perhaps, another RCT will be necessary for US review. As the patent expiration for infliximab in the United States is expected December 2014, it is likely these answers will emerge in the coming 12 to 18 months.

Demonstrating biosimilarity

The guidelines for demonstrating biosimilarity between newly developed agents and the innovator or ‘bio-original’ includes a number of clear milestones. The amino acid composition and terminal amino acid sequence of the biosimilar protein or peptide must be identical to that of the original product. The presence of disulfide bonds, sulphydryl groups glycosylation and other determinants of protein folding must also be identical as changes in protein folding may lead to altered immunogenicity or activity. These characteristics can be tested using a variety of techniques, as described in the EMA and FDA documents discussing scientific considerations25,32 including isofrom pattern, determination of extinction coefficients, electrophoretic patterns following digestion of proteins or carbohydrates, changes in migration during liquid chromatography and spectroscopic profiles. Although higher order structure of the product cannot be tested directly in activity assays, binding assays (for ligands and antibodies) and in vitro biological activity assays can ultimately provide a demonstration that the material is biologically identical to the bio-original.

Most reviews of the topic suggest that biosimilars may differ by some other characteristic(s) not adequately tested by the assays described above. In this regard, it is interesting to note that, unlike small molecules, there is generally thought to be greater batch-to-batch variation in biologic agents than would be permissible in small molecule pharmaceutical agents. Nonetheless, this variation is acceptable if potency is maintained, and there is no evidence of further obvious deviation from the immunogenicity or function of the original. Indeed, the goal of regulators is to determine that biosimilars will not differ from the original product by more than the
batch-to-batch variation that is already acceptable. In one sense, this has become common practice, as manufacturing of originator products has undergone multiple alterations over time as scale up processes or new manufacturing sites are introduced, and have been specified in International Conference on Harmonization Harmonised Tripartite Guideline, Topic Q6B. Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological products.

Information regarding manufacturing changes, in very general terms, is available from EMA, but is confidential between sponsor and FDA. In another sense, regulation of batch-to-batch variation has become more challenging as increasingly batches have become so large that a single batch may account for an entire year’s production run of the product in the United States or EU.

Conclusions

Despite the challenges, it is clear that biosimilar mAbs and ceptics are upon us, in rheumatology, dermatology, gastroenterology and oncology. A biosimilar to Remicade is expected to be marketed in the EU before the end of the year, and this and other products in the United States as patents lapse or are licensed, as several biosimilars are in RCT and under review at FDA. The regulatory requirements of EMA and FDA for demonstration of biosimilarity should be considered sufficiently stringent to ensure confidence in use of an approved biosimilar. The issue of substitution without knowledge of the HCP may ultimately be legislatively prohibited. Thus, the promise of biosimilars remains their significant economic savings while offering comparable safety and efficacy profiles.

References


Clinical potential of gene therapy: towards meeting the demand
J. L. Macpherson1,3 and J. E. J. Rasko1,2,3

1Cell and Molecular Therapies, Royal Prince Alfred Hospital, 2Gene and Stem Cell Therapy Program, Centenary Institute, Camperdown and 3Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

Key words genetic therapy, genetic vector, clinical trial, review.

Abstract
Since the discovery that new genetic material could be transferred into human cells resulting in induced expression of genes and proteins, clinicians and scientists have been working to harness the technology for clinical outcomes. This article provides a summary of the current status of developments within the broad discipline of clinical gene therapy. In pursuing the treatment of diverse clinical conditions, a wide variety of therapeutics, each tailor-made, may be required. Gene therapy offers the possibility of accurately and specifically targeting particular genetic abnormalities through gene correction, addition or replacement. It represents a compelling idea that adds a new dimension to our portfolio of credible therapeutic choices.

Introduction
Gene therapy can be defined as the introduction of genes into human cells to restore normal cellular function. The rate of progress in the development of genetic therapies has varied over the past 20 years with alternating waves of enthusiasm and reservation across a wide variety of diseases. There are two main gene delivery strategies: ex vivo and in vivo (Fig. 1), and a broad range of tools to assist with the gene transfer (Table 1). Different approaches are more appropriate for different conditions. Some of the more notable successes in the field occurred in early, open-label clinical trials for monogenic diseases, including X-linked severe combined immunodeficiency (SCID-X1)1 and adenosine deaminase-severe combined immunodeficiency (SCID-ADA).2 More recently, promising results for the treatment of both rare inherited diseases like Leber congenital amaurosis1,4 and common haematological malignancies involving B lymphocytes have been obtained.3–7 A few of the clinical successes will be described and the path to implementation discussed.

Background and history
The phrase ‘genetic engineering’ was first coined in the 1930s. Over the years, the definition has changed from the concept of selective breeding of plants and animals, to our current definition, which evolved in the 1960s when genes were first transferred to bacteria and then human cells. Virologists had known for a long time about the efficiency with which diverse viruses could subvert mammalian cell replication machinery for their own propagation. The new genetic technology was used to introduce foreign genes into viruses and then to transfer efficiently these genes to human cells.
Mechanisms for the introduction of new genetic information into cells were developed through the systematic and progressive modification of viruses, based on a deep understanding of viral replicative processes. Viruses insert their genetic information into cells and use the cells machinery to replicate. We can exploit this innate ability and use viruses in the field of gene therapy to introduce genetic material that can correct or overcome a genetic insufficiency. The new genetically engineered viruses are known as viral vectors, and these have been widely used for the delivery of genes to human cells. Usually, the viral genomes have been gutted in order to render the vectors replication incompetent. Most, if not all, of the genes required for viral replication that are usually provided by the viral genome in cis are deleted and replaced by the new gene therapeutic payload. In order to prevent recombination and the recreation of viral vectors, specific mutations are introduced, and sequences known to be involved in splicing and recombination are eliminated. This is a primary safety feature of viral vectors, but there are many others introduced over time that will be discussed below. These viral vectors are manufactured in well-characterised cells in vitro by the provision, in trans, of the genes necessary for replication and encapsulation.

No single vector developed to date possesses all the characteristics required to target the efficient delivery of genetic material to specific cells and tissues, and that lacks local and systemic toxicity. In different circumstances, the duration and amount of gene expression required differs. Various vectors can efficiently enter target cells to provide either short-term or sustained gene (RNA) and protein expression (Table 1). The term transduction is used to encompass both the entry of a vector into a cell, and the subsequent expression of the therapeutic RNA and protein. In this way, transduction efficiency is used as a measure of the success of gene transfer. It should be noted that many of the tools available to measure gene

Table 1  Gene therapy delivery agents and associated features

<table>
<thead>
<tr>
<th>Vector subtype</th>
<th>Transduction efficiency</th>
<th>Transduce non-dividing cells</th>
<th>Integration</th>
<th>Copy number</th>
<th>Gene expression</th>
<th>Immune response</th>
<th>Production scale-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposome plasmid DNA</td>
<td>High to low</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
<td>Stable</td>
<td>Yes</td>
<td>Easy</td>
</tr>
<tr>
<td>Gammaretrovirus</td>
<td>High</td>
<td>No</td>
<td>Yes, enriched near transcription start sites</td>
<td>Low</td>
<td>Stable</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>Lentivirus</td>
<td>High</td>
<td>Yes</td>
<td>Yes, semi-random</td>
<td>Low</td>
<td>Stable</td>
<td>No</td>
<td>Complex</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>High</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>Transient</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adeno-associated virus</td>
<td>Lower</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>Stable</td>
<td>Low</td>
<td>Complex</td>
</tr>
</tbody>
</table>

Figure 1  Gene therapy delivery (A) Delivery of injectable viral vectors to an organ or systematically with subsequent targeted cellular uptake in vivo. (B) Modification of isolated target cells using retroviral vectors ex vivo and delivery of gene-modified cells obtained from the patient (autologous) or a matched donor (allogeneic).
expression can only be applied at the population level and so provide an average or approximation of expression. From extensive preclinical and laboratory experiments employing polymerase chain reaction analysis and other molecular biology techniques, we know that in a population of cells that is reported to have a transduction efficiency of 50%, some cells will contain more than one copy of the gene while others will not carry the gene at all. While the use of flow cytometry can provide information at the single cell level, this technique is only suitable for the evaluation of gene transfer when the therapeutic is a detectable protein. There are many RNA-based therapies currently in development.

Vector modifications have been introduced, particularly over the past 10 years. These have improved safety, especially the integrating gammaretroviral vectors. These vectors were among the first to be used in clinical trials, and it is estimated that over 2000 clinical trial subjects have received cells modified with gammaretroviral vectors. Perhaps the best-known diseases treated with retrovector vectors include the primary immunodeficiencies and other rare monogenic disorders. A summary of the long-term follow up of academic gene therapy trials for primary immunodeficiencies is shown in Table 2.

**Clinical development timeline**

In the early 1970s, the concept of replacing a defective gene with a functional one using genetic engineering was proposed as a possible treatment option. In the mid-1980s, clinician researchers first began to repair defective gene function in faulty human cells, thus demonstrating proof of concept for translation to the clinic and the path to therapeutic reality.

The concept behind gene therapy is simple: either to deliver a healthy gene, to correct or to compensate for a gene that is missing, or is defective, or to introduce a novel gene that can effect correction of the defective phenotype. Gene therapy could work by preventing a protein from doing something that causes harm, restoring the normal function of a protein, giving proteins new functions or enhancing the existing functions of other normal proteins. In recent years, we have seen publications and editorials in leading journals with catchy titles, such as ‘Gene therapy for severe combined immunodeficiency’.

<table>
<thead>
<tr>
<th>Conditioning regimen</th>
<th>Disorder</th>
<th>Enrolment open</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No conditioning</td>
<td>SCID-X1</td>
<td>1999–2006</td>
<td>• 17/20 infants with gene-corrected T cells • 5- to 12-year follow up • 5 patients developed leukaemia; clonal insertion of vector in near oncogene • 1 patient died, others responded to chemotherapy and/or transplant • Most patients retain functional immunity • 1 older patient did not show improvement</td>
</tr>
<tr>
<td>No conditioning</td>
<td>SCID-X1</td>
<td>2004–</td>
<td>• 3/5 adolescents demonstrate gene-corrected cells after &gt;2–3 years • Some clinical benefit in remaining patients who engrafted • No adverse events related to gene transfer to date</td>
</tr>
<tr>
<td>Non-ablative</td>
<td>SCID-ADA</td>
<td>2000–2012</td>
<td>• 40 patients with immunological and metabolic correction, and clinical improvement • Up to 10-year follow up • 29 no longer require enzyme replacement therapy • No adverse events related to gene transfer to date</td>
</tr>
<tr>
<td>No conditioning</td>
<td>CGD</td>
<td>1995–1998–</td>
<td>• 8/10 patients gene-corrected cells within 3–6 weeks • Possible clinical benefit in all patients (transient) • Non-ablative conditioning may explain lack of long-term response • No adverse events related to gene transfer</td>
</tr>
<tr>
<td>Low intensity</td>
<td>CGD</td>
<td>2003–</td>
<td>• 5 patients • &gt;40% of cells with corrected gene at 1.5 years in 2/2 patients • &gt;2 years follow up • 1 patient demonstrated functional immunity • No persistent efficacy • 3 patients developed myelodysplastic syndrome</td>
</tr>
</tbody>
</table>

Only conditions where at least two centres have been involved in similar studies are included. Most primary immunodeficiencies are now being treated on a collaborative basis with investigators in Italy, France, Germany, UK and USA all contributing to the one study. CGD, chronic granulomatous disease; SCID-ADA, adenosine deaminase-severe combined immunodeficiency; SCID-X1, X-linked severe combined immunodeficiency.
immunodeficiency: are we there yet?\textsuperscript{11} and 'The gene therapy journey for hemophilia: are we there yet?'\textsuperscript{25} So what has changed since Dusty Miller proclaimed 'Gene therapy comes of age'\textsuperscript{26} over 20 years ago? Is gene therapy a clinical reality, or do we still have a long way to go?

Clinical research into gene therapy’s safety and effectiveness began in 1990 when a 4-year old girl became the first gene therapy patient at the National Institutes of Health (NIH) Clinical Center in Bethesda.\textsuperscript{27} A deficiency of the adenosine deaminase gene results in profound immunodeficiency and susceptibility to infections. In this landmark experiment, her own white blood cells were corrected by insertion of the missing gene, and then re-infused to repopulate her immune system. At the time, no one knew if this gene therapy would work, or for what diseases this might be an appropriate therapeutic strategy. In less than 25 years, we have gone from hoping that the approach would offer an alternative treatment paradigm, to having clear clinical benefit in several indications, including adenosine deaminase deficiency,\textsuperscript{2,16–18} and with at least three gene therapy products on the worldwide market.\textsuperscript{28,29}

The history of gene therapy and the overall timeline has parallels to those seen for both monoclonal antibodies\textsuperscript{30} and bone marrow transplantation.\textsuperscript{31} Both offered early promise but were slow to gain significant momentum due to unexpected side-effects and/or limited efficacy. Like most new experimental therapies, the success of monoclonal antibodies was not guaranteed. Over the ensuing years, many changes have been introduced to improve outcomes. The first monoclonal antibodies were murine and were subject to immune clearance. Improvements in genetic engineering and rational design led to the introduction of first chimeric mouse-human antibodies through targeted mutations and later to the introduction of fully humanised antibodies. Nowadays, new antibodies and biosimilars are approved for sale every year. However, like most new drugs, the number of antibodies that make it all the way through clinical trials and to the market is a very small fraction of those proposed as therapies. In the field of gene therapy, we have been overly optimistic about the probability of success for each of the myriad treatments that have made it into the clinic. We should temper our enthusiasm with a reality check. Only a handful of the hundreds of potential products may become widely available for our patients.

### Clinical success and innovation

In 2000, one of the first great successes for gene therapy was announced. Children with SCID-X1 could be cured.\textsuperscript{1} Gammaretroviral vectors had been initially chosen for clinical use due to the ability of the powerful viral promoter or long terminal repeat (LTR) and viral enhancer/promoter combination to drive gene expression constitutively in a variety of target cell types. These vectors were known to integrate stably into the genome, and insertional oncogenesis was a theoretical possibility. In early 2003, the risk became a reality with the first reported case of leukaemia occurring in one of the infants treated in the French SCID-X1 study. This was followed shortly thereafter by three additional cases of insertion mutagenesis in that study, and later one case in the similar trial conducted in the UK.\textsuperscript{19,20} These events prompted an extremely thorough investigation of insertion events, not only in these children but in almost all studies using similar retroviral vectors.\textsuperscript{10} Despite the large number of patients who received gene-modified cells, the severe adverse outcomes have remained restricted to this one genetic disease. Children with the related disease SCID-ADA did not show any increase in leukaemia, nor was leukaemia observed in other conditions, including chronic granulomatous disease.\textsuperscript{12,13} Even the outgrowth of a clone of gene-modified cells was not in and of itself evidence of oncogenesis, although other problems were noted (Table 2).\textsuperscript{12,16,17,21,34}

However, the proven risk and ongoing concern that such events may still unfold in other conditions have driven research to derive safer delivery vectors. Two main strategies have been pursued. Variants of gammaretroviral vectors in which the LTR was disabled by mutation and transgene expression driven by a cellular promoter had been available for many years. Cellular promoters often have lower expression but are less prone to methylation and associated promoter shutdown. This self-inactivating (SIN) technology was already in mainstream use in the new generation of lentiviral vectors in development.\textsuperscript{15–17} The SIN gammaretroviral vectors were fast-tracked and enhanced to promote expression of the foreign gene, and at the same time studied intensively with regard to insertion and genotoxic potential.\textsuperscript{9,22} In some instances, these vectors have rapidly moved into the clinic since they can be manufactured in the same way as the earlier gammaretroviral vectors.

Lentiviral vectors based on human immunodeficiency virus (HIV-1) were developed initially to aid in the transduction of non-dividing haemopoietic stem cells.
Cytokine activation to move cells into the G1 phase of the cell cycle is still required, although cell division is not. The development of SIN lentiviral vectors progressed with their first clinical use in France, with two boys treated for a rare X-linked genetic disorder, adrenoleukodystrophy.\textsuperscript{35}

**Clinical trials**

Taking a genetic therapy to the clinic requires four key elements: a sound scientific basis, a clinical champion, willing participants and money. Before any basic research discovery can be taken to the clinic, extensive \textit{in vitro} and \textit{in vivo} evaluations must be undertaken to determine the likely efficacy and safety of the approach. This is not unique to gene therapies but a general requirement in the development of all therapeutic options. Gene therapies do pose some additional challenges particularly for therapies that involve cells or proteins that are not present in other species. The laboratory and preclinical evaluation that is required will be driven by the proposed indication and route of administration. A short summary of the questions that should be addressed is listed in Table 3.

The manufacturing costs for gene therapies are presently very high per dose. Even for the \textit{in vivo} vectors that can be manufactured in bulk for the preparation of many doses, the scale-up of complex cell expansion and subsequent purification of the viral particles is challenging. Similarly, for most of the \textit{ex vivo} approaches, there are challenges with manufacture of vector, plus there is also the challenge of manufacturing a patient’s own cells. In many cases, the cells must be infused fresh, and so they often need to be made in a specialised facility that is in close proximity to the clinical care facility. Furthermore, participants of clinical trials are usually observed very closely for the first 12 months following treatment, and for many vectors they are then followed for life to assess the long-term benefits and safety of these approaches. This imposes a substantial burden on clinical trials staff, particularly when patients have been recruited to study from distant locations. The importance of a strong relationship with gene therapy recipients is essential to maximise the ability to retain subjects on study with attendance at all scheduled visits, including long-term safety follow up.

Nevertheless, the promise of gene therapy is such that this approach has been evaluated in a variety of clinical indications worldwide (Table 4). Wiley, the publisher of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Considerations for gene therapy applications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific</strong></td>
<td><strong>Ethical</strong></td>
</tr>
<tr>
<td>Is there a sound basis for the proposed genetic correction? &amp; Does the participant truly understand the risks?</td>
<td></td>
</tr>
<tr>
<td>Does a protein need to be expressed or just RNA? &amp; What are the risks of germline gene modification?</td>
<td></td>
</tr>
<tr>
<td>How much expression is required and for how long? &amp; Would we consent for our children to participate?</td>
<td></td>
</tr>
<tr>
<td>Will the immune system react? &amp; Does the risk/benefit need to favour the individual or the patient population?</td>
<td></td>
</tr>
<tr>
<td>Which cells should be modified? &amp; Should rare or common diseases be the focus of gene therapy development?</td>
<td></td>
</tr>
<tr>
<td>Will there be off-target effects? &amp; Is efficacy been demonstrated in a relevant animal model?</td>
<td></td>
</tr>
<tr>
<td>Has efficacy been demonstrated in a relevant animal model? &amp; Should deaths on trial alter research efforts?</td>
<td></td>
</tr>
<tr>
<td>Is the toxicological profile known? &amp; Who will decide which patients can receive gene therapy?</td>
<td></td>
</tr>
<tr>
<td>Does it matter if the gene is expressed at high levels or in different cells? &amp; Who will pay?</td>
<td></td>
</tr>
<tr>
<td>Which cells should be modified? &amp; Has efficacy been demonstrated in a relevant animal model?</td>
<td></td>
</tr>
<tr>
<td>Should rare or common diseases be the focus of gene therapy development? &amp; Will there be off-target effects?</td>
<td></td>
</tr>
<tr>
<td>Will the immune system react? &amp; How much expression is required and for how long?</td>
<td></td>
</tr>
<tr>
<td>Which cells should be modified? &amp; Does a protein need to be expressed or just RNA?</td>
<td></td>
</tr>
<tr>
<td>will the immune system react? &amp; How much expression is required and for how long?</td>
<td></td>
</tr>
<tr>
<td>Which cells should be modified? &amp; Does a protein need to be expressed or just RNA?</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4** Gene therapy clinical trials expressed as percentage of the 1970 trials listed in the online Wiley database in September 2013 (http://www.abedia.com/wiley/)

<table>
<thead>
<tr>
<th>Clinical indication</th>
<th>%</th>
<th>Continent</th>
<th>%</th>
<th>Delivery vector type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers</td>
<td>64.2</td>
<td>Australia/NZ</td>
<td>1.6</td>
<td>Adeno-associated virus</td>
<td>5.2</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>8.1</td>
<td>Asia</td>
<td>4.4</td>
<td>Adenovirus</td>
<td>23.5</td>
</tr>
<tr>
<td>Gene marking</td>
<td>2.5</td>
<td>USA</td>
<td>62.7</td>
<td>Gamma retrovirus</td>
<td>19.1</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>2.6</td>
<td>Europe</td>
<td>25.9</td>
<td>Lentivirus</td>
<td>3.3</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>8.2</td>
<td>Multi-country</td>
<td>4.0</td>
<td>Other viruses</td>
<td>16.0</td>
</tr>
<tr>
<td>Inflammatory diseases</td>
<td>0.7</td>
<td></td>
<td></td>
<td>plasmid or naked DNA</td>
<td>23.2</td>
</tr>
<tr>
<td>Monogenic diseases</td>
<td>8.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological diseases</td>
<td>1.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular diseases</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trials are grouped by clinical indication, geographical location by continent and delivery vector type.
one of the leading gene therapy journals, has attempted to collate the clinical trials into a publicly accessible database. However, the database is limited by the non-uniform way in which data and outcomes are collected. While the data suggest that 1.6% of trials have been conducted in Australia, it is possible that some of the trials listed for the region are also listed in other sections of the database. The other important information not captured in the Wiley database is the number of patients treated. Most studies that are listed on the clinicaltrials.gov site include the proposed number of subjects to be recruited, but the actual number recruited is often not available. Studies may close early, or never recruit at all. Even for the commercially sponsored gene therapy trials, including those that have progressed to market approval, the total number of subjects is small (Table 5). Based on recruitment estimates, the number treated with gene therapies in Australia is likely to be a few hundred at most, with many studies only involving a handful of patients.

In the USA, the NIH has been instrumental in supporting gene therapy trials, through the provision of centralized viral vector manufacturing capability, the support of cell manufacturing facilities, clinical care facilities, as well as the salary support of clinical investigators. In other countries like Australia, investigator-initiated studies are financed in a piecemeal fashion, and thus usually only involve a small number of participants. Increasingly, particularly for rare conditions, collaborations involving investigators from across the world are working to develop a single protocol so that the data can be compared and combined (see also Table 2).

Recently, clinical trials of adeno-associated virus-mediated delivery of the factor IX gene in patients with haemophilia B, conducted by two independent groups, have shown great promise and factor VIII strategies are not far behind. Furthermore, treatment of deficiencies of globin synthesis using a lentiviral vector to deliver the beta-globin gene has been gaining momentum. VRX-496 was the first HIV-1-based vector tested in humans. It was reported that the capacity for replication was an advantage in the treatment of HIV-1. Despite early promise, the technology has been replaced by the development of a similar vector that acts as a vaccine.

To date, the most convincing preclinical and clinical data for the treatment of HIV-1 are for a surface-expressed C46 peptide that acts by binding HIV-1 glycoprotein 41, and this prevents membrane fusion and viral entry. This C46 molecule was evaluated in a small phase I study using CD4+ T-lymphocyte delivery, and more recently has been evaluated by several independent academic groups using CD34+ haemapoietic stem cell delivery in both in vitro and in vivo models. It appears to be the most potent inhibitor of HIV-1 replication reported, and it has been included in the newest gene therapy approach under development (Table 6). The first patients have been treated, but outcome data are not expected for at least 2 years (G. Symonds, pers. comm., 2014).

Competitive edge

The recent entry of the major biopharmaceutical company, Novartis, into the gene therapy space has reinvigorated gene therapy, for haematological malignancies in particular. Concerns about how to scale up manufacture and how to secure a reliable supply of the materials and reagents required for manufacture can now be addressed. However, the downside for the myriad of academic investigators interested in employing this approach for their own patients is that securing supply and protecting a market involve the application of an intellectual property portfolio. Already, deals have been done that provide an exclusive licence to key technology in the field of CAR-T cells for cancer. There will likely be other deals that eventually make it impractical for anyone else to pursue independently potential CAR-T cell therapies for cancer. This is disappointing given the growing interest in this technology in Australia.

Gene therapy in Australia

In general, Australian clinical medicine and standards of care are held in high esteem on the international stage, along with particular biomedical research fields. At present, in Australia, the only gene therapy options available for patients are still small-scale, early phase, investigator-sponsored, academic clinical trials. With the Therapeutic Goods Administration’s new regulatory framework for biologics, cost recovery model and the revised code of good manufacturing practice, conduct of academic trials is becoming more expensive. Review and
<table>
<thead>
<tr>
<th>Company</th>
<th>Location</th>
<th>Product name</th>
<th>Disease indication</th>
<th>Genetic therapy</th>
<th>Patients treated in trials</th>
<th>Development stage</th>
<th>Estimated cost in Australian dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiBiono</td>
<td>China</td>
<td>Gendicine</td>
<td>Head and neck squamous cell carcinoma</td>
<td>Adenovirus-p53</td>
<td>135</td>
<td>Approved in China 2003; estimated 6000 patients treated by 2007 with trials in many other cancers</td>
<td>$650 per dose</td>
</tr>
<tr>
<td>Sunway Biotech</td>
<td>China</td>
<td>Oncorine</td>
<td>Head and neck carcinoma</td>
<td>Adenovirus serotype 5- oncolytic</td>
<td>Not known</td>
<td>Approved in China 2005</td>
<td>$630 per dose</td>
</tr>
<tr>
<td>uniQure</td>
<td>Netherlands</td>
<td>Glybera</td>
<td>Orphan indication Lipoprotein lipase deficiency</td>
<td>Adeno-associated virus lipoprotein lipase</td>
<td>27</td>
<td>Approved for marketing in European Union in November 2012; USA, Canada and other markets pending</td>
<td>$1.4M per patient</td>
</tr>
<tr>
<td>Ark Therapeutics</td>
<td>UK, Finland</td>
<td>Cerepro</td>
<td>Glioma</td>
<td>Adenovirus-thymidine kinase</td>
<td>251</td>
<td>Submitted in Europe in 2008, rejected 2009, withdrawn 2010 (was available under named patient access in France)</td>
<td>—</td>
</tr>
<tr>
<td>Ark Therapeutics</td>
<td>UK, Finland</td>
<td>Trinam</td>
<td>Vascular graft occlusion</td>
<td>Adenovirus serotype 5-VEGF</td>
<td>Not known</td>
<td>Phase Iib, fast track status by FDA; orphan drug status in both USA and Europe</td>
<td>—</td>
</tr>
<tr>
<td>Oxford BioMedica</td>
<td>UK</td>
<td>TroVax</td>
<td>Various cancers</td>
<td>Vaccinia ST4 (tumour associated antigen)</td>
<td>&gt;500</td>
<td>Lead product in phase II</td>
<td>—</td>
</tr>
<tr>
<td>Oxford BioMedica</td>
<td>UK</td>
<td>ProSavin</td>
<td>Neurodegenerative</td>
<td>Lentiviral dopamine synthesis enzymes</td>
<td>15</td>
<td>More potent product now in development</td>
<td>—</td>
</tr>
<tr>
<td>Transgene</td>
<td>France</td>
<td>TG4010</td>
<td>Non-small cell lung cancer</td>
<td>Vaccinia MUC1/IL2 (tumour genes)</td>
<td>1200</td>
<td>Phase III data pending; partnership with Novartis; Pipeline of other products</td>
<td>—</td>
</tr>
<tr>
<td>AnGes MG/Vical</td>
<td>Japan, USA</td>
<td>Collatagene</td>
<td>Critical limb ischaemia, Peripheral arterial disease</td>
<td>Plasmid hepatocyte growth factor</td>
<td>560 planned</td>
<td>Peripheral arterial disease marketing application withdrawn in Japan; phase III worldwide; fast track status for critical limb ischaemia in USA in 2010</td>
<td>—</td>
</tr>
<tr>
<td>Mologen AG</td>
<td>Germany</td>
<td>MGN1703 dSLIM</td>
<td>Colorectal cancer</td>
<td></td>
<td>59</td>
<td>Phase III anti-cancer therapeutics</td>
<td>—</td>
</tr>
</tbody>
</table>
approval of protocols under the Clinical Trial Exemption scheme can be prolonged and expensive, prompting academic investigators to seek ways to expedite access to products in clinical trials through the Clinical Trial Notification (CTN) scheme. The most logical way to bring new gene therapies to our patients is through collaborations with academic investigators based at large centres in the USA and Europe, and to enrol patients in already approved protocols. This is considerably easier since it means that the US or European regulatory submission can be used as evidence of review of the clinical trial protocol and vector/cell manufacturing methods, thereby facilitating conduct under the CTN scheme.

**Conclusion**

Gene therapy is still a long way from standard of care. Optimism is sustained, and with the right combination of good basic science, clinical champions, enthusiastic patients, professional organisations and willing payers, we will continue to see the evaluation of genetic therapies for a broad range of conditions. The entry by large pharmaceutical companies into the field will be disruptive but should drive more rapid development timelines, and ultimately our patients will have access to better treatment options within a shorter time frame. It remains to be seen how reimbursement will be managed.

**References**

40 Monahan PE, Gui T. Gene therapy for hemophilia: advancing beyond the first


Medical practitioners’ knowledge and self-reported practices of substitute decision making and implementation of advance care plans

C. Cartwright,1 J. Montgomery,2 J. Rhee,3 N. Zwar3 and A. Banbury1

1ASLaRC Aged Services Unit, Southern Cross University, Gold Coast, Queensland, 2Advance Care Planning, NSW Health, and 3School of Public Health and Community Medicine, University of New South Wales, Sydney, New South Wales, Australia

Key words
advance directive, geriatrics, ageing.

Abstract

Background: Advance care planning (ACP) provides patients with the ability to make their decisions known about how they would like to be treated if they lose capacity. Medical practitioners have a key role to play in providing information on ACP to their patients. This research explores their knowledge and attitudes to advance care planning and how this affects their practice.

Aim: The objective of this study is to assess the NSW medical practitioners’ knowledge and self-reported practice of ACP.

Methods: A postal survey of a random sample of 650 general practitioners plus 350 medical specialists from specialties most often involved in end-of-life decisions was conducted. Respondents’ work location post codes were subsequently used to assign respondents to one of the eight NSW Area Health Services. The main outcome measures were medical practitioners’ knowledge of and practice pertaining to ACP.

Results: Thirty-four per cent of specialists (n = 110) and 24% of general practitioners (n = 150) responded; the majority of respondents had heard of all ACP options. However, respondents’ understanding of the uses and legal requirements of the relevant ACP options vary widely.

Conclusions: Respect for patient wishes expressed in advance directives is reassuringly high. The findings suggest significant misunderstanding by medical practitioners of terminologies and systems around substitute decision-making for incompetent persons. Further education and standardisation of terminologies and systems across different jurisdictions would assist in addressing these issues. Low response rate, relating to only one legal jurisdiction, means results may not be generalisable.

Introduction

In the past few decades, an ageing population, prevalence of dementia, rising healthcare costs, increasing concerns about the unacceptable quality of the dying process and the shift to increased patient involvement in decisions about their care1–3 have focused attention on advance care planning (ACP) both in Australia4 and internationally.5,6

ACP is a process which assists people with decision-making capacity, ideally in consultation with their healthcare providers and other important people in their lives, to make decisions based on their values, beliefs and goals, and about what medical treatments they would or would not want in the future if they could no longer speak for themselves.7,8

Several Australian studies have found limited knowledge, understanding and use of ACP among medical practitioners and the wider community.2,9,10 Poor understanding of who has legal authority to give consent for medical treatment for a patient without capacity was evident.2,11 Studies in Queensland12 and South Australia13 also found low levels of formal ACP in general practitioner (GP) surgeries. There has been some progress in implementing ACP in Australia through the Commonwealth’s Palliative Care in Residential Care programme and the ‘Respecting Patient Choices’ (RPC) programme,14 a comprehensive ACP programme which began in Australia in 2002. Detering et al.,15 using the RPC programme in a university hospital in Melbourne, demonstrated the potential for ACP to impact positively on the...
dying process for patients in hospital. Of the 56 participants who died in the 6-month trial period, those who completed ACP (intervention group) were significantly more likely than those in the control group to have their wishes known and followed; ACP also enhanced the experience of family members of participants. The authors concluded that ‘Advance care planning improves end of life care and patient and family satisfaction and reduces stress, anxiety and depression in surviving relatives’ (p. 1).

There has also been work on implementing ACP in the Residential Aged Care setting in metropolitan NSW. However, Bezzina and Shanley et al. found that such implementation was not consistent, even in facilities in the same area, and depended on the particular inclination of staff members. In September 2012, the Royal Australian College of General Practitioners released a position statement on ACP which advocated integrating it into general practice.

For ACP benefits to be realized, medical practitioners must have an accurate knowledge of the law relating to ACP in order to assist their patients to undertake ACP and to identify who the legally authorised substitute decision maker (SDM) is for patients without capacity.

In 2011, The clinical, technical and ethical principal committee of the Australian Health Ministers’ Advisory Council published a national framework for advance care directives to support the development of nationally consistent legislation governing ACP. At present, the law is different in every state/territory, with different terminology, documentation and order of SDM. For example, in some states and territories, a SDM appointed by the person themselves is called a medical agent, an enduring power of attorney (EPoA) for health matters or an enduring guardian (EG). The legislative options for ACP in NSW are as follows: appointment of an EG under the Guardianship Act 1987 (NSW) and completion of a written advance care directive (ACD). (The study questionnaire used the term advance directive (AD); however, as the commonly accepted term in NSW is now advance care directive or ACD, we have used that term except where we specifically refer back to the questionnaire.) ACD is legally binding under the common law (not statutory law) in NSW (confirmed by the 2009 NSW supreme court case, Hunter and New England Area Health Service v A [2009] NSWSC 761). (EPoA in NSW applies only to decisions about property and money.) If no EG has been appointed to make healthcare decisions, the legislation specifies an order of authority, referred to as person responsible (PR), that is, spouse, non-professional carer, close relative or friend (not next-of-kin). SDM provisions come into effect only when the person concerned has lost the capacity to make their own decisions.

In 2009, a survey of medical practitioners in NSW was undertaken to assess their levels of knowledge, and related practice, with respect to ACP.

Methods

A questionnaire, modified from previous studies in Queensland and the NT, was developed to test participants’ awareness and applied knowledge of ACP instruments in NSW. Questions and scenarios presented reflected the NSW legislative provisions.

Ethics approval was obtained from Southern Cross University Human Research Ethics Committee.

The five-page questionnaire and covering letter were mailed to a random sample of 650 GP and 350 medical specialists from specialties most likely to be involved in ACP, end-of-life decision making and acute resuscitation scenarios. This included acute care physicians (e.g. intensive care, emergency and anaesthetics), geriatricians, palliative care physicians and oncologists. Respondents were ‘assigned’ to one of the eight NSW Area Health Service (AHS) regions existing at that time on the basis of the work-related post code provided by them in the completed questionnaire.

The questionnaires were anonymous with no identifying codes. A Reply-Paid envelope was provided with a Reply-Paid card, indicating completion of the questionnaire and a request for feedback from the study to be returned separately to the questionnaire. A follow-up reminder was sent 3 weeks after original posting.

The questionnaires were coded and entered into an spss 17 database (SPSS, Chicago, IL, USA). Descriptive statistics and Chi-squared analyses were generated.

Results

After removing duplications, deceased, retired or not in clinical practice, and non-NSW medical practitioners, the sample size was 328 specialists and 629 GP. The response rate was as follows: specialists 34% (n = 110), GP 24% (n = 150) and overall rate of 27% (n = 260). Response rates by AHS for specialists ranged from 18% to 50%; for GP, from 15% to 35%; and overall, from 19–36%. The highest response rate for specialists and overall was from North Sydney/Central Coast AHS, and for GP, it was from the North Coast AHS. Table 1 presents the demographic characteristics of the 254–258 respondents who answered these questions. There was an almost equal representation of men and women among GP (52%:48%), whereas 78% of specialists were men and only 22% women.
Respondents were asked whether before completing the questionnaire they had heard of AD; EPoA; EG or PR. Table 2 presents the responses to the question.

Previous studies have found differences in practitioners’ knowledge of ACP by a range of demographic variables.9 Chi-squared analyses were conducted for responses by specialist/GP, age, gender, specialty, religion, years in practice and AHS; such differences could indicate future areas for research or continuing professional development. Results are reported only where differences reached significance.

A majority of respondents had heard of all four options (AD 80%, EPoA 93%, EG 79% and PR 72%), with no significant differences between specialists and GP. However, women (87% and 99%) were significantly more likely than men (76% and 89%) to have heard of ACD (\(\chi^2_{1, 4.56}; P = 0.033\)) and EPoA (\(\chi^2_{1, 8.31}; P = 0.004\)) respectively.

To determine the respondents’ knowledge and understanding of SDM instruments, they were asked four questions and presented with two scenarios. First, they were asked how often they ask their patients if they have given anyone EPoA for financial matters; 11% said they always or usually ask, 24% sometimes ask and 65% never or rarely ask.

Second, they were asked if they thought EPoA gave the person appointed the authority to make healthcare decisions; 46% correctly understood that EPoA does not allow the appointee to make healthcare decisions, 30% were unsure and 23% answered incorrectly that it did; there was no significant difference between specialists and GP.

Third, respondents were asked whether any of their patients had told them that they had appointed an EG or if they had recommended to any patient that they do so: 37% of specialists and 49% of GP had patients who had appointed an EG; 23% of specialists and 50% of GP had recommended to patients that they do so. Differences between specialties reached significance with respect to having been told by a patient that they had appointed an EG as follows: geriatricians (100%; \(n = 12\)), palliative care specialists (80%; \(n = 8\)), intensive care specialists (50%; \(n = 3\)), GP (49%; \(n = 71\)), emergency physicians (29%; \(n = 4\)), oncologists (25%; \(n = 4\)) and anaesthetists (18%; \(n = 9\)) (\(\chi^2_{10, 44.299}; P < 0.001\)).

Chi-squared analyses were conducted for responses by specialist/GP, age, gender, specialty, religion, years in practice and AHS; such differences could indicate future areas for research or continuing professional development. Results are reported only where differences reached significance.

A majority of respondents had heard of all four options (AD 80%, EPoA 93%, EG 79% and PR 72%), with no significant differences between specialists and GP. However, women (87% and 99%) were significantly more likely than men (76% and 89%) to have heard of ACD (\(\chi^2_{1, 4.56}; P = 0.033\)) and EPoA (\(\chi^2_{1, 8.31}; P = 0.004\)) respectively.

To determine the respondents’ knowledge and understanding of SDM instruments, they were asked four questions and presented with two scenarios. First, they were asked how often they ask their patients if they have given anyone EPoA for financial matters; 11% said they always or usually ask, 24% sometimes ask and 65% never or rarely ask.

Second, they were asked if they thought EPoA gave the person appointed the authority to make healthcare decisions; 46% correctly understood that EPoA does not allow the appointee to make healthcare decisions, 30% were unsure and 23% answered incorrectly that it did; there was no significant difference between specialists and GP.

Third, respondents were asked whether any of their patients had told them that they had appointed an EG or if they had recommended to any patient that they do so: 37% of specialists and 49% of GP had patients who had appointed an EG; 23% of specialists and 50% of GP had recommended to patients that they do so. Differences between specialties reached significance with respect to having been told by a patient that they had appointed an EG as follows: geriatricians (100%; \(n = 12\)), palliative care specialists (80%; \(n = 8\)), intensive care specialists (50%; \(n = 3\)), GP (49%; \(n = 71\)), emergency physicians (29%; \(n = 4\)), oncologists (25%; \(n = 4\)) and anaesthetists (18%; \(n = 9\)) (\(\chi^2_{10, 44.299}; P < 0.001\)).

Chi-squared analyses were conducted for responses by specialist/GP, age, gender, specialty, religion, years in practice and AHS; such differences could indicate future areas for research or continuing professional development. Results are reported only where differences reached significance.

A majority of respondents had heard of all four options (AD 80%, EPoA 93%, EG 79% and PR 72%), with no significant differences between specialists and GP. However, women (87% and 99%) were significantly more likely than men (76% and 89%) to have heard of ACD (\(\chi^2_{1, 4.56}; P = 0.033\)) and EPoA (\(\chi^2_{1, 8.31}; P = 0.004\)) respectively.

To determine the respondents’ knowledge and understanding of SDM instruments, they were asked four questions and presented with two scenarios. First, they were asked how often they ask their patients if they have given anyone EPoA for financial matters; 11% said they always or usually ask, 24% sometimes ask and 65% never or rarely ask.

Second, they were asked if they thought EPoA gave the person appointed the authority to make healthcare decisions; 46% correctly understood that EPoA does not allow the appointee to make healthcare decisions, 30% were unsure and 23% answered incorrectly that it did; there was no significant difference between specialists and GP.

Third, respondents were asked whether any of their patients had told them that they had appointed an EG or if they had recommended to any patient that they do so: 37% of specialists and 49% of GP had patients who had appointed an EG; 23% of specialists and 50% of GP had recommended to patients that they do so. Differences between specialties reached significance with respect to having been told by a patient that they had appointed an EG as follows: geriatricians (100%; \(n = 12\)), palliative care specialists (80%; \(n = 8\)), intensive care specialists (50%; \(n = 3\)), GP (49%; \(n = 71\)), emergency physicians (29%; \(n = 4\)), oncologists (25%; \(n = 4\)) and anaesthetists (18%; \(n = 9\)) (\(\chi^2_{10, 44.299}; P < 0.001\)).
Differences also reached significance in relation to medical practitioners advising patients to appoint an EG (<\chi^2_{10} = 67.424; P < 0.001) with very few respondents except geriatricians (83%; n = 10), palliative care specialists (80%; n = 8) and GP (50%; n = 73) having advised their patients to do so (all <8%).

Last, participants were asked whether it would be helpful to know who has legal authority to give consent for treatment if one of their patients loses decision making capacity. Overwhelmingly (96% specialists and 93% GP), respondents thought this would be helpful.

Scenarios were presented to assess respondents’ applied knowledge of ACP. Scenario 1 related to a frail, older, non-competent patient who had expressed his wishes in a valid AD. They were asked to what extent they agreed with each of four actions they might take if they did not agree with the patient’s wishes (response options: from 1 = strongly agree to 5 = strongly disagree).

- Treat the patient as you think best, regardless of the AD (<\chi^2 = 6.624, P = 0.009) strongly agreed/agreed they would seek substitute consent from the NSW public guardian to treat the patient as they (the respondent) thought best. The majority of respondents (77% of specialists and 76% of GP) strongly agreed/agreed that they would follow the AD, even if they did not agree.

Differences by age group reached significance for two options: the oldest group was significantly more likely than the two younger groups to strongly agree/agree that they would treat the patient regardless of the AD (60+ = 28%; 40−59 = 9%; <40 = 10%) and significantly less likely to disagree/strongly disagree that they would do so (60+ = 57%; 40−59 = 79%; 40 = 80%; \chi^2_4 = 13.914; P = 0.008). The oldest group of respondents was significantly more likely than the two younger groups to strongly agree/agree that they would ask the patient’s PR for consent to treat the patient as they (the respondent) thought best (60+ = 57%; 40−59 = 37%; <40 = 22%; \chi^2_4 = 17.138; P = 0.002).

Response differences only reached significance in relation to asking the PR for consent by years as a medical practitioner, with those longest in practice more likely to strongly agree/agree that they would do so (>20 years 43%; 11–20 years 29%; 1–10 years 34%; \chi^2_4 = 9.742; P = 0.045).

Differences by specialty reached significance in relation to the first three options. The majority (77% of specialists and 76% of GP) said that they would follow the patient’s wishes even if they did not agree with the AD (which accords with the law in NSW); 75% of respondents (84% of specialists and 68% of GP; \chi^2_2 = 7.664, P = 0.022) disagreed/strongly disagreed that they would treat the patient as they thought best regardless of the AD. Only 13% said that they strongly agreed/agreed with taking this action.

Overall, 38% (27% of specialists and 48% of GP; \chi^2_2 = 10.067; P = 0.007) of respondents strongly agreed/agreed they would ask the patient’s PR for consent to treat the patient as they (the respondent) thought, whereas only 17% (12% of specialists and 21% of GP; \chi^2_2 = 6.493, P = 0.039) strongly agreed/agreed they would seek substitute consent from the NSW public guardian to treat the patient as they (the respondent) thought best. The majority of respondents (77% of specialists and 76% of GP) strongly agreed/agreed that they would follow the AD, even if they did not agree.

Response differences only reached significance in relation to asking the PR for consent by years as a medical practitioner, with those longest in practice more likely to strongly agree/agree that they would do so (>20 years 43%; 11–20 years 29%; 1–10 years 34%; \chi^2_4 = 9.742; P = 0.045).

Differences by religion reached significance only in relation to treating the patient regardless of the AD where those with no affiliation (83%) were significantly more likely than those of ‘other’ religions (60%) to follow the AD (\chi^2_4 = 12.390; P = 0.15).

Scenario 2 involved an 87-year-old non-competent woman in a residential aged care facility. She has two children, an older son and a daughter, who had been caring for her mother at home; the daughter holds her mothers’ EPoA. The patient does not have an AD, and her children disagree about her treatment. The son believes he has the right to make decisions about his mother’s healthcare because he is the eldest and next-of-kin. The daughter believes that she has the right to make the decisions because she has been managing her

Table 3 Responses to scenario 1

<table>
<thead>
<tr>
<th>Possible options</th>
<th>Strongly agree/agree</th>
<th>Neither agree nor disagree</th>
<th>Disagree/strongly disagree</th>
<th>Mean/5:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total % (n)</td>
<td>GP % (n)</td>
<td>Spec % (n)</td>
<td></td>
</tr>
<tr>
<td>Treat regardless of AHCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ask person responsible for consent</td>
<td>13 (31)</td>
<td>16 (22)</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td>Ask public guardian for consent</td>
<td>38 (94)</td>
<td>47 (66)</td>
<td>27 (28)</td>
<td></td>
</tr>
<tr>
<td>Follow the directive</td>
<td>17 (41)</td>
<td>21 (29)</td>
<td>12 (12)</td>
<td></td>
</tr>
<tr>
<td>Total (GP Spec)</td>
<td>76 (193)</td>
<td>76 (109)</td>
<td>77 (84)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total % (n)</td>
<td>GP % (n)</td>
<td>Spec % (n)</td>
<td></td>
</tr>
<tr>
<td>Treat regardless of AHCD</td>
<td>12 (30)</td>
<td>16 (22)</td>
<td>8 (8)</td>
<td>75 (183)</td>
</tr>
<tr>
<td>Ask person responsible for consent</td>
<td>14 (35)</td>
<td>13 (18)</td>
<td>16 (17)</td>
<td>48 (116)</td>
</tr>
<tr>
<td>Ask public guardian for consent</td>
<td>20 (49)</td>
<td>23 (32)</td>
<td>17 (17)</td>
<td>63 (150)</td>
</tr>
<tr>
<td>Follow the directive</td>
<td>18 (44)</td>
<td>19 (27)</td>
<td>16 (17)</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Total (GP Spec)</td>
<td>75 (183)</td>
<td>68 (95)</td>
<td>84 (88)</td>
<td>3.96</td>
</tr>
</tbody>
</table>

AHCD, Advance Health Care Directive; GP, general practitioner; Spec, specialist.
mother’s affairs and has EPoA. Respondents were asked who they thought has the legal right to make healthcare decisions for this woman. Although 54% correctly nominated the daughter as the person with such authority, 65% of those respondents said that this was because the daughter has EPoA; only 35% correctly recognised that the daughter was the PR because she had been the main non-professional carer.

Discussion

The majority of respondents had heard of all four ACP options. EPoA was the most the most widely heard-of option and the instrument that respondents had most experience with. However, although awareness of the EPoA instrument was high, respondents did not routinely ask patients whether they had given anyone EPoA, with over half never or rarely asking the question. Over half (53%) of the respondents were unsure or incorrect in their understanding that in NSW, an EPoA does not allow the person appointed to make healthcare decisions. This may lead a practitioner to accept the decision of a person who does not have legal authority to make medical decisions for the patient. If the decision was disputed by the person who did have authority, this may result in conflict or even legal action. Overwhelmingly, both groups reported that they would like more education about who has the legal authority to give consent to treatment for a patient without capacity. The demonstrated lack of knowledge may partly explain why most respondents did not routinely ask patients if they had undertaken ACP options. The specialties with the highest percentage having been told by patients that they had appointed an EG, or advising patients to do so (i.e. geriatricians and palliative care specialists) is not surprising as they would be most likely to have ongoing interactions with older and/or terminally ill patients. Thus, they would have more opportunity than most of the other specialties, except perhaps GP, to make such recommendations.

The responses to the scenarios indicated that the majority of respondents would respect the patient’s autonomy and follow their wishes in an ACD even if they did not agree with them. Of note, the oldest age group of respondents was least likely to follow the ACD. ACDs have only started to be used to any major degree in Australia in the last 10–15 years and would not have been part of older doctors’ standard training or practice. It is possible, therefore, that their knowledge may not be as up-to-date as that of younger doctors.

Limitations of the study

The overall response rate was 27%. Although it is not uncommon for surveys of medical practitioners (particularly GP) to achieve low response rates in relation to end-of-life issues, it nevertheless limits generalisability, and results of the study must be considered with caution. However, our sample was similar to the population of medical practitioners in NSW overall, although there were slightly more female GP than for NSW as a whole. There were also more anaesthetists than other specialists among respondents, which reflects their predominance among NSW specialists in the selected specialties.

Other limitations included the following: the study relied on participants reporting their own practice; the scenarios were hypothetical and not ‘real’ cases; and in hypothetical scenario 1, respondents were asked to imagine themselves in a situation where they disagreed with the ACD without a precise reason being given for their disagreement, and the responses were also not mutually exclusive. Therefore, the results should be taken as an indication of respondents’ attitudes rather than a precise indication of what they would have actually done.

Conclusion

Results indicate that medical practitioners need better understanding about which ACP options apply to which situation. Although further education may help to address this issue, encouraging proactive practitioner involvement in the ACP process and developing systems to support the facilitation and documentation of ACP discussions may help to minimise and increase the chance that patients’ wishes regarding end-of-life care will be respected.

Future research should explore strategies to improve practitioners’ knowledge of the law in this area.

References

Using periodic point-prevalence surveys to assess appropriateness of antimicrobial prescribing in Australian private hospitals

M. O. Cotta,1,2 M. S. Robertson,3 L. M. Upjohn,1 C. Marshall,1,2 D. Liew2 and K. L. Buising1

1Victorian Infectious Diseases Service, Melbourne Health, 2Department of Medicine, University of Melbourne, and 3Epworth HealthCare, Melbourne, Victoria, Australia

Key words
antimicrobial, point-prevalence, appropriateness, treatment, surgical prophylaxis.

Correspondence
Menino O. Cotta, Victorian Infectious Diseases Service, Melbourne Health, 300 Grattan Street, Parkville, Vic. 3050, Australia.
Email: menino.cotta@unimelb.edu.au

Received 14 October 2013; accepted 7 December 2013.
doi:10.1111/imj.12353

Abstract
Background and Aims: Appropriateness of antimicrobial use is a measure of key importance in evaluating safety and quality of prescribing but has been difficult to define and assess on a wide scale. Published work is limited and has generally focused on tertiary public hospitals, whereas the private sector provides a significant proportion of care in many countries. Information on prescribing in the private hospital context is needed to identify where intervention might be required. An antimicrobial prescribing survey tool was utilised to assess the appropriateness of antimicrobial prescribing among large private hospitals in Australia.

Methods: ‘Appropriateness’ of antimicrobial therapy was evaluated by a team consisting of an infectious diseases physician and specialist infectious diseases pharmacist based on clear criteria.

Results: Thirteen hospital-wide point-prevalence surveys were conducted. Three thousand, four hundred and seventy-two inpatient medication charts were reviewed to identify 1125 (32.4%) inpatients on 1444 antimicrobials. An indication was documented in 911 (63.1%) of surveyed prescriptions, and overall, 757 (52.4%) of antimicrobials were assessed as appropriate. Antimicrobials prescribed for treatment had a higher proportion of appropriateness when compared with antimicrobials prescribed for surgical prophylaxis (80.4% vs 40.6%). The main reason for a treatment prescription to be considered inappropriate was incorrect selection, while prolonged duration (>24 h) was the main reason for inappropriate surgical prophylaxis prescriptions.

Conclusions: This study provides important data on antimicrobial prescribing patterns in Australian private hospitals. Results can be used to target areas for improvement, with documentation of indication and surgical antibiotic prophylaxis requiring initial attention.

Introduction
Surveillance of antimicrobial use and ‘appropriateness’ of antimicrobial prescriptions have been identified as central to building effective antimicrobial stewardship (AMS) programmes in hospitals.1,2 Point-prevalence surveys capture information about antimicrobial use and have been used to assess the effects of AMS interventions at local, national and international levels.1,4 Appropriateness of a prescription is an important quality measure, yet it can be difficult to define for auditing.

An antimicrobial prescribing survey (APS) tool for Australian hospitals was developed by the Melbourne Health AMS Research Group in 2011. This tool was initially based on an international tool6 but required modifications to meet local needs, including clearer definitions and online training for auditors to improve usability. The new tool was tested across four Australian states in 35 public hospitals in 2011, with many of the participating hospitals using it to conduct hospital-wide point-prevalence surveys. The audit tool was specifically designed to allow auditors to judge the appropriateness of
the prescription in a consistent manner according to clear criteria.

In Australia, private hospitals provide approximately one third of all hospital beds and treat 40% of all inpatients, yet no data currently exist on patterns of antimicrobial use in this sector. These hospitals differ from public hospitals in that therapeutic decisions are usually made by visiting specialist clinicians who are not employed by the hospitals. Rather, they have a direct private arrangement with patients for managing their hospitalised care. This contrasts from the public hospital sector where there is management by teams involving employed junior medical staff.

The casemix in private hospitals can also differ significantly from the public sector in Australia. An example of this is that private hospitals, despite only representing one third of all hospital beds, provide more than three-quarters of all orthopaedic knee procedures. In terms of AMS resources, there is currently a dearth of information on what activities are currently taking place and what resources are available in the Australian private hospital sector. Although this could potentially be true for some hospitals in the public sector, state-wide public hospital initiatives such as initial funding for electronic-based antimicrobial approval systems in 2008, has most likely meant that this sector is advancing in the provision of AMS programmes.

It is unknown whether in private hospitals, there is more appropriate antibiotic use, possibly because of the seniority of the prescriber, or perhaps less appropriate prescribing, as private hospitals are perceived to have a very limited scope in influencing visiting specialists in their clinical practice.

The aim of this prospective, multicentre study was to utilise the newly developed APS tool to examine antimicrobial use and to assess the appropriateness of antimicrobial prescribing in Australian private hospitals.

**Methods**

**Study setting**

Three large private hospitals in Australia participated in a series of point-prevalence surveys. Hospital A has 450 beds, a 15-bed intensive care unit (ICU) and approximately 85 beds dedicated to rehabilitation services. Hospital B has approximately 220 beds, including an 18-bed critical care unit inclusive of an ICU and a 24-bed cardiac unit. Hospital C has approximately 200 beds, including an eight-bed ICU and 44 labour ward beds. Point-prevalence surveys were conducted every 3 months commencing February 2012 for Hospital A and May 2012 for Hospitals B and C.

A hospital-wide census was taken on the morning of each point-prevalence survey. Data collectors were assigned beds from a printed list and were asked to review all corresponding patient medication charts. Patients were included in the survey if they were an inpatient on the morning of the survey day. Patient areas excluded from the survey included labour ward beds, emergency department beds and any patients admitted to day-only stay wards such as Day Oncology and dialysis.

**Data collected**

Experienced clinical research coordinators were trained to collect data through provision of an information pack and a training session prior to administering the point-prevalence survey. Data were collected from all inpatients being prescribed at least one antimicrobial at the time of chart review. Data collectors had access to the admission and progress notes, surgical notes, medication charts, and pathology and microbiology results.

Antimicrobial therapy was deemed to be for surgical prophylaxis if documented as such in any of the medication chart, patient progress notes, preoperative assessment documents and postoperative surgical prescriptions. If no indication was documented, the antimicrobial was deemed to be for surgical prophylaxis if prescribed intraoperatively or during the immediate postoperative period, and if there was no other indication clearly documented and no relevant microbiology results available. Antimicrobial therapy was deemed for treatment of infection (‘treatment prescriptions’) or non-surgical prophylaxis if documented as such in patient progress notes or on the medication chart. Antimicrobials were categorised as ‘non-assessable’ if no clear indication was documented in the notes and the antimicrobial was not likely to be for surgical prophylaxis.

‘Appropriateness’ of antimicrobial therapy was assessed by an infectious diseases (ID) clinician and a specialist ID pharmacist, who reviewed clinical information against the national Therapeutic Guidelines: Antibiotic. Antimicrobial selection, dose, frequency, duration (for prophylaxis prescriptions only), hypersensitivity contraindication and microbiology investigation results (including antibiotic susceptibilities of any identified pathogens) were considered by the assessors. An ‘allergy mismatch’ was noted if the antimicrobial was contraindicated based on documented hypersensitivity information, while ‘microbiology mismatch’ was documented if the antimicrobial prescribed did not match pathogen susceptibility data. Duration of treatment was not considered for treatment prescriptions as this is often dependent on clinical variables that were not assessable. If there was a lack of
information about the infection purportedly being treated, the treatment order was judged to be ‘non-assessable’.

Surgical antibiotic prophylaxis (SAP) was judged to be inappropriate for the following reasons: if antimicrobial selection, dosage or frequency were not concordant with the Therapeutic Guidelines: Antibiotic,10 if an ‘allergy mismatch’ were present, or if prophylaxis duration was greater than 24 h. Antimicrobials could be judged inappropriate for more than one identified reason. If consensus on appropriateness could not be reached by the assessment team, the decision was referred to an independent senior ID clinician. Where applicable, data were also collected regarding site of infection and type of surgery.

Statistical analysis

As each hospital-wide point-prevalence survey represented a census of all inpatients on the day of the survey, all results were without sampling error. Data are reported descriptively.

Results

Thirteen hospital-wide point-prevalence surveys were conducted during the study period from February 2012 to February 2013. Hospital A participated in five surveys, while four surveys were conducted at each of Hospitals B and C. A total of 3472 inpatient medication charts was reviewed with 1125 patients (32.4%) on 1444 antimicrobials during the study period. Summary data of all surveyed prescriptions at each hospital is shown in Table 1. Sixty-nine per cent of all patients on antimicrobial therapy in Hospital A were admitted under a surgical casemix, while 48% and 37% of all patients on antimicrobial therapy were surgical cases in Hospitals B and C respectively. Appropriateness of prescriptions for treatment and SAP are shown in Table 2. Less than half of SAP prescriptions were documented as such. Of all prescriptions reviewed, 47.3% were for treatment, with the respiratory tract and skin and soft tissue being the most common sites of infection (Table 3). SAP accounted for 32.6% of prescriptions and more than half of these were for orthopaedic surgical cases (Table 4). Figures 1 and 2 show the percentage of inappropriate prescriptions for treatment and SAP, respectively, for each hospital during

Table 1 Summary data of surveyed prescriptions at each hospital: documentation of indication and appropriateness assessment

<table>
<thead>
<tr>
<th>Patient charts reviewed</th>
<th>Hospital A (n = 2206)</th>
<th>Hospital B (n = 622)</th>
<th>Hospital C (n = 644)</th>
<th>Total (n = 3 472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on antimicrobial therapy</td>
<td>716 (32.5)</td>
<td>228 (36.7)</td>
<td>181 (28.1)</td>
<td>1125 (32.4)</td>
</tr>
<tr>
<td>Antimicrobial prescriptions reviewed</td>
<td>(n = 911)</td>
<td>(n = 299)</td>
<td>(n = 234)</td>
<td>(n = 1 444)</td>
</tr>
<tr>
<td>Antimicrobial prescriptions where indication documented</td>
<td>526 (57.7)</td>
<td>216 (72.2)</td>
<td>169 (72.2)</td>
<td>911 (63.1)</td>
</tr>
<tr>
<td>Antimicrobial prescriptions assessed as appropriate</td>
<td>449 (49.3)</td>
<td>175 (58.5)</td>
<td>133 (56.8)</td>
<td>757 (52.4)</td>
</tr>
<tr>
<td>Antimicrobial prescriptions assessed as inappropriate</td>
<td>276 (30.3)</td>
<td>70 (23.4)</td>
<td>43 (18.4)</td>
<td>389 (27.0)</td>
</tr>
<tr>
<td>Antimicrobial prescriptions that were non-assessable</td>
<td>186 (20.4)</td>
<td>54 (18.1)</td>
<td>58 (24.8)</td>
<td>298 (20.6)</td>
</tr>
</tbody>
</table>

In Tables 1 and 4, ‘Range’ refers to the results obtained across point-prevalence surveys undertaken at each hospital.

Table 2 Appropriateness of treatment and surgical antibiotic prophylaxis (SAP) prescriptions

<table>
<thead>
<tr>
<th>Treatment prescriptions</th>
<th>Total (n = 683)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Range (%)</td>
</tr>
<tr>
<td>Treatment prescriptions assessed as appropriate</td>
<td>549 (80.4)</td>
</tr>
<tr>
<td>Treatment prescriptions assessed as inappropriate</td>
<td>99 (14.5)</td>
</tr>
<tr>
<td>Treatment prescriptions that could not be assessed</td>
<td>35 (5.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAP prescriptions</th>
<th>Total (n = 471)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Range (%)</td>
</tr>
<tr>
<td>SAP prescriptions assessed as appropriate</td>
<td>191 (40.6)</td>
</tr>
<tr>
<td>SAP prescriptions where indication was documented</td>
<td>204 (43.3)</td>
</tr>
</tbody>
</table>
The study period. The most common reasons for inappropriateness was ‘incorrect drug/drug combination’ for treatment prescriptions and ‘prolonged duration (>24 h)’ for SAP (Fig. 3).

**Discussion**

These data suggest that the burden of antimicrobial use in large Australian private hospitals is comparable with that described in tertiary public hospitals in the existing published literature, with around one-third (32.4%) of inpatients receiving antimicrobials on any given day across the 13 hospital-wide point-prevalence surveys. International hospital point-prevalence surveys have previously shown the proportion of patients on antimicrobials to range from 16% to 32%,\(^5,6,11–13\) while one previous hospital-wide survey in an Australian public hospital recorded 43% of inpatients being on antibiotics.\(^14\)

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Sites of infection and appropriateness of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 684) (%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>214 (31.3)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>122 (17.6)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>83 (12.1)</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>70 (10.2)</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>62 (9.1)</td>
</tr>
<tr>
<td>Not specified (including febrile neutropenia)</td>
<td>41 (6.0)</td>
</tr>
<tr>
<td>Bacteraemia/fungemia</td>
<td>33 (4.8)</td>
</tr>
<tr>
<td>Gastrointestinal (e.g. salmonellosis, <em>Clostridium difficile</em> infection)</td>
<td>23 (3.4)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>13 (1.9)</td>
</tr>
<tr>
<td>Otorhinolaryngology</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>9 (1.3)</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

The total number of sites of infection (n = 684) is greater than the number of ‘treatment prescriptions’ (n = 683) because some antimicrobials were prescribed for more than one site of infection.

The total number of sites of infection (n = 684) is greater than the number of ‘treatment prescriptions’ (n = 683) because some antimicrobials were prescribed for more than one site of infection.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Types of surgery and appropriateness of prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 471) (%)</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>244 (51.8)</td>
</tr>
<tr>
<td>Cardiothoracic</td>
<td>76 (16.1)</td>
</tr>
<tr>
<td>General surgery</td>
<td>39 (8.3)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>35 (7.4)</td>
</tr>
<tr>
<td>Plastics</td>
<td>22 (4.7)</td>
</tr>
<tr>
<td>Vascular</td>
<td>21 (4.5)</td>
</tr>
<tr>
<td>Urology</td>
<td>18 (3.8)</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>9 (1.9)</td>
</tr>
<tr>
<td>Otorhinolaryngology</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Maxillofacial</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

General surgery includes upper gastrointestinal and colorectal surgery.

© 2013 The Authors
Internal Medicine Journal © 2013 Royal Australasian College of Physicians
This study identified key areas for improvement in antimicrobial prescribing practice in the private hospital setting. One important potential quality indicator for antimicrobial prescribing assessed by this study was whether an indication for antimicrobial therapy was documented in patient notes. Hospitals B and C had a higher documentation rate (72% each) than that reported in a previous international study (64%), whereas hospital A had a lower rate (58%). For SAP, documentation was particularly poor with only prescriptions for gynaecological surgery having a documentation rate of greater than 50%. The proportion of antimicrobial prescriptions where appropriateness was ‘non-assessable’ because of poor documentation ranged from 12.8% to 38%. Without adequate documentation, communication between staff members is impeded, and opportunities to evaluate and review medication use are limited. Strategies to encourage or enforce (in the case of mandatory fields in electronic prescribing) such documentation should be further explored.

Of those prescriptions that were assessable, approximately 80% of prescriptions for treatment of infection were judged to be appropriate. Of the 99 treatment prescriptions judged as inappropriate, incorrect antimicrobial selection was the main problem. This suggests that better access to prescribing guidelines and education initiatives may be required to help improve empirical prescribing decisions. In addition, more timely access and response to microbiology results and perhaps better liaison with clinical microbiologists may also be necessary to improve the adequacy of directed antimicrobial therapy.

SAP accounted for a third (32.6%) of all antimicrobial prescriptions surveyed during the study period. In comparison with treatment prescriptions, the appropriateness of prescriptions for SAP was low. In fact, only SAP for orthopaedic and neurosurgical procedures had appropriateness greater than 50%. The main reason for SAP to be judged as inappropriate was prolonged durations of therapy (greater than 24 h). The recommendations for SAP in the national guidelines, Therapeutic Guidelines: Antibiotic, are for one to two perioperative doses of antibiotics, with no recommendation for antibiotic therapy to continue beyond 24 h after surgery for most operations. However, findings in this study suggest that SAP is routinely being continued beyond 24 h, with no justification documented. A previous study conducted in Australia looking specifically at SAP in public hospitals found a much higher rate of compliance with the national guidelines. However, assessment of appropriateness in that study was made on the basis of antibiotic choice and the timing of the first dose in relation to the time of surgery. Duration of prophylaxis, as an appropriateness criterion, was excluded for the simple reason of poor documentation.

The second most common reason for inappropriate SAP was incorrect antibiotic selection. It was interesting to note that a high proportion of these incorrect selections was due to the use of oral antibiotics, which were used in a high proportion of patients undergoing plastics and urological procedures. Oral antibiotics also significantly contributed to prolonged SAP as all of these were prescribed for greater than 24 h, sometimes up to a week postoperatively. This finding suggests that the use of local SAP guidelines may be an important starting point for private hospitals to consider.

Overall, the rate of inappropriate prescribing over time seemed to remain consistent; however, there was an
observed decrease in the percentage of inappropriate treatment prescriptions over time for hospital B, while an opposite pattern was observed for hospital C. A trend analysis of these data was not performed as there are only a limited number of data points for each hospital and no interventions performed during the study period. However, it will be interesting to see if these observations continue in any future point-prevalence surveys, particularly after introduction of an AMS programme at each of the hospitals.

The results of the present study provide the most detailed picture of contemporary antimicrobial prescribing in Australian private hospitals. Furthermore, accuracy of the data in representing day-to-day prescribing of antimicrobials has been enhanced by the fact that point-prevalence surveys were carried out quarterly over a 12-month period. Use of an assessment team consisting of an ID clinician and a specialist ID pharmacist supports the concept of antimicrobial management teams that contribute to improved quality and safety of antimicrobial prescribing. The regular surveillance of antimicrobial use and appropriateness is important for private facilities seeking to implement AMS programmes and interventions in the future.

Limitations to this study include that the information collected was dependent on the training and knowledge of individual data collectors. Although each of these data collectors was provided with an information pack and detailed in-service, variability between data collectors could not completely be eliminated. In addition, assessment of appropriateness was based on data collected at that particular point in time and information that potentially affected antimicrobial use that was not documented could not be taken into account. Also, appropriateness of antimicrobial selection was based on the assumption that the clinician diagnosis was accurate. The duration of therapy was not assessed for prescriptions other than SAP, which might further affect the assessment of appropriateness. It was important to note that analysis of inappropriate selection was not differentiated based on the spectrum of activity (i.e. either excessively broad or narrow for the intended indication). Future studies should aim to use a more detailed framework in defining appropriateness so as to identify reasons for non-concordant selection of antimicrobials. Finally, although this study gave an in-depth view of antimicrobial prescribing in the three hospitals surveyed, these hospitals represent only a small proportion of all private hospitals in Australia. There is future scope to conduct multiple point-prevalence surveys in a larger group of Australian private hospitals.

Conclusion

The present study indicates that there may be significant issues with antimicrobial prescribing in the Australian private hospital sector, with lack of documentation of indication being one such issue highlighted. Antimicrobials prescribed for treatment were generally appropriate; however, inappropriate therapy was observed to occur frequently in SAP, and this should be a major target for any future AMS initiatives.

Acknowledgements

The authors acknowledge Gerlinda Amor (Epworth Research Institute), Louise Lyons (Epworth Research Institute), Vasantha Pather (Epworth Research Institute), Cath Savage (Epworth Research Institute) and Hilary Young (Epworth Research Institute) for assisting with data collection.

References

Deteriorating patients managed with end-of-life care following Medical Emergency Team calls

J. Orosz,1 M. Bailey,2 M. Bohensky,3 M. Gold,4 S. Zalstein5,6 and D. Pilcher1,2

1Intensive Care Unit, Alfred Hospital; 2Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University; 3Melbourne EpiCentre, Department of Medicine, Royal Melbourne Hospital; 4Palliative Care Medicine, Alfred Hospital, Melbourne, Victoria; 5Department of Anaesthesia and Perioperative Medicine, Royal Hobart Hospital, and 6School of Medicine, University of Tasmania, Hobart, Tasmania, Australia.

Key words
intensive care, ethics, end-of-life issues.

Correspondence
Judit Orosz, Intensive Care Unit, Alfred Hospital, Commercial Road, Melbourne, Vic. 3004, Australia.
Email: oroszjudit3@gmail.com

Received 21 May 2013; accepted 9 December 2013.

doi:10.1111/imj.12350

Abstract

Aim: To describe the characteristics of patients whose end-of-life care was initiated in response to a Medical Emergency Team (MET) call and to develop a predictive score to aid prospective identification of these patients.

Methods: Retrospective cohort study of all MET calls in a tertiary teaching hospital between April 2010 and March 2011. All inpatients attended by the hospital MET. The main outcome measures were patient demographics, admission features and comorbidities in active and palliative patients, timing, frequency, physiology, and interventions in active and palliative MET calls.

Results: One thousand, five hundred and sixty-seven MET calls were called for 1073 patients. Sixty (5.6%) patients had at least one MET call resulting in initiation of end-of-life care. Palliative MET call patients compared with active patients were older (76.4 vs 65.9 years; P < 0.0001), had a shorter hospital stay (7.5 vs 12 days; P = 0.0002), had increased in-hospital mortality (73.3% vs 13.5%; P < 0.001), had higher Charlson comorbidity scores (3.1 vs 2.1; P = 0.0002) and were more likely to receive multiple MET calls (1.95/patient vs 1.43/patient; P = 0.011). Patient physiological parameters were worse at palliative MET calls. Prior history of malignancy, hemiplegia and peripheral vascular disease, and increasing age were independently associated with initiation of end-of-life care and were used to derive a 13-point predictive score. Patients with a score of 7 or more had a 20% chance of having a palliative MET call.

Conclusion: Prospective identification of patients requiring palliative care may be possible prior to MET involvement. This may allow more timely and appropriate end-of-life discussions.
Introduction

Death in hospital is often preceded by clinical deterioration that can be recognised by abnormalities of commonly measured physiological parameters. Medical Emergency Teams (MET) – otherwise known as rapid response teams – provide timely response to these abnormal physiological markers in order to intervene before the patient deteriorates to an unsalvageable condition. MET intervention includes a rapid assessment, stabilisation and prioritisation for further care by a critical care capable team. However, not all such deteriorating patients are admitted to the intensive care unit (ICU). Excluding patients who arrest and die at the MET call, the largest proportion of patients do not require ICU admission and remain on the ward without any limitations placed on treatments.

A second group is recognised as not appropriate for critical care interventions, and their treatments are limited from this point. What ensues is either ward-based care with curative and supportive intent, but withholding critical care interventions, or initiation of end-of-life care, including withdrawal of active treatments. Inappropriate resuscitation of terminally ill patients causes loss of patient dignity and may cause distress to the patient, their relatives and clinical staff. In addition, end-of-life episodes associated with ICU interventions have been found to cost nearly three times more than terminal episodes without ICU care. The MET system provides an opportunity to identify a subgroup of patients where initiation of end-of-life care might be preferable to escalation to more invasive and possibly futile therapies.

The aim of this study was to determine the prevalence and characteristics of end-of-life care at MET calls, to determine pre-existing patient factors that were associated with subsequent palliative MET calls and to develop a scoring system that might assist in prospective identification of these patients.

The authors hypothesised that there might be features of patients commencing end-of-life care at a MET call that were recognisably different to those managed without limitation and that might be identifiable before the MET is activated. This would potentially allow more timely end-of-life care to be initiated by appropriate clinicians. The authors also sought to examine whether MET calls that resulted in initiation of end-of-life care were different in terms of patient physiology at the time of MET call (including the trigger for the call), timing and frequency of MET calls and interventions during the MET calls.

Methods

The hospital ethics committee approved the project as a low-risk study; the need for informed consent was waived (project No. 515/11).

Setting

The Alfred Hospital is a tertiary referral teaching hospital in Melbourne, Victoria, Australia with about 30 000 admissions per annum, with specialist services including trauma, comprehensive cancer services, blood diseases, bone marrow transplant and neurosurgery; statewide services include heart and lung transplantation, mechanical cardiac support, cystic fibrosis, burns, human immunodeficiency virus/acquired immunodefiency syndrome, haemophilia, sexual health, and hyperbaric medicine. It is also the national centre for paediatric lung transplantation.

The Alfred Hospital MET service began in 2001. It is led by a senior intensive care registrar and includes a senior intensive care nurse, a medical registrar and an intern. Members of the primary treating team also attend the calls during in-hours or informed of all MET calls after hours. Major decisions (e.g. admission to ICU, treatment limitations or initiation of end-of-life treatment) are always discussed with the primary treating consultant or the consultant on call. The MET is available 24 h a day. Activation occurs through previously validated and published criteria (threatened airway, respiratory rate >35 or <6, oxygen saturation<90% on oxygen, systolic blood pressure <90 mmHg or >200 mmHg, a heart rate >140 or <40 per minute, repeat or prolonged seizure or decreased Glasgow Coma Scale (GCS) >2 points, serious concern/pain). The calling criteria are recognised throughout the hospital. A dedicated electronic MET database was introduced in March 2010. Data were entered retrospectively after each MET call by nursing members of the MET and by trained dedicated data collectors employed by the ICU. Ten per cent of the MET database records from the study period were double-checked by the study authors.

The study included all hospital in-patients who had a MET call between April 2010 and March 2011. The information from the patients at these MET calls was then matched electronically to their demographic and diagnostic coding data recorded on the hospital administrative database. Hospital administrative data are collected by trained data coders who review the notes of all hospital patients once discharged from hospital. The administrative data are entered prospectively, audited regularly and submitted to the local Victorian Department of Health on a monthly basis.

The study looked at the involvement of the palliative care team in patient care during the hospital stay.
Palliative care service is available 24 h a day consulting all hospital wards and consists of a palliative care consultant, a registrar and a nurse.

**Definitions and variables collected**

A ‘Palliative MET call’ was defined if the MET team initiated withdrawal of active management or commencement of end-of-life care. The MET call was ‘active’ if the treatment plan and patient outcome was anything other than palliation (ICU admission, active ward-based management with or without limitations, transfer to operating theatre or monitored ward, successful or unsuccessful resuscitation.) It was a team decision whether a MET call was palliative or active, with the involvement of senior clinicians, patient and family members whenever possible. Any patient who had a ‘Palliative MET call’ (irrespective of whether this was the first or a subsequent MET call) was analysed in the palliative patient group.

The following data were collected in a de-identified manner: basic patient demographics (age, gender), admission features (admitting unit specialty, length of hospital stay), MET features (time of day, number of MET calls and procedures performed by the MET), hospital outcome (survival to discharge, discharge destination, death and time from MET to death) and involvement of the palliative care team. The Charlson score and component comorbidities were derived from procedural and diagnostic coding listed in the hospital admission database using the International Classification of Diseases, 10th revision, Australian Modification.³ The Charlson comorbidity score, although initially developed in 1987 to predict mortality at 1 year among patients being considered for breast cancer clinical trials⁴ has been applied to risk adjust mortality outcomes more broadly in other hospital populations.⁵ It was thus considered an appropriate tool to classify patients’ pre-existing levels of comorbidity. Physiological variables on arrival of the MET were extracted (systolic and diastolic blood pressure, heart rate, respiratory rate, GCS, oxygen saturation, inspired oxygen flow rate, respiratory rate).

**Statistics**

Data were analysed using STATA Version 12.0 (StataCorp, College Station, TX, USA). Univariate comparisons were made using Chi-squared tests for proportion, Student’s t-tests for normally distributed data and Wilcoxon rank-sum tests otherwise. Parametric data were presented as means with standard deviations, non-parametric data as medians with interquartile ranges and categorical variables as number (%). Two-sided P values less than 0.05 were considered significant. Multivariate logistic regression analysis was undertaken at a patient level to identify pre-existing factors independently associated with having a palliative MET call. The multivariate model was constructed using both stepwise selection and backwards elimination techniques before undergoing a final assessment for clinical and biological plausibility. A predictive score for identifying patients ‘at risk of a palliative MET call’ was derived using weightings relative to the statistical significance of variables in the final multivariate model. While age was initially considered as a continuous variable, it was found to be equally as informative when dichotomising into above and below 70 (the median value).

**Results**

During the 12-month period from April 2010 to March 2011, the MET was activated 1969 times to 1370 patients. There were 30 660 hospital admission episodes longer than 1 day during the study period, excluding psychiatry admissions. The overall MET call rate was 64.2/1000 hospital admissions. We were able to match data of the MET database with the hospital admission database in 1073 patients. Of the 297 unmatched patients, 22 were day case patients with length of stay less than 24 h, 23 were psychiatry in-patients, and 21 were patients whose initial MET call was either in outpatients, on the doorstep of the hospital or in buildings attached to the hospital. The remaining 231 could not be matched due to missing or inaccurate medical record numbers or missing admission and discharge data required to match a patient to the correct hospital episode (Fig. 1).

**Patient characteristics**

Table 1 describes the characteristics of the 1073 patients who had one or more MET calls. Sixty patients (5.6%) had at least one MET call resulting in initiation of end-of-life care. Patients receiving a palliative MET call (palliative group) were older, had shorter hospital stays, had higher mortality, had higher Charlson comorbidity scores with malignancy and peripheral vascular disease occurring significantly more frequently, were more likely to be under a medical rather than surgical parent unit, and were more likely to be reviewed by the Palliative Care Team during their hospital admission. Patients in the palliative group received more MET calls per patient. In the palliative group, 25 patients (41.7%) were referred to and seen by the palliative care team following initiation of end-of-life-care. In-hospital mortality in the palliative group was 73.3% (44/60 patients), 25 patients (25/44–56.8% of the deceased) died within 24 h of the palliative
MET call. Of the 16 patients in the palliative group who were discharged from hospital alive, eight had been reviewed by the Palliative Care Team.

**MET call characteristics**

During the study period, 1567 MET calls were called on 1073 patients. There were 64 MET calls where palliative care was instituted (in 60 patients). In 37 instances, this was the patient’s first MET call. Table 2 shows the comparison of active and palliative MET call characteristics. Physiological parameters were generally worse at palliative MET calls (lower systolic blood pressure, higher respiratory rate, lower oxygen saturations, higher inspired oxygen levels, lower Glasgow Coma Scores). Neurological failure and respiratory failure was the trigger of palliative MET calls more often than in the active MET calls. Palliative MET calls were also more likely to result in no interventions during the call.

**The Potential Palliative Patient score: predictors of a palliative MET call**

Multivariate logistic regression analysis demonstrated that age, malignancy, hemiplegia and peripheral vascular disease were all independently associated with initiation of end-of-life care after a MET review (Table 3). A 13-point score was developed: ‘The Potential Palliative Patient (PPP)’ Score (Table 4). Patients with a score of 7 or more had a one in five chance of having a palliative MET call during their hospital stay (Table 5).

**Discussion**

We conducted a retrospective cohort study of MET calls in a teaching hospital in Melbourne over a 12-month period. We have found that those patients commencing end-of-life care after a MET call are more likely to be of advanced age, have a shorter hospital stay, and have malignant disease, hemiplegia or peripheral vascular.
Patients who have palliative MET calls often have multiple other MET calls and physiological parameters are more severely deranged at palliative MET calls than at active MET calls. These key characteristics may have a role in recognising patients for whom end-of-life care discussions are appropriate prior to MET calls in order that these discussions can occur at a time of relative clinical stability rather than during an acute clinical deterioration. This will allow involvement of the patient in these discussions and also medical staff who may have had the opportunity to establish rapport with the patient. It might also allow

Table 1 Baseline characteristics of patients managed with end-of-life care after MET call (palliative patients) compared to active MET call patients

<table>
<thead>
<tr>
<th></th>
<th>Active patients (n = 1013)</th>
<th>Palliative patients (n = 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of MET calls</td>
<td>1450</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>Number of MET calls per patient</td>
<td>1.43</td>
<td>1.95</td>
<td>0.011</td>
</tr>
<tr>
<td>Seen by Palliative Care Team during admission</td>
<td>65 (6.4)</td>
<td>25 (41.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)†</td>
<td>65.9 (18.5)</td>
<td>76.4 (13.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender, number (%)</td>
<td>445 (43.9)</td>
<td>26 (43.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>Treating unit, number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>711 (70.2)</td>
<td>52 (86.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgical</td>
<td>302 (29.8)</td>
<td>8 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Total length of stay in hospital (days)‡</td>
<td>12 (6–22)</td>
<td>7.5 (3.5–17.5)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Length of stay in hospital before first MET call (days)‡</td>
<td>6.3 (1–7.2)</td>
<td>6.3 (1–7–7.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Average Charlson score (number)†</td>
<td>2.1 (2.3)</td>
<td>3.1 (2.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Comorbidities based on Charlson, number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant tumour, metastasis</td>
<td>61 (6.0)</td>
<td>13 (21.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumour, leukaemia, lymphoma</td>
<td>157 (15.5)</td>
<td>17 (28.3)</td>
<td>0.009</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>27 (2.7)</td>
<td>5 (8.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>240 (23.7)</td>
<td>17 (28.3)</td>
<td>0.66</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>9 (0.9)</td>
<td>0 (0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>95 (9.4)</td>
<td>8 (13.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes, complicated</td>
<td>59 (5.8)</td>
<td>4 (6.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>Diabetes, uncomplicated</td>
<td>45 (4.4)</td>
<td>1 (1.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>24 (2.4)</td>
<td>1 (1.7)</td>
<td>0.73</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>37 (3.7)</td>
<td>0 (0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>152 (15)</td>
<td>10 (16.7)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>60 (5.9)</td>
<td>7 (11.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>13 (1.3)</td>
<td>1 (1.7)</td>
<td>0.80</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>153 (15.1)</td>
<td>11 (18.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Moderate/severe kidney disease</td>
<td>179 (17.7)</td>
<td>13 (21.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Moderate/severe liver disease</td>
<td>35 (3.5)</td>
<td>0 (0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Dementia</td>
<td>45 (4.4)</td>
<td>4 (6.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Admission source of patients, number (%)</td>
<td>1013 (100)</td>
<td>60 (100)</td>
<td>0.06</td>
</tr>
<tr>
<td>Aged care residential facility</td>
<td>20 (2.0)</td>
<td>2 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Dialysis admission</td>
<td>4 (0.4)</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Elective admission</td>
<td>207 (20.4)</td>
<td>6 (10)</td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>656 (64.8)</td>
<td>49 (81.7)</td>
<td></td>
</tr>
<tr>
<td>Transfer from other hospital</td>
<td>115 (11.4)</td>
<td>2 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Other§</td>
<td>11 (1.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hospital outcome of patients, number (%)</td>
<td>1013 (100)</td>
<td>60 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>137 (13.5)</td>
<td>44 (73.3)</td>
<td></td>
</tr>
<tr>
<td>Discharge to other hospital</td>
<td>281 (27.7)</td>
<td>8 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Discharge home</td>
<td>500 (49.4)</td>
<td>7 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Transitional care</td>
<td>14 (1.4)</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Discharge to private hospital</td>
<td>47 (4.6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Aged care</td>
<td>13 (1.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other¶</td>
<td>21 (2.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

†Mean (standard deviation). ‡Median (interquartile range). §Includes statistical admissions (administrative process when the hospital records a new episode of care with a new care type within one hospital stay). ¶Includes statistical discharges, absconded, discharged at own risk. AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; MET, Medical Emergency Team.
The initial goal of the introduction of MET was to improve hospital outcomes with timely restorative care for deteriorating patients in order to reduce the frequency of cardiac arrests and improve the utilisation of critical care beds. The only multicentre, cluster-randomised, controlled trial of MET (MERIT) to date did not show a significant decrease in the incidence of Table 4 The ‘PPP’ score (value range 0–13)

<table>
<thead>
<tr>
<th>Score value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant tumour, metastasis</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Hemiplegia</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

Area under receiver operator characteristic = 0.730. Hosmer–Lemeshow C statistic = 0.66, P value = 0.72. PPP, Potential Palliative Patient.
cardiac arrest, unplanned ICU admissions or unexpected deaths. The MERIT and other studies have highlighted the role played by the MET system in issuing of treatment limitation orders, recognition of the imminently dying and initiation of end-of-life care, consistent with our study. Deployment of the MET team may be associated with improved end-of-life management and psychosocial care. It is estimated in our hospital that about 25% of dying patients are seen by the Palliative Care Team, while in our study, a MET call where end-of-life care was instituted, resulted in the involvement of palliative care services in 40% of cases. This may suggest that a MET call increases the likelihood of involvement of palliative care services, which would in turn be expected to result in improved end-of-life care. Despite this, over half of the patients who had palliative MET calls were not seen by specialists in end-of-life care.

Patients received end-of-life care after a MET call were more likely to receive multiple MET calls and had more significant abnormalities of physiological variables in multiple domains, particularly worse respiratory status, GCS and systolic blood pressure. It is possible that the MET was activated too late to be able to salvage the patient and that it was the degree of physiological derangement alone that led to the decision to palliate a patient who might have otherwise had active therapy if detected earlier. It may reflect that these dying patients are in a more advanced and rapid deterioration, therefore meeting MET call criteria more often. It is possible that medical and nursing staff do not recognise that a patient is dying or may be hesitant to make decisions regarding end of life in the absence of senior medical staff involved in the patient’s care. Alternatively, medical and nursing staff may already be aware that palliation is the patient’s best interest, but they wait until severe physiological derangement occurs to act on it formally. Whether future early and more senior involvement at MET calls will initiate timely quality end-of-life care cannot be determined from this study.

Palliative patients had a shorter hospital stay, and over half of these patients died within 24 h of initiation of end-of-life care. This is probably a reflection of the more rapid decline of dying patients after admission to hospital and the consequence of treatment limitations after the MET call. It may also reflect more severe baseline illness and comorbidity levels where there can be multiple episodes of acute deterioration from which the patient makes a partial recovery and working out, which is the final straw, can be more challenging. The association of end-of-life care initiation after MET calls with malignant tumour or metastatic cancer is not surprising, given that these conditions are progressive and often incurable. The independent association between advanced age, hemiplegia, peripheral vascular disease and initiation of end-of-life care at a MET call allowed the creation of a predictive score that enables identification of patients at risk of subsequently having a palliative MET call and in whom quality of care might be improved by early identification of the need for palliative intervention.

Generalisability of our study is limited by its retrospective single-centre design with relatively small numbers of patients managed with end-of-life care compared with other published studies. With only 60 patients having a palliative MET score, there were insufficient data to enable a holdout sample to be generated ensuring that the PPP score will need to be validated in an external population. As a consequence, its applicability to more modern MET call systems remains unknown. The authors are not aware of any similar predictive tools, but we would encourage future research to investigate its use in other institutions and its potential applicability to other patient groups who might benefit from earlier institution of palliative care. The impact of incomplete matching of patients between MET call and administrative databases on our findings is unknown. Although the possibility of bias in extracting subjective data exists, data were collected and entered into the MET call and hospital administrative databases by trained dedicated data collectors. In addition, an audit of 10% of randomly selected medical records confirmed consistency of recorded variables. Our hospital policy does not allow teams to flag patients as ‘Not for MET calls’ unless they have been formally commenced on end-of-life care. Even then, this practice is discouraged because MET calls for ‘symptom control’ or for ‘any cause for concern by staff’ are still considered appropriate in patients undergoing end-of-life care. Thus, although ‘missed’ MET calls may have biased our results, we consider their number is likely to be low. This is supported by the high number of MET calls (64.2/1000 hospital admissions) at our hospital compared with others.

**Conclusion**

Our study provides an insight into end-of-life care triggered by MET calls. As patients approach the end of life,
their disease process will create life-threatening situations, yet invasive interventions are less likely to provide benefit. Knowing when it is time to change from life-prolonging treatment to palliative care, focused on quality of life and comfort, is emotionally and clinically challenging for patients, families, nursing and medical staff in these unexpected situations. MET team members in our hospital routinely consult families in these situations and try to take the patients’ wishes into account when known, but with little prior knowledge of the patient, it is often very difficult to provide optimal care in every aspect of end-of-life care. It was not the original aim of MET teams to trigger consideration of initiating end-of-life care or to provide end-of-life care for patients, but it is increasingly being recognised as part of the MET call team duties. Education of members of the MET is necessary to improve their ability to recognise dying patients, provide adequate, patient-centred end-of-life care, and to facilitate effective communication with patients, their families and other healthcare providers. Whether using the resources and skills of MET teams is the optimal and cost-effective approach to improve end-of-life care is uncertain. However, it is possible to pinpoint pre-existing factors that may allow prospective scoring of patients and identification of those at risk prior to needing MET involvement, thereby allowing end-of-life discussions in a more timely and appropriate way. We encourage further work to validate the PPP score as a predictive tool for early identification of patients who might benefit from palliative care intervention.

References

Early hyperglycaemia and the early-term death in patients with spontaneous intracerebral haemorrhage: a meta-analysis

X. Tan,1 J. He,2 L. Li, G. Yang,3 H. Liu,4 S. Tang1 and Y. Wang1

1Department of Endocrinology, 9th People’s Hospital of Chongqing, 2The Key Laboratory of Laboratory Medical Diagnostics in the Ministry of Education and Department of Clinical Biochemistry, College of Laboratory Medicine, Chongqing Medical University, 3Department of Endocrinology, the Second Affiliated Hospital, Chongqing Medical University, Chongqing, China, and 4Department of Pediatrics, University of Mississippi Medical Center, Jackson, Mississippi, USA

Abstract

Background and Aims: Stroke is often accompanied by hyperglycaemia, and this has an important impact on prognosis. The aim of this study was to investigate the relationship between early hyperglycaemia and the outcome of spontaneous intracerebral haemorrhage (sICH).

Methods: A systematic literature search on PubMed, Embase, Cochran, WANFANG DATA, VIP and CNKI databases was conducted, and eight eligible studies were retrieved. Relative risks and 95% confidence interval (CI) in the hyperglycaemia group compared with the non-hyperglycaemia group were calculated and meta-analysed when possible.

Results: Eight controlled trials and cohort studies totalling 3756 patients addressing early hyperglycaemia and the outcome of sICH were compiled for this meta-analysis. Cut-off points for defining hyperglycaemia was 6.1–8.3 mmol/L, and the median cut-off value was 7.5 mmol/L. Studies were assigned to one of the two subgroups: the group A (for studies with the values of glucose concentrations above the median cut-off) and the group B (for studies with the values of glucose concentrations below the median cut-off). The RR for short-term death associated with hyperglycaemia was 3.65 (95% CI (3.08, 4.33); \( P < 0.0001 \)). In the subgroup analysis, the relative risk values were 3.46 (95% CI (1.66, 7.20); \( P = 0.0009 \)) and 3.53 (95% CI (2.92, 4.26); \( P < 0.00001 \)) for the groups A and B respectively. The publication bias showed that Egger’s test (\( P > 0.1 \)), Begg’s test (\( P > 0.05 \)) and Ns0.05 exceeded included studies.

Conclusions: Early hyperglycaemia can significantly increase the rate of early-term death in patients with sICH, independent of the cut-off points for hyperglycaemia.

Introduction

Spontaneous intracerebral haemorrhage (sICH) is a bleeding that arises in the brain parenchyma in the absence of trauma or surgery. This type of haemorrhage accounts for 10–15% of all strokes and is associated with a higher mortality rate than either ischaemic stroke or subarachnoid haemorrhage.1,2 Clinical outcome depends on the severity of the initial haemorrhage, but complications such as recurrent bleeding, secondary ischaemia, hydrocephalus and general medical complications also play an important role in clinical outcome.3–6 Analysis of risk factors for primary and secondary damage, especially if these can be modified, is important because it has the potential to improve treatment.
Hyperglycaemia is a frequent finding in critically ill patients admitted to the intensive care unit. In recent years, it has been found that early stroke is often accompanied by hyperglycaemia, and this has an important impact on prognosis. Capes et al.'s reports have shown that acute hyperglycaemia in non-diabetic patients with cerebral infarction is associated with significant increase in hospital mortality. However, the relationship between hyperglycaemia and prognosis in patients with haemorrhagic stroke is unclear. No systematic review has fully assessed all available studies to characterise potential association between hyperglycaemia and mortality in these patients. Therefore, we conducted a meta-analysis of randomised, controlled trials to examine the effects of early hyperglycaemia on early-term mortality among patients with sICH. Furthermore, we conducted subgroup analyses and examined the separate effects of different glucose concentrations on the mortality rate of these patients.

Methods

Data sources and searches

We searched the databases of Pubmed, Embase, Cochran, WANFANG DATA, VIP and CNKI for articles dated from October 1990 to June 2012. All searches used the following medical subject headings: ‘cerebral hemorrhage’, ‘intracerebral hemorrhage/ICH’, ‘stroke’, ‘blood glucose’ and ‘hyperglycaemia’. These searches were restricted to publications limited to research on humans. A manual search of references cited in the published studies and relevant review articles was also performed to identify additional investigations suitable for our purpose. For unpublished and published studies that were not exhaustively disclosed, an attempt was made (through email) to contact principal investigators in order to retrieve missing data. Finally, well-known experts in this area were contacted to ensure that all relevant data were captured.

Study selection

The identification of relevant abstracts and the selection of studies based on the criteria described later were performed independently by two authors (Yongyong Chen and Xinhu), and any discrepancy was resolved by a third investigator. Studies were included if they met the following criteria: (i) the diagnosis of sICH was confirmed by computed tomography scan or magnetic resonance imaging; (ii) the level of patients’ blood glucose within 24 h of admission and criteria to define hyperglycaemia and non-hyperglycaemia were available in the data; and (iii) data were available on the rate of early-term death (the outcome had to be assessed on discharge or within 30 days of onset) in both groups. We excluded the following: (i) studies that did not exclude recurrent episodes of haemorrhage, traumatic haemorrhage, subarachnoid, subdural or extradural haemorrhage, thrombolysis/ tumour associated sICH or haemorrhagic transformation of ischaemic stroke; and (ii) studies that did not explicitly report patient follow ups or the timing of blood glucose measurement.

Data extraction and quality assessment

The following variables in each study were extracted: (i) title, primary author’s name, year and source of publication; and (ii) study design, patient demographics, mean age, time of blood glucose determination, time of outcome assessment, definition of hyperglycaemia, numbers of patients and mortality rate of each group. When an article complied with the inclusion criteria but lacked information on parameters for analysis or when outcomes were reported but not related to hyperglycaemia, we approached the authors to obtain these data. Because studies had to fulfil these strict inclusion criteria, further formal quality assessment was not undertaken.

Data synthesis and analysis

Statistical analysis was performed using the Review Manager (RevMan) version 4.2 for Windows Software (The Nordic Cochrane Centre, Copenhagen, Denmark). For the assessment of the strength of the association between early hyperglycaemia and the early-term death in patients with sICH, the relative risk (RR) of early-term death at 95% confidence interval (CI) were extracted from the individual studies and verified with the raw data if provided; otherwise, the RR and 95% CI were calculated directly from the raw data. In the subgroup analysis, we explored the effects of the cut-off value used to define hyperglycaemia (cut-off value of hyperglycaemia: 7.5 mmol/L) on the strength of the association between hyperglycaemia and early-term death. To this end, studies were assigned to one of the following two subgroups, group A for studies with cut-off values for hyperglycaemia above the median across all studies and group B for studies with cut-off values below this median. Heterogeneity among studies was assessed with Cochrane’s Q test (significant probability value set at <0.10). To generate a summary of the RR and the corresponding 95% CI for the early-term death in patients with hyperglycaemia compared with patients with normal-glycaemia, if $P < 0.10$, the RR and the 95% CI were pooled using a random-effects model (RevMan Version 4.2.10). Otherwise, the RR and the 95% CI were pooled using a fixed-effect model (RevMan Version 4.2.10).
1621 potentially eligible reports identified and screened for retrieval

1290 reports excluded: 930 no spontaneous intracerebral haemorrhage
252 same articles among database
18 case reports
90 reviews

331 reports retrieved for detailed

310 reports excluded:
236 did not exclude a recurrent episode of haemorrhage, traumatic haemorrhage, subarachnoid, subdural or extradural haemorrhage, thrombolysis/tumour associated sICH
43 the time of assessment of prognosis of sICH was indefinite
16 data missing as message to authors not answered
15 glucose levels or rate of hyperglycaemia not reported

21 reports possibly retrieved

13 studies excluded:
6 could not find population of sICH
5 no definition of cut-off value of hyperglycaemia
2 cut-off values of hyperglycaemia

Finally 8 studies retrieved

Figure 1 Flow diagram of search strategy and study selection. sICH, spontaneous intracerebral haemorrhage.

Effects model. The \( I^2 \) was calculated, describing the percentage of total variation across studies because of heterogeneity rather than chance. \( I^2 \) values of 25%, 50% and 75% corresponded to cut-off points for low, moderate and high degrees of heterogeneity. Finally, a fixed-effects model was performed (STATA Version 10) on all studies, defining \( P = 0.10 \) and \( I^2 = 42.0\% \) as no statistical heterogeneity. In the subgroup analysis, group A was assessed by a random-effects model with \( P = 0.03 \), \( I^2 = 66\% \) suggesting statistical heterogeneity, whereas group B was assessed by a fixed-effect model with \( P = 0.39 \), \( I^2 = 0\% \); no statistical heterogeneity was found. Publication bias was evaluated by Egger’s linear regression method. In Beggs test, with \( Z < 1.96 \) and \( P > 0.05 \), no publication bias was suggested. Other conditions did support the possibility of publication bias. ‘Fail safe N’ (Nfs) is a useful mathematical measure for the stability of results. In this analysis, we calculated the \( \text{Nfs}_{0.05} \) as \( P = 0.05 \).

Results

Search results

One thousand, six hundred and twenty-one articles identified from Pubmed, Embase, Cochran, WANFANG
DATA, VIP and CNKI were analysed; of these, 1595 were excluded based on their titles and abstracts. After detailed evaluation of potential eligibility, eight studies met all the inclusion criteria and were retrieved for meta-analysis.9–16 The trial flowchart is summarised in Figure 1.

Baseline characteristics of the studies, glucose and hyperglycaemia

Characteristics of the studies included in the meta-analysis are presented in Table 1. In total, data from 3756 patients in eight studies were included in which 1486 patients were in the hyperglycaemia group (group A) and 2270 patients were in the non-hyperglycaemia group (group B). The glucose level drawn on admission was used to define hyperglycaemia in five of the eight studies (with cut-offs ranging from 7.2 to 8.3 mmol/L).9–12,15 Another three studies determined hyperglycaemia based on fasting glucose levels (>6.1 mmol/L) on the morning after admission.13,14,16 Therefore, the cut-off values used to define hyperglycaemia varied considerably from study to study (range from >6.1 to >8.3 mmol/L). The average study size was 469.5 patients with a range of 100–1239 patients.

Hyperglycaemia and clinical outcome

As shown in Figure 2, the data from the eight studies demonstrate that the RR of early-term mortality (death during hospital stay or within 1 month of onset) was significantly associated with sICH with hyperglycaemia. There was a 3.65-fold increased risk of mortality in patients with hyperglycaemia compared with patients without hyperglycaemia (pooled RR = 3.65, 95% CI (3.08, 4.33), \(P < 0.00001\)) after the onset of sICH. In the subgroup analysis, in group A with hyperglycaemia (27.5 mmol/L), the pooled RR was 3.46 (95% CI (1.66, 7.20); \(P = 0.0009\)) (Fig. 3), whereas in group B with hyperglycaemia <7.5 mmol/L, the pooled RR was 3.53 (95% CI (2.92, 4.26); \(P < 0.00001\)) (Fig. 2). Egger’s test did not show publication bias in any of these studies with \(P = 0.776\), 95% CI of intercept (−3.48, 2.72), \(NFS_{0.05} = 710.72\). In the subgroup analysis, there were \(P = 0.46\), 95% CI (−14.41, 9.37) and \(NFS_{0.05} = 82.58\) in group A, while \(P = 0.80\), 95% CI (−16.32, 18.71), \(NFS_{0.05} = 302.40\) in group B. The results showed that there was a symmetrical funnel plot without publication bias in both groups.

Discussion

This meta-analysis showed that hyperglycaemia on admission was a frequent finding and may be associated with higher risk of early-term mortality in patients with sICH. Some reports have raised several possibilities that
may account for the association between hyperglycaemia and poor prognosis after sICH. It is also notable that the effect of hyperglycaemia on neural cell death around the haematoma is more pronounced in patients with impaired glucose tolerance.17 The summarised speculations for hyperglycaemia-induced brain injury are as follows. (i) The direct toxic role of hyperglycaemia on the ischaemic brain, accumulation of lactate and intracellular acidosis.18,19 (ii) Free-radical formation is increased with hyperglycaemia-induced brain injury. The free radicals and nitric oxide increase blood brain barrier (BBB) permeability and brain oedema.20–22 (3) Hyperglycaemia induces bradykinin-mediated brain oedema with inflammation. Bradykinin, in fact, increases BBB permeability and facilitates extravasation by dilation of arterial blood vessels.23 (4) Hyperglycaemia causes acute elevation of cytosolic free calcium as a result of increased calcium influx.24,25 Rising calcium concentration in the cytoplasm causes calcium influx into mitochondria and disrupts mitochondrial membrane potential and normal metabolism, leading to cell death. All these neurotoxic effects may be particularly important in sICH. In addition, hyperglycaemia at admission and during the clinical course is associated with various in-hospital complications such as respiratory failure, nosocomial infections and impaired wound healing, all of which are contributors to poor outcome.26

It was revealed that sICH patients with undiagnosed diabetes mellitus or stress hyperglycaemia have a higher risk of vascular disease than patients with normal glycaemia.27 However, it is difficult to determine whether hyperglycaemia preceded the onset of sICH or was induced by sICH. There are several potential explanations for the high glucose levels of patients at admission with sICH. First of all, hyperglycaemia could be a secondary phenomenon related to a transient stress reaction induced by the sICH. Indeed, previous studies showed that as a component of the stress response, excess release of catecholamine results in glycogenolysis and increases hepatic glucose production. Second, increased epinephrine stimulates glucagon release and glycogenolysis or interferes with insulin-mediated glucose uptake.28 In addition, there may be an increase in insulin resistance induced by sICH in these patients. All of these factors can result in increased blood glucose levels. A preceding report revealed that sICH is associated with glucose intolerance
from peripheral insulin resistance with decreased pancreatic insulin secretion. Furthermore, hyperglycaemia may also be due to the onset of previously unrecognised diabetes induced by sICH. Regardless of its cause, high glucose levels on admission may be a predictor of mortality in patients with sICH. In our subgroup analysis, sICH patients with hyperglycaemia had an increased risk of mortality 3.65-fold compared with patients without hyperglycaemia.

**Conclusion**

Our results showed that hyperglycaemia at admission may be an important risk factor of early-term death in patients with sICH. However, this may not be influenced by the defined glucose cut-off. Therefore, the effective treatment of hyperglycaemia is one of the most attractive novel targets for acute sICH therapy. Unfortunately, however, most studies included in this review did not provide detailed data on glycaemic control. Therefore, we were unable to infer whether glycaemic control would alter the outcome of sICH.

Limitations of this meta-analysis must be considered. First, the quality of individual studies was not always optimal, as shown by the general lack of information on blinding and recruiting of consecutive patients for all studies. Second, there is heterogeneity of RR across studies, corresponding in part to heterogeneity in study definitions. Third, data on clinical outcomes are very limited. More studies specifically designed to evaluate clinical outcomes are needed. Finally, because we limited our search to English and Chinese language articles, we may have missed some studies published in other languages. Therefore, the association between early hyperglycaemia and early-term mortality requires further ad hoc studies.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyperglycaemia</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 BG&gt;=7.5mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casaubon 2007</td>
<td>28</td>
<td>53</td>
<td>13</td>
<td>85</td>
</tr>
<tr>
<td>Franke 1992</td>
<td>17</td>
<td>66</td>
<td>5</td>
<td>78</td>
</tr>
<tr>
<td>Kimura 2007</td>
<td>2</td>
<td>25</td>
<td>9</td>
<td>75</td>
</tr>
<tr>
<td>Stead 2010</td>
<td>52</td>
<td>118</td>
<td>7</td>
<td>119</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>262</td>
<td>357</td>
<td>28.0%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>99</td>
<td>34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.35; Chi² = 8.81, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 3.32 (P = 0.0009)

| 1.1.2 BG<7.5mmol/L |               |         |            |                     |
| Chen wanshan 2009  | 82            | 382     | 42         | 646                 |
| Feng Shutao 2006   | 60            | 230     | 33         | 345                 |
| Godoy 2008         | 97            | 175     | 15         | 120                 |
| Liu Yunhai 2005    | 100           | 437     | 47         | 802                 |
| Subtotal (95% CI)  | 1224          | 1913    | 72.0%      | 72.0%               |
| Total events       | 339           | 137     |            |                     |

Heterogeneity: Tau² = 0.00; Chi² = 3.01, df = 3 (P = 0.39); I² = 0%
Test for overall effect: Z = 12.98 (P < 0.00001)

| Total (95% CI)     | 1486          | 2270    | 100.0%     | 100.0%              |
| Total events       | 438           | 171     |            |                     |

Heterogeneity: Tau² = 0.05; Chi² = 12.04, df = 7 (P = 0.10); I² = 42%
Test for overall effect: Z = 10.32 (P < 0.00001)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%

<table>
<thead>
<tr>
<th>Control</th>
<th>Hyperglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.35 (1.97, 6.05)</td>
<td>7.49 (3.55, 15.81)</td>
</tr>
<tr>
<td>3.45 (1.97, 6.05)</td>
<td>7.49 (3.55, 15.81)</td>
</tr>
<tr>
<td>3.14 (1.57, 10.30)</td>
<td></td>
</tr>
<tr>
<td>0.67 (0.15, 2.88)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3 Pooled analyses on early death associated with hyperglycaemia in patients with sICH. Included studies were subdivided according to the cut-off value used in each individual study to define hyperglycaemia into studies with a definition of hyperglycaemia ≥7.5 or <7.5 mmol/L (random-effects model). CI, confidence interval.
References

Adherence and outcomes of patients prescribed dabigatran (Pradaxa) in routine clinical practice


1Capital and Coast DHB, Wellington, 2Cardiology Department, 3Hutt Valley DHB, 4Ropata Medical Centre and 5NaeNae Medical Centre, Lower Hutt, New Zealand

Key words
anticoagulant, atrial fibrillation, epidemiology, compliance, complication.

Correspondence
Katie Thorne, Capital and Coast DHB, Riddiford Street, Newtown, Wellington 6021, New Zealand.
Email: katie.thorne@ccdhb.org.nz

Received 1 August 2013; accepted 29 December 2013.
doi:10.1111/imj.12370

Abstract
Aim: To explore and detail clinical experiences of dabigatran, a novel anticoagulant, after it became available in New Zealand in July 2011.

Methods: A cohort of patients was recruited from Hutt Hospital and the two largest primary care practices in the Hutt Valley region. They were included if they took at least one dose of dabigatran between July 2011 and April 2012. Participants undertook a questionnaire 3–12 months after starting dabigatran assessing adherence, perceived side-effects and complications. Those presenting due to an adverse event were analysed separately.

Results: Of 102 patients identified, 92 were recruited to this study. At a median of 8 months, 70% of participants were still taking dabigatran, significantly lower than in the RE-LY trial at 12 months (P = 0.0002). The commonest reason given for discontinuation was gastrointestinal (GI) side-effects. Rates of serious adverse outcomes on dabigatran therapy were relatively low. Patients expressed polarised comments, both positive and negative, regarding their experiences of dabigatran.

Conclusions: A high rate of discontinuation of dabigatran, mainly due to GI symptoms, was observed. There does not appear to be any specific predictor of dabigatran tolerance. When prescribed according to guidelines, rates of serious adverse events associated with dabigatran appear to be low.

Introduction
Warfarin has been the mainstay of stroke risk reduction in atrial fibrillation (AF), despite many problems with its use. Dabigatran, a novel direct thrombin inhibitor, has shown equivalence (at 110 mg dosing) and superiority (at 150 mg) to warfarin for thromboembolism prevention in the RE-LY trial, a randomised controlled trial, but trial data do not necessarily translate to routine clinical practice.

Data from routine clinical practice have been recently published from European and North American pharmacovigilance agencies, supporting the external validity of RE-LY. However, there are limited published data from Australasia. While Australia does not yet have a significant number of patients on dabigatran, and debate is ongoing regarding licensing, New Zealand has been treating patients with this agent since July 2011. In New Zealand, there have been several cases of major haemorrhage associated with use of dabigatran, as detailed by Harper et al. Prescriber error, impaired renal function, patient age and complications arising from the lack of a reversal agent were deemed responsible. Given the limited data regarding dabigatran use in routine practice, with significant concerns regarding its licence to all medical practitioners, the limitations of a single randomised control trial and significant potential for harm, we undertook a prospective observational study to determine demographic and clinical characteristics of patients taking dabigatran (focusing particularly on dosing of dabigatran in relation to renal function), adherence to dabigatran, perceived side-effects, complications and patient comments on their experience of taking dabigatran.

Methods
Patients were recruited from medical services at Hutt Hospital and the two largest primary healthcare organisations (PHO) in Lower Hutt city. Clinicians including doctors, nurses and pharmacists were informed about
Table 1  Patient demographics

<table>
<thead>
<tr>
<th>Group still on dabigatran (n = 64)</th>
<th>Group on alternative treatment (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;64</td>
<td>13 (20%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>65–74</td>
<td>19 (30%)</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>75–80</td>
<td>10 (16%)</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>22 (34%)</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>33 (51.5%)</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>50–100</td>
<td>57 (89%)</td>
<td>27 (96.4%)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>1 (1.5%)</td>
<td>1 (3.5%)</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>36 (56.2%)</td>
<td>12 (42.8%)</td>
</tr>
<tr>
<td>31–59</td>
<td>28 (43.7%)</td>
<td>14 (50%)</td>
</tr>
<tr>
<td>Dabigatran 110 mg BD</td>
<td>41 (64%)</td>
<td>15 (33%)</td>
</tr>
<tr>
<td>CHADS2 score (mean)</td>
<td>2.5</td>
<td>1.9</td>
</tr>
<tr>
<td>HASBLED score (mean)</td>
<td>2.5</td>
<td>2.1</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate.

The study. They contacted the investigators if they encountered patients either already taking dabigatran or initiated dabigatran. Patients in primary care prescribed dabigatran were identified by searching electronic medical records databases. Duplicates were removed through comparison of unique healthcare identifiers and name.

Inclusion criteria were prescription of dabigatran and having taken at least one dose between July 2011 and April 2012. Eligible patients were posted information packs (Appendices S2 and S3). They were subsequently contacted by telephone and a questionnaire (Appendix S1) was undertaken. Electronic clinical records from Hutt Valley District Health Board and the PHO were reviewed for relevant clinical details. Patients were excluded if they could not be contacted, verbal consent was not given, if they had not taken at least one dose of dabigatran or were deceased at the time of the questionnaire.

Data were collected on baseline demographic and clinical information (Table 1). Renal function was determined using serum creatinine and patient’s age using the estimated glomerular filtration rate (eGFR), (determined using the Modification of Diet in Renal Disease formula). CHADS2 and HASBLED scores were calculated. If dabigatran had been stopped, the reason for discontinuation was recorded as free text. Those patients switched to other anticoagulants or who ceased anticoagulation were considered as ‘others’ in the results.

Adverse events were collated, including myocardial infarction (MI), thromboembolic events and bleeding episodes. Diagnoses of adverse outcomes were made by two independent physicians. MI was diagnosed as in clinical guidelines, with two of three criteria met from clinical presentation, ECG changes and rise in high sensitivity troponin T. Stroke was diagnosed using clinical presentation associated with neuroimaging changes (either computed tomography (CT) or magnetic resonance imaging brain). Venous thromboembolism was diagnosed using leg Doppler ultrasound or CT pulmonary angiogram. Bleeding was categorised according to RE-LY trial criteria into major bleeding (drop in haemoglobin greater than 20 g/L, need for transfusion of at least 2 units of red blood cells or symptomatic bleeding in a critical area/organ) and minor bleeding (all other bleeding).1

Data were recorded in a password-protected database only accessible to the researchers. We compared the difference between dabigatran and ‘other’ groups as well as comparing our study population with that of the RE-LY trial. Fisher’s exact test was used to determine the difference between proportions and Student’s t-test was used to compare between means. Two sided P-values were calculated. STATA (version 8, College Station, TX, USA) was used for statistical analysis. Total numbers of adverse events are described, but due to small sample size, inferential statistics were not calculated.

Ethical approval for this study was obtained from the Central Regional Ethics Committee, New Zealand.

Results

One hundred and two patients were identified and 92 recruited to the study (Fig. 1). Of patients excluded, three did not take dabigatran after prescription, three patients did not give consent, two patients were not contactable and two patients were deceased. One patient had a fatal stroke while switching from dabigatran to warfarin and one died of pneumonia, apparently unrelated to their anticoagulation. Thirty-five patients were recruited from primary care and 57 from hospital.

Seventeen of the 92 participants (18%) were aged under 65 years, 27 (29%) between 65 and 75, and 48 (53%) were over the age of 75. Mean age was 73 years old, and 43 (42%) of participants were male. Two participants weighed less than 50 kg, 83 were between 50 and 100 kg and 7 were greater than 100 kg. All patients had an eGFR over 30 mL/min/1.73 m², and 49 patients (53%) had an eGFR greater than 60 mL/min/1.73 m². Of the total group enrolled, 56 (61%) were prescribed 110 mg twice daily dose and the remainder (36 patients) were dosed at 150 mg twice daily.

This is different to the population of RE-LY, where it was prescribed in a randomised 1:1 ratio. All patients were prescribed an appropriate dose of dabigatran for age.
and renal function. The indication for 89 patients was AF, one had atrial flutter, and two patients, who could not take warfarin, were prescribed following venous thromboembolism (VTE) (one pulmonary embolism and one deep vein thrombosis). Baseline characteristics are shown in Table 1, listed according to dabigatran continuation at the time of questionnaire.

Thirty-eight patients were initiated on dabigatran in July 2011, the first month it became available in New Zealand. Sixty-four patients (70%) were still taking dabigatran 3–12 months (median 8 months) after its initiation. Reasons for cessation are shown in Figure 2. The majority of patients who discontinued due to gastrointestinal (GI) side-effects did so within a few days of the first dose. Of the 28 patients who discontinued, 15 switched to warfarin, 10 were taking aspirin, one was using enoxaparin, one was taking aspirin and clopidogrel and one was not taking any anticoagulant or antiplatelet agent.

There were no significant differences in discontinuation rates by baseline demographic or clinical data, except by CHADS2 score. Patients with higher CHADS2 score were significantly more likely to continue dabigatran.

Of the total cohort, only one was taking aspirin and dabigatran simultaneously, again very different to the RE-LY cohort of whom 20% were taking aspirin and dabigatran (40% at baseline). Our cohort is more reflective of modern practice in Australasia.

Patients’ comments regarding dabigatran were polarised. Positive remarks about dabigatran included ‘it’s great stuff. I’ll never go back to warfarin’, ‘I really don’t miss all those blood tests’ and ‘I like not having to change doses all the time’. Some of the negative comments included: ‘I just didn’t feel safe with no antidote’, ‘terrible heartburn, couldn’t stand the stuff’ and ‘my surgeon told me to swap since I would need lots of operations this year’. Twenty-three patients (25%) said they had missed at least one dose of dabigatran.

Adverse events were seen at time of entry to the study cohort in two patients. One had an ischaemic stroke and MI, and the other had an ischaemic stroke. Among the other 90 patients, one had a MI, one had VTE, one had three discrete transient ischaemic attacks, one had a major (life threatening) bleed and nine had minor bleeds. The adverse events while taking dabigatran are presented in Table 2.

**Discussion**

Our data provide useful information for doctors and their patients considering dabigatran. Compared with our

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Group still on dabigatran (n = 64)</th>
<th>Group on alternative treatment (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>VTE</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TIA</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Life-threatening bleed</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Minor bleed</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; TIA, transient ischaemic attack; VTE, venous thromboembolism.
study’s patients, the population of RE-LY showed predominance of men (63% vs 42%), younger cohort (mean age 71 vs 73) and less comorbid population (CHADS2 2.1 vs 2.3) which is in keeping with differences between patients seen in randomised control trials compared with those in real life.

Contrary to the observation of Harper et al., we did not observe inappropriate prescription of dabigatran according to renal function. This may reflect educational initiatives undertaken by Best Practice Advisory Centre, and initiatives by local prescribers within the Hutt Valley District Health Board catchment. This is reassuring and suggests that prescribers can be educated to operate within accepted guidelines. Numbers of adverse reactions reported to New Zealand Centre for Adverse Drug Reaction Monitoring have reduced significantly during the last 6 months. This decline may reflect prescribers becoming accustomed to dabigatran rather than a true reduction in adverse events.

Most patients were initiated on dabigatran in July, reflecting the start of its fully funded availability in New Zealand. The discontinuation rate in this study was 30%, at median 8 months (range 3–12 months), with the rate at 12 months likely to be higher. This discontinuation rate is significantly higher than the observed rate of 15% at 12 months in the RE-LY trial \( P = 0.0002 \). A higher rate of cessation is to be expected in routine clinical practice. It is important that patients are advised to seek medical advice regarding alternative anticoagulants, since sudden cessation of dabigatran could lead to potential adverse outcomes. In this study, all patients who discontinued dabigatran did so in consultation with a doctor. There were no significant differences between the characteristics of the group still taking dabigatran and those who switched to other treatments, except in CHADS2 score. It is unclear why a lower CHADS2 should lead to greater intolerance, and without a biologically plausible reason, we suspect that this is not a true finding.

Occurrence of GI symptoms was the most common reason given for patients stopping dabigatran. This is a well-recognised side-effect due to dabigatran’s formulation. The majority of patients who discontinued dabigatran did so within days of its initiation. It was not possible to collect meaningful data on this, as many patients were unable to recall exact date of cessation. Some patients were initiated on a proton pump inhibitor (PPI), with subsequent relief from GI symptoms, and were able to continue dabigatran. We did not collect data on the number of patients who received antacid therapy and then continued on dabigatran, but this could be considered in future studies. Subgroup analysis in the RE-LY trial showed that interaction between PPI and dabigatran was not clinically relevant, suggesting this is a reasonable strategy for patients who develop dyspepsia.

One patient was advised to stop dabigatran by their surgeon, who was concerned about how to stop and start dabigatran periprocedurally. Though guidelines for perioperative management of dabigatran are available, experience is limited. This may improve with more experience and time.

This study’s patient numbers are too small to complete meaningful statistical analysis and draw robust conclusions regarding outcomes, but rates of adverse events appear comparable with those seen in the RE-LY trial. Patients who presented at Hutt hospital due to dabigatran-related adverse events and not already recruited were excluded from adverse event analysis as this could cause significant increase in bias towards adverse outcomes. Only a small proportion of the study sample had adverse events. Interestingly, rates of major and minor bleeding appear to be less than that of RE-LY population.

A larger proportion of our study was taking the lower dose of dabigatran and only one patient was taking a combination of aspirin and dabigatran.

Careful dosing in an older population with a higher CHADS2 score provides reassurance that it can be used safely in a non-trial setting, but need for prescriber education is reinforced. This was carried out in New Zealand both by Boehringer Ingelheim and independent clinical prescribing information sources. This study has some limitations, including its small sample size. Patient identification at Hutt Hospital was opportunistic and it is therefore possible that some inpatients were missed, though this is felt unlikely. Our removal of duplicate patients identified in both primary and secondary care is reassuring in this respect. Most patients were prescribed dabigatran for non-valvular AF, though we did not review if echocardiograms had excluded valvular pathology.

Follow-up periods between RE-LY and our study are not compatible and longer follow ups may lead to lesser adherence and more complications. However, most patients who could tolerate dabigatran stopped in the first few days to weeks and the rest seemed to be able to continue it longer term. Time from initiation of dabigatran to phone interview was variable, which is an inherent weakness of our study design.

Some of the data collected were based on patient recall and are subjective; there was no simple way to verify the information. We also did not collect information on patients who died or did not want to participate, which unfortunately introduces some bias, though participation in the study was high.

Our study also has several strengths. There are limited data on post-marketing experience of dabigatran, particularly in routine clinic practice, and we think this study
is a valuable addition. Over 90% of eligible patients participated in data collection, a very high rate for a questionnaire-based survey. To maximise this, we posted written information, subsequently contacting patients by phone, making multiple attempts if not successful initially. All patients taking dabigatran enrolled at two PHO were included. We believe the total study group is a fair representation of the population in the Hutt Valley region taking dabigatran. For all patients recruited, we were able to review all patient records, to speak to all patients and to obtain information regarding their experiences of dabigatran. Qualitative data of patients’ reasons for stopping dabigatran have not been published elsewhere to our knowledge.

We believe these results could give reassurance to clinicians and patients in New Zealand and other countries regarding the safe use of dabigatran when used appropriately both in primary and secondary care. However, our results may not be generalisable as the dosing and patient characteristics, including demographics and renal function, may differ in those populations.

Conclusions
This study demonstrates that in routine clinical practice, compared with the clinical trial setting, a higher proportion of patients stopped dabigatran, most commonly due to GI side-effects. There does not appear to be a particular group of patients who are significantly more likely to encounter problems and discontinue dabigatran, though a difference in CHADS2 scores was noted. Serious adverse event rates appear to be low and compatible with clinical trial data when prescribed according to published guidelines. Larger studies and ongoing pharmacovigilance activities are needed to determine the long-term safety and efficacy of dabigatran, as well as to investigate further concomitant use of acid neutralising medications.

References

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

Appendix S1 Questionnaire.

Appendix S2 Patient Information Sheet.

Appendix S3 Written consent form.
Metformin usage in type 2 diabetes mellitus: are safety guidelines adhered to?

W. Huang,1 R. L. Castelino1 and G. M. Peterson1,2

1Unit for Medication Outcome Research and Education, School of Pharmacy and 2Faculty of Health Science, University of Tasmania, Hobart, Tasmania, Australia

Key words
metformin, type 2 diabetes mellitus, inappropriate usage, contraindication, renal function.

Correspondence
Weiyi Huang, School of Pharmacy, University of Tasmania, Sandy Bay Campus, Hobart, Tas. 7001, Australia.
Email: weiyi.huang@utas.edu.au

Received 22 September 2013; accepted 31 December 2013.
doi:10.1111/imj.12369

Abstract

Aim: To (i) evaluate the prescribing patterns of metformin in patients with type 2 diabetes mellitus (T2DM) and determine the prevalence of contraindications to its use, especially renal impairment, and (ii) identify potential cases of lactic acidosis (LA) related to metformin usage.

Method: This retrospective study reviewed all patients with a diagnosis of T2DM and taking metformin who was admitted to a major teaching hospital over an 8-month period. Data including demographics, medical conditions, medications at admission and discharge, and relevant pathology results were extracted from medical records.

Results: A total of 301 patients (209 medical patients, 92 surgical patients) taking metformin were included. According to guidelines, approximately 31% and 21% of patients received metformin inappropriately (in the presence of contraindications or in excessive dosage) at admission and discharge, respectively. At admission, 65 patients (n = 301, 21.6%) on metformin had at least one contraindication to its use, and 42 patients (n = 254, 16.5%) were prescribed an excessive dosage according to their renal function. At discharge, 43 patients (n = 301, 14.3%) continued on metformin with at least one contraindication and 21 patients (n = 191, 11%) received an excessive dosage according to their renal function. Four patients had evidence of LA (plasma lactate concentration > 5.0 mmol/L and pH < 7.35) without clinical diagnosis.

Conclusion: Metformin was often used in patients with contraindications to its use, or in higher than recommended dosages. Reconsideration of the official prescribing information for metformin may be warranted as the risk of harm appears to be very low.

Introduction

Metformin, a biguanide anti-diabetic agent, is an insulin sensitisser that is used as the first-line oral medication in the treatment of type 2 diabetes mellitus (T2DM). In Australia, the prescribing of metformin has gradually increased,1 largely because of its benefits over other anti-diabetic agents. In 2012, diabetes experts in the United States and Europe declared that metformin is the first choice for all patients with T2DM.2 The Australian National Health and Medical Research Council is considering a similar recommendation.3 In particular, metformin does not cause weight gain and is generally associated with a low risk of hypoglycaemia.4 It has been shown that metformin-treated patients experienced significant reductions in the risk of myocardial infarction and diabetes-related, as well as all-cause, mortality.4 The United Kingdom Prospective Diabetes Study 10-year follow up demonstrated the significant benefit on cardiovascular disease end-points and total mortality in metformin-treated patients.5

Despite the evidence base for the benefits of metformin, concerns still remain about its side effects, particularly the perceived risks of lactic acidosis (LA).6,7 especially in patients with renal impairment. LA associated with metformin is a rare condition with an estimated prevalence of 4.3 cases per 100 000 patient-years.8 However, LA has a 50% fatality rate,9,10 and hence, most
current guidelines recommend that metformin be avoided or used with dosage adjustment/caution in patients with coexisting conditions that are likely to increase the risk of LA. Specifically, it is recommended that metformin should be avoided in patients with a creatinine clearance (CrCl) less than 30 mL/min or estimated glomerular filtration rate (eGFR) less than 30 mL/min per 1.73 m², severe hepatic impairment, moderate to severe heart failure, severe infection, ketoacidosis, and respiratory failure. In addition, it is recommended that metformin should be used with caution in older people and in patients undergoing major elective surgery, with close monitoring of renal function. Furthermore, it is also recommended to avoid metformin in patients who are at a high risk of postoperative complications, such as sepsis or acute renal failure.

In practice, a major dilemma is that strict limitations in metformin usage are presented in the official product information (PI) and current guidelines; however, the incidence of LA associated with metformin seemingly remains low, including in those whom contraindications exist. Recent evidence suggested that these contraindications might be overly conservative. Hence, the main aim of this study was to evaluate the local prescribing of metformin in patients with T2DM, and identify potential LA cases related to metformin usage. The specific objective was to determine if the prescribing of metformin was in accordance with current guidelines, especially in patients in whom renal impairment or contraindications exist.

**Methods**

This retrospective audit included patients with T2DM who were admitted to the Royal Hobart Hospital (RHH), Tasmania, between 1 January and 31 August 2012. RHH is the principal referral hospital in Tasmania; it has 550 beds serving around 240,000 people in the region. The study was approved by the Tasmania Health and Medical Human Research Ethics Committee (Reference number: H0012876).

Medical and surgical patients were included in the study if they met all of following criteria (Fig. 1): (i) aged over 18 years and had T2DM, (ii) were being treated with metformin at admission and (iii) had at least an overnight stay in the hospital. Patients with a primary diagnosis of acute kidney failure (AKF) were excluded. In patients who had more than one overnight admission during the study period, only the first admission record was included. Patients’ medical records both at admission and discharge were reviewed. Data extracted included demographics, medical conditions, medications at admission and discharge, and relevant pathology results (e.g. blood glucose, HbA1c, plasma lactate level, pH, eGFR, serum creatinine, albumin, total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT)). The medical conditions or reasons for admission identified from the medical record at admission were coded according to the International Classification of Diseases (10th Edition).
In this study, inappropriate use of metformin was defined as having a contraindication to the use of metformin, identified according to: Australian Medicines Handbook (AMH) 2013 – metformin,13 Diabetes Australia – current guidelines for the management of T2DM,14 Therapeutic Guidelines21 and the official PI for metformin (Glucophage®16). Contraindications included: acute significant blood loss, cardiac failure, dehydration, diabetic ketoacidosis, gangrene, hepatic dysfunction, pancreatitis, pulmonary embolism, myocardial infarction, renal failure, respiratory failure, shock, sepsis and severe infection.

For the purpose of identifying contraindications, in the absence of a documented diagnosis, hepatic dysfunction15 was defined as biochemical evidence of hypoalbuminaemia and abnormal serum levels of at least two of the following: total bilirubin, ALT, ALP or GGT. Moderate to severe cardiac failure23 was identified by patients’ pharmacological treatment, which included an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, beta-blocker and spironolactone with/without digoxin. Renal function13 was identified by calculating the CrCl using the Cockcroft-Gault equation. In cases where CrCl could not be calculated, eGFR was used. Metformin was considered contraindicated in patients with a CrCl less than 30 mL/min or eGFR less than 30 mL/min per 1.73 m². The dosage of metformin was considered inappropriate in: a dosage higher than 2 gram per day for patients with a CrCl between 60 and 90 mL/min15 or an eGFR between 60 and 90 mL/min per 1.73 m², or 1 gram per day for patients with a CrCl between 30 and 60 mL/min15 or an eGFR between 30 and 60 mL/min per 1.73 m². LA was identified when the plasma lactate concentration was > 5.0 mmol/L and pH < 7.35.24,25

In patients who underwent planned (elective) surgery, it was also determined whether metformin had been discontinued at least 48 h prior to the surgery and restarted no earlier than 48 h following the surgery, only after the renal function had been re-evaluated and found to be normal.10

The data were summarised and analysed using Microsoft Excel 2010 and spss for Windows version 20 (SPSS Inc., Chicago, IL, USA).

Results

A total of 1274 admissions was recorded during the study period with coding as T2DM. After assessment against the study criteria, 301 patients were included (Fig. 1). The mean ± standard deviation age of the study sample was 68 ± 12.1 years (range: 24–98 years) and 60% were male (Table 1). The majority of patients (n = 188, 62.4%) was aged 65 years or over, while 16% (n = 48) were aged 80 years or over. Of the 301 patients, 92 patients were admitted for surgery, 47 of whom underwent elective surgery. The most common reasons for admission included diseases of the circulatory system (n = 87, 28.9%) followed by diseases of the endocrine system (n = 28, 9.3%).

Of the 301 patients using metformin at admission, 114 patients (37.9%) were prescribed metformin as monotherapy for diabetes, 141 patients (46.8%) were on dual therapy, and 43 and 3 patients (14.3% and 1%) were on triple and quadruple therapy, respectively.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of the study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Value (n)†</td>
</tr>
<tr>
<td>Age (mean ± SD; years)</td>
<td>68 ± 12.1</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>182, 60%</td>
</tr>
<tr>
<td>Weight (mean ± SD; kg)</td>
<td>89.8 ± 26.0 (n = 172)</td>
</tr>
<tr>
<td>Height (mean ± SD; cm)</td>
<td>167.4 ± 10.7 (n = 63)</td>
</tr>
<tr>
<td>BMI (mean ± SD; kg/m²)</td>
<td>32.7 ± 7.8 (n = 63)</td>
</tr>
<tr>
<td>HbA1c (mean ± SD; %)</td>
<td>8.6 ± 2.2 (n = 107)</td>
</tr>
<tr>
<td>Lactate (mean ± SD; mmol/L)</td>
<td>2.1 ± 1.5 (n = 114)</td>
</tr>
<tr>
<td>Serum creatinine (SCr) (mean ± SD; mmol/L)</td>
<td>91 ± 38 (n = 282)</td>
</tr>
<tr>
<td>Number of regular medications</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>Number of PRN medications</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>Metformin dosage (mean ± SD; mg/day)</td>
<td>1506.8 ± 662.1 (n = 267)†</td>
</tr>
<tr>
<td>Duration of hospitalisation (median, IQR; days)</td>
<td>5, 2–9</td>
</tr>
</tbody>
</table>
| Reasons of admission (top 5) (number of patients (%)) | 1.0%
| Disease of circulatory system (ICD10-I) | 87 (28.9%)
| Endocrine, nutritional and metabolic diseases (ICD10-E) | 28 (9.3%)
| Injury, poisoning and certain other consequences of external causes (ICD10-S and T) | 25 (8.3%)
| Neoplasms (ICD10-C and D) | 24 (8.0%)
| Diseases of respiratory system (ICD10-J) | 20 (6.6%) |
| Other medications for T2DM treatment at admission (number of patients) | 1.0%
| Insulin | 109 (36.2%)
| Sulfonylureas | 96 (31.9%)
| Thiazolidinediones | 15 (5.0%)
| DPP-4 inhibitors | 12 (4.0%)
| Acarbose | 0 (0%)
| Exenatide | 5 (1.7%) |

†n = 301, unless stated specifically. †The dosage was not recorded in 35 patients. BMI, body mass index; IQR, interquartile range.
tion to the use of metformin, with the most common contraindication being cardiac failure (Table 2), while 42 patients (16.5%) were prescribed an excessive dosage at admission based on their renal function (Table 3). Out of the 93 patients who were receiving metformin inappropriately at admission, in 53 patients (57%), metformin was continued at discharge despite a contraindication to its use or at an inappropriate dose. At discharge, 43 patients (n = 301, 14.3%) had at least one contraindication and 21 patients (n = 191, 11%) received an excessive dosage according to their renal function. In 47 elective surgical patients (from a total of 92 surgical patients), metformin was not ceased or re-started in accordance with guidelines in 19 (40.4%).

Of 111 patients with a plasma lactate level and metformin dosage being reported at admission, 82 patients (n = 111, 73.9%) had a value within the normal range (less than 2.4 mmol/L) and 25 patients (n = 111, 22.5%) had a level between 2.4 and 5.0 mmol/L. Four patients had a plasma lactate level higher than 5.0 mmol/L and pH less than 7.35, but none of them had a recorded diagnosis of LA (Table 4). All four patients had at least one comorbidity (seizure, cardiac arrest or sepsis) that could have been associated with LA.26 One patient (patient 4, Table 4) died within 24 h after admission, with sepsis and non-ST segment elevation myocardial infarction as the cause of death. The other three patients had their lactate level managed back to the normal range soon after admission. In all three patients, metformin was withheld during hospitalisation and re-commenced at discharge.

**Discussion**

Approximately 31% and 21% of patients were prescribed metformin inappropriately at admission and discharge, respectively. There were four patients identified with LA according to biochemical definition in our study, but three patients survived after the emergency admission and were

<table>
<thead>
<tr>
<th>Table 2 Contraindications to the use of metformin at admission (n = 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindications</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Cardiac failure (moderate to severe)</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Gangrene</td>
</tr>
<tr>
<td>Liver dysfunction</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
</tr>
<tr>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>CrCl (mL/min) &lt; 30</td>
</tr>
<tr>
<td>eGFR (mL/min per 1.73 m²) &lt; 30‡</td>
</tr>
<tr>
<td>Respiratory failure</td>
</tr>
</tbody>
</table>

†Some patients had more than one contraindication to use metformin.  
‡Patients reported with eGFR are not including those reported with CrCl.

<table>
<thead>
<tr>
<th>CrCl (mL/min) or eGFR (mL/min per 1.73 m²)</th>
<th>Dosage of metformin (mg/day)</th>
<th>≤500</th>
<th>&gt;500–1000</th>
<th>&gt;1000–2000</th>
<th>&gt;2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adm</td>
<td>Dis</td>
<td>Adm</td>
<td>Dis</td>
<td>Adm</td>
</tr>
<tr>
<td>&gt;90</td>
<td>8</td>
<td>8</td>
<td>20</td>
<td>19</td>
<td>47</td>
</tr>
<tr>
<td>60–89</td>
<td>2</td>
<td>10</td>
<td>37</td>
<td>26</td>
<td>38</td>
</tr>
<tr>
<td>30–59</td>
<td>11</td>
<td>11</td>
<td>21</td>
<td>19</td>
<td>30</td>
</tr>
<tr>
<td>&lt;30 (metformin contraindicated)</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Patient number with CrCl at admission, n = 149; at discharge, n = 138. Patient number with eGFR: at admission, n = 105; at discharge, n = 53. Adm, at admission; CrCl, creatinine clearance; Dis, at discharge; eGFR, estimated glomerular filtration rate.

<table>
<thead>
<tr>
<th>Table 4 Patients reported with increased lactate level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient no.</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

†Patient 4 died within 24 h after admission. eGFR, estimated glomerular filtration rate; F, female; M, male; NSTEMI, non-ST segment elevation myocardial infarction; SCr, serum creatinine.

© 2014 The Authors  
Internal Medicine Journal © 2014 Royal Australasian College of Physicians
likely to be the major risk factor in developing LA. 

3. The association between metformin and LA could be overemphasised. In addition, it has been reported that diabetes per se, rather than metformin therapy, was more likely to be the major risk factor in developing LA. 

4. Compared with non-diabetic patients, micro- or macrovascular disease in diabetic patients may also contribute to the development of acidosis, potentially by causing tissue hypoxia. 

Metformin seems generally safe for use in most patients, even in those with contraindications. Scheen and Paquot recently published a review suggesting that conditions such as mild-to-moderate chronic kidney disease and stable congestive heart failure should not be considered as contraindications to the usage of metformin. In our study, metformin was continued at discharge despite a contraindication to its use, or at an inappropriate dose, in 57% patients who were prescribed the drug inappropriately at admission. These patients may have been admitted to the hospital because of reasons unrelated to diabetes. Doctors, understandably, might have been reluctant to make changes to the therapy if the patients’ blood glucose levels were well controlled. A retrospective study in Canada found that 58 patients (28% of total) who were dispensed metformin had at least one contraindication, which included congestive heart failure, hepatic dysfunction and renal insufficiency; 50 of these 58 patients (86%) were continued on metformin after their contraindication(s) were identified.

Renal impairment is one of the major contraindications to the use of metformin as it is excreted unchanged through the kidney and could accumulate in renal impairment, thereby increasing the risk of LA. In addition, lactate metabolism and excretion through the kidneys may be reduced in patients with renal impairment, further increasing the risk of LA. Although the AMH and guidelines in Australia do not have the same recommendation as the PI, that metformin should be avoided in CrCl less than 60 mL/min, dosage reduction according to renal function is recommended. LA may be more likely in patients with AKF, rather than chronic kidney disease. Patients with a diagnosis of AKF were not included in this study. Metformin was used in 13 patients with CrCl < 30 mL/min or eGFR < 30 mL/min per 1.73 m² at admission (Table 2). One of these had a lactate level of 10.1 mmol/L (sepsis was more likely to be responsible in this case; Table 4).

Similar results were found in studies elsewhere suggesting that metformin was frequently used in patients with renal impairment without developing LA. A cohort study on almost 52 000 T2DM patients in Sweden showed that metformin as monotherapy, compared with other oral anti-diabetic agents, was associated with a reduced risk of acidosis/serious infection, and all-cause mortality in patients with an eGFR between 45 and 60 mL/min per 1.73 m². Similar results were also seen in patients with an eGFR between 30 and 45 mL/min per 1.73 m².

Recent studies have suggested that metformin could be used safely in patients with renal impairment by controlling its plasma concentration and not exceeding 5 mg/L. It was shown that the peak plasma metformin level would not exceed 5 mg/L in 95% of patients if the maximum daily dosage was restricted to 500, 1000, 2000 and 3000 mg in patients with CrCl of 15, 30, 60 and 120 mL/min, respectively. In addition, it was found that the plasma lactate did not have a significant correlation with either metformin plasma concentration or dosage. However, clinical outcome studies regarding the safety of metformin in patients with renal impairment are lacking. It has been suggested that it would be more appropriate to adjust the dose of metformin according to renal function and monitor closely for any side effects rather than ceasing metformin therapy.
Similarly, we could not identify the severity of patients’ cardiac failure. Given that recent clinical trials have shown benefits in patients with cardiovascular disease and cardiac failure, it might be appropriate to continue metformin in patients who have well-controlled cardiac failure rather than ceasing it.

### Conclusion

Metformin was prescribed inappropriately in almost one third of the study patients, according to the current PI and guidelines. However, metformin appeared generally safe to be used in these patients, with no increased risk of acidosis. Cases of elevated lactate levels were identified, but these patients were also found to have other underlying clinical conditions associated with an increased risk of LA.

Together with previous findings, the evidence presented in this study suggests that the cautions/contraindications stated in the PI and guidelines seem overly conservative including the attention on metformin-associated LA. Further clinical outcome studies in specific population groups are warranted to guide prescribers and the official PI should be reassessed and updated to reflect the current clinical practice. Thus, considerably more patients may be considered for treatment with metformin given its substantial benefits.

### References

27 Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV. Comparative outcomes study of metformin intervention versus conventional approach the COSMIC Approach Study. Diabetes Care 2005; 28: 539–43.
Fatalities and hospitalisations due to acute poisoning among New Zealand adults

R. Peiris-John, B. Kool and S. Ameratunga

Section of Epidemiology and Biostatistics, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

Key words
poisoning, mortality, hospitalisation, adult.

Correspondence
Roshini Peiris-John, Section of Epidemiology and Biostatistics, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand.
Email: r.peiris-john@auckland.ac.nz

Received 27 August 2013; accepted 20 December 2013.
doi:10.1111/imj.12364

Abstract

Background: Acute poisoning accounts for a significant proportion of the total burden of disease worldwide. While the rate of poisoning fatalities in New Zealand is comparable to other industrialised countries, demographic trends in incidence, particularly including socio-economic indicators and substances involved, are less well known.

Aim: To determine demographic patterns and substances related to acute poisoning fatalities and hospital admissions in New Zealand among people at the age of 25 years or older.

Methods: Records with a poisoning external cause of injury code were identified using the national mortality (1999–2008) and hospital discharge (2000–2009) databases, and population-based incidence and trends were analysed.

Results: The 1841 fatalities and 29 881 primary hospital admissions over the 10-year period accounted for mean annual rates of 7.1 and 115.4/100 000, respectively. The majority of deaths from acute poisoning were among males with the converse for hospitalisations for self-poisoning. While hospitalisation for intentional poisoning decreased with advancing age, admissions for unintentional poisoning increased, especially in Pacific people at the age of 65 years or older. Overall, fatality and hospitalisation rates increased with increasing deprivation. Two thirds of deaths and hospitalisations were due to intentional self-poisoning. Carbon monoxide was involved in most fatal intentional self-poisoning events, while pharmaceuticals were the main agent involved in fatal unintentional poisonings and poisoning admissions, irrespective of intent.

Conclusions: The majority of hospitalisations and deaths due to poisoning in New Zealand adults are intentional self-harm episodes. A comprehensive approach to monitoring poisoning, the underlying risks and the implementation of interventions is required to minimise risks.

Introduction

Globally, poisoning accounts for approximately 1.2 million deaths and 1.7% of the total burden of disease, with approximately 71% of the estimated 346 000 deaths from unintentional poisoning in 2004 considered preventable through known strategies improving chemical safety. In 2002, the total burden of suicides from pesticide poisoning alone was estimated to be 258 000, corresponding to approximately one third of the world’s suicides.

Rates of fatalities and hospitalisations for poisoning vary between regions and countries, and by age, gender, ethnicity, substance involved and intent. Previous studies in New Zealand have shown the annual rate of poisoning fatalities to be comparable to other industrialised countries, although fatalities from unintentional poisoning were lower. Based on a comprehensive chemical injury surveillance system, the hospitalisation rate for chemical injury in New Zealand was estimated at 212.8/100 000 in 2008. However, this report did not distinguish between poisonings and other chemically induced adverse events, such as burns, or examine if rates of injury changed over time or varied by socio-economic status.

In order to address the knowledge gaps and inform poison prevention strategies, we examined a decade of recent data from New Zealand’s national minimum
dataset to describe the socio-demographic and time trends, and substances involved in poisonings, in people at the age of 25 years and older.

**Methods**

Data on fatalities and hospitalisations for poisoning during a 10-year period were obtained from national mortality and morbidity databases compiled by the New Zealand Ministry of Health. All deaths in New Zealand are registered in the mortality dataset, while all admissions to public hospitals are recorded in the morbidity dataset. International Classification of Disease, Tenth Revision (ICD-10 AM) external cause of injury codes (E-codes) X40-49 (unintentional poisoning), X60-69 (intentional poisoning), X85-90 (assault involving poisoning), Y10-19 (poisoning events of undetermined intent) and Y352 (legal interventions involving gas) were used to identify poisoning admissions and deaths. Table 1 provides a summary of substances listed under intentional and unintentional poisoning E-codes. All adults at the age of 25 years or older who had poisoning codes of interest recorded in any one of the first three E-codes were included in the analysis. In New Zealand, a third of hospital admissions for unintentional poisoning are discharged within 24 h, and short-stay admissions are variably captured in national databases. To reduce biases in the estimates of incidence of poisoning, only admissions of at least 24 h were selected. All primary inpatient admissions to hospital for poisoning between January 2000 and December 2009, or who died as a result of poisoning between January 1999 and December 2008, in New Zealand were included.

Poisoning incidence rates were stratified by age group, gender, ethnicity, deprivation index and intent. Prioritised ethnicity, in which a single ethnic group is allocated to each individual using a priority system (Maori – New Zealand’s indigenous population, Pacific Peoples, Asian, Other groups, New Zealand European), was used in the analysis of ethnicity-based information. The New Zealand Deprivation Index 2006 (NZDep06) was used to determine socio-economic status. This is an area-based index of deprivation ranging from 1 (least deprived) to 10 (most deprived). Annual and ethnic-specific rates were calculated using the 2006 Census data and intercensal estimates.

Statistical analysis was performed using SPSS version 12.01 (SPSS Inc., Chicago, IL, USA). Ethical approval for

<table>
<thead>
<tr>
<th>E-code</th>
<th>Poisoning by and exposure to:</th>
<th>Examples</th>
</tr>
</thead>
</table>
| X40, X60 | Nonopioid analgesics, antipyretics and antirheumatics | 4-aminophenol derivatives, non-steroidal anti-inflammatory drugs (NSAID), 
pyrazolone derivatives, salicylates |
| X41, X61 | Antiepileptic, sedative-hypnotic, antiparkinsonian and psychotropic drugs, not elsewhere classified (NEC) | Antidepressants, barbiturates, hydantoin derivatives, iminosilbenes, 
methaqualone compounds, neuroleptics, psychostimulants, succinimides, 
and oxazolidinediones, tranquilizers |
| X42, X62 | Narcotics and psychodyseptics (hallucinogens), NEC | Cannabis (derivatives), cocaine, codeine, heroin, lysergide (LSD), mescaline, 
methadone, morphine, opium (alkaloids) |
| X43, X63 | Other drugs acting on the autonomic nervous system | Anticholinergics, antimuscarinics, spasmyloptics, cholinergics, antiadrenergics, 
adrenergics |
| X44, X64 | Other and unspecified drugs, medicaments and biological substances | Agents primarily acting on smooth and skeletal muscles and the respiratory system, 
anesthetics (general/local), drugs affecting the cardiovascular and 
gastrointestinal systems, hormones and synthetic substitutes, systemic and 
haematological agents, systemic antibiotics and other anti-infectives, 
therapeutic gases, topical preparations, vaccines, water-balance agents and 
drugs affecting mineral and uric acid metabolism |
| X45, X65 | Alcohol | Alcohol not otherwise specified, 1-butanol, ethanol, 2-propanol, methanol, 
1-propanol, Fusel oil |
| X46, X66 | Organic solvents and halogenated hydrocarbons and their vapours | Benzene and homologues, tetrachloromethane, chlorofluorocarbons, 
petroleum (derivatives) |
| X47, X67 | Other gases and vapours | Carbon monoxide, tear gas, motor (vehicle) exhaust gas, nitrogen oxides, sulfur dioxide, utility gas |
| X48, X68 | Pesticides | Fumigants, fungicides, herbicides, insecticides, rodenticides, wood preservatives |
| X49, X69 | Other and unspecified chemicals and noxious substances | Corrosive aromatics, acids and caustic alkalis, glues and adhesives, metals 
including fumes and vapours, paints and dyes, plant foods and fertilizers, 
poisoning NOS, poisonous foodstuffs and poisonous plants, soaps and detergents |

© 2013 The Authors
Internal Medicine Journal © 2013 Royal Australasian College of Physicians
this study was obtained from the Ministry of Health’s Multi-region Ethics Committee (MEC/11/EXP/083).

Results

Fatalities

From 1999 to 2008, the 1841 fatalities from acute poisoning among those who are 25 years and older accounted for a fatality rate of 7.1/100 000/year (range: 6.5–7.8/100 000/year). Overall, the male fatality rate was more than double the female rate (10.1 and 4.4/100 000; \( P < 0.001 \)). Fatality rates declined with increasing age, with rates highest among those at the age of 35–44 years (10.3/100 000) and lowest among adults over 64 years (4.6/100 000). Fatality rates increased with increasing deprivation (4.3/100 000 in deciles 1–3 and 8.8/100 000 in deciles 8–10). Seventy-one per cent (1302 cases) of poisoning deaths were attributed to intentional self-harm, 22.9% (423 cases) were unintentional, and in 6.0% (111 cases) the intent was undetermined. Most fatal poisoning events were recorded as occurring at home (63.4%), while the location was unknown in 19.9%.

Intentional self-poisoning

There were 1302 intentional self-harm poisoning deaths during the 10-year review period, with 29.2% of fatalities occurring in the 35–44 age group (6.2/100 000/year). In general, fatality rates decreased with age (Fig. 1a). Male fatality rates were, on average, more than double the female rates (7.3 and 3.0/100 000/year). Europeans had the highest rate of intentional poisoning fatalities across all age groups, followed by those of Māori ethnicity (Fig. 2a). Fatality rates increased as deprivation increased, with rates highest among those living in the most deprived areas (\( P < 0.001 \)) (Fig. 3a). Almost two thirds of deaths involved the ICD category ‘other gases and vapours’, 92.7% of which were due to carbon monoxide poisoning. One-third of deaths were due to pharmaceuticals (E-codes X40-X44), the majority of which were ‘narcotics and psychosleptics NEC’, mainly ascribed to codeine or morphine (50.0%) and methadone (44.1%) (Fig. 4a). ‘Alcohol’ was involved in 18.1% of deaths.

Unintentional poisoning

There were 423 unintentional poisoning deaths during the 10-year period, a third (35.2%) involving 35- to 44-year-olds. Fatality rates among males decreased with age and were higher than rates for females for the 25–34 age band. Female rates were lowest in 25- to 34-year-olds and relatively stable beyond. Males and females had similar rates for people 55 years and over (Fig. 1a). In general, Māori had the highest crude fatality rate, followed by European rates, but rates among those who are 65 years or more were higher among Pacific people (Fig. 2a). Fatality rates in all age groups increased with levels of deprivation (\( P < 0.001 \)) (Fig. 3a). Over three quarters (77.6%) of unintentional poisoning deaths involved pharmaceuticals (E-codes X40-X44), the majority of which were ‘narcotics and psychosleptics NEC’, mainly ascribed to codeine or morphine (50.0%) and methadone (44.1%) (Fig. 4a). ‘Alcohol’ was involved in 18.1% of deaths.

Hospitalisations

Between 2000 and 2009, there were 29 881 hospital admissions for poisoning (115.4/100 000/year), with an in-hospital fatality rate of 4.2%. Annual rates of hospitalisations for poisoning over the 10-year period remained relatively stable, varying from 104.9 to 120.5/100 000/year. The annualised admission rate for females was higher than the male rate (136.6 and 92.2/100 000; \( P < 0.001 \)); the rate among people residing in the most deprived areas (130.3/100 000) was more than double the rate of those living in the least deprived areas (58.6/100 000) (\( P < 0.001 \)). Sixty-five per cent of admissions were due to intentional self-poisoning (19 285 cases), 28.8% were unintentional (8601 cases) and 6.6% were of undetermined intent (1972 cases).

Intentional self-poisoning

The female admission rate (95.8/100 000) was more than 1.5 times the male rate (51.1/100 000) (\( P < 0.001 \)). Europeans had the highest admission rate (25.6/100 000), followed by Māori (7.7/100 000). Admission rates for intentional self-poisoning declined with increasing age, with the gender and ethnic differences attenuating with increasing age (Figs 1b,2b). Admission rates increased with increasing levels of deprivation, with more than a 2.5-fold higher rate among those residing in the most deprived areas (114.4/100 000) compared with those living in the least deprived areas (40.8/100 000) (\( P < 0.001 \)) (Fig. 3b). Over three quarters of intentional self-poisoning admissions involved pharmaceuticals (E-codes X60-X64), predominantly ‘antiepileptics, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified (NEC)’ (Fig. 4b). Almost one-fifth of the admissions involved ‘alcohol’. The majority of intentional self-poisoning events occurred at home (63.6%), while the location was recorded as ‘unknown’ in 24.9% of cases.
Unintentional poisoning

Admission rates increased with age (Fig. 1b), with rates among the oldest adults (≥ 75 years) more than double the rate among the youngest age group of 25–34 years (P < 0.001). There was no significant difference in admission rates by gender for unintentional poisonings (34.4/100 000 in males and 32.1 in females; P = 0.002). Rates were highest among Pacific people (49.5/100 000), followed by those of Māori (48.5/100 000) and European (37.8/100 000) ethnicity (Fig. 2b). As deprivation increased, admission rates increased threefold, from 17.8/100 000 among those residing in the least deprived areas to 54.9/100 000 among those from the most deprived areas (P < 0.001) (Fig. 3b). Over two thirds of unintentional poisoning admissions involved pharmaceuticals, the majority of which was in the category ‘other and unspecified drugs, medicaments and biological substances’ (Fig. 4b). Almost one-fifth of admissions was due to ‘other and unspecified chemicals and noxious substances’, mainly ascribed to noxious substances eaten as food (22%). Forty per cent of unintentional poisoning events occurred at home (n = 3457), with the place of occurrence noted as ‘school, other institution, and public administrative area’ in 25.3% and unknown for 24.5%.

Discussion

Each year in New Zealand, an average of 200 deaths and 3000 admissions to hospital of people at the age of 25 years or more are attributed to acute poisoning. Over two
thirds of fatalities and admissions to hospital for acute poisoning were defined as suicide or self-harm. In general, poisoning fatalities are more common in males than females. The converse applied to hospitalisations for self-poisoning. Fatalities and hospitalisations increased with socio-economic deprivation. Carbon monoxide was involved in most fatal intentional self-poisoning events, while pharmaceuticals were the main agent involved in fatal unintentional poisonings and poisoning admissions, irrespective of intent. Hospitalisation rates for unintentional poisoning were highest among older Pacific people. Most acute poisonings occurred at home, and noxious substances eaten as food were an important contributor.

**Study limitations and strengths**

This study utilised population-based databases that have complete registration of deaths and public hospital admissions with near-complete coding of external cause for injuries. However, poisonings leading to admissions for less than 24 h, treated in primary care setting, hospital emergency departments or at home, were not included in the present study, and therefore the study did not estimate the impact of poisonings that are of lesser severity. A degree of misclassification is also likely with previous research in New Zealand noting E-codes were incorrect at the level of the fourth digit, and that the error rate in
hospital discharge records of E-codes for intentional self harm was 14.7% and the diagnosis code for poisoning was 9.4%. Lack of specificity of ICD codes limits the identification of specific causative agents. We assigned the broad class of poisoning agent based on first-listed external cause code, which precluded evaluating multiple agents involved.

Acknowledging these limitations, this study provides a contemporary profile on the mortality and hospital admissions for poisoning using national databases. The annual rate of fatalities from poisoning in this study is similar to that found in other high-income countries, although hospitalisation rates are lower than in Nordic countries. Global comparisons, however, are difficult due to a paucity of similar studies and problems associated with comparability of these studies when available. Moreover, there is a tendency for groups working on injury data to focus primarily on unintentional poisoning.

The preponderance of males among fatalities and females among hospitalisations is consistent with previous research. Our finding that poisoning rates were higher in more deprived neighbourhoods has similarities to data from the United Kingdom and Canada. Some international studies have acknowledged important ethnic differences in rates of poisoning. In New Zealand, the highest rates of poisoning were generally apparent in Māori and New Zealand European ethnic groups. While intentional poisoning rates were lower among Pacific people, older Pacific adults had the highest unintentional poisoning ethnic-specific rates. It is important to note that the aggregated data included in the ‘Asian’ category may mask subgroups that could also have risks of poisoning, especially South Asians.

The findings of this study have implications for public health policy, clinical practice and future research. Key areas of relevance include the need for improvements in...
coding and data collation to inform surveillance and monitoring, reduction in unsafe drug use and improvements in prescribing practices, context-specific knowledge on risk factors, and the development and implementation of effective home interventions that target intentional and unintentional poisoning.

In New Zealand, the place of poisoning was not recorded in one in five poisonings, and the substances involved were identifiable only in broad classes of agents. Improving the completeness and specificity of ICD codes used in New Zealand’s national minimum dataset and utilising data from complementary data sources (e.g. National Poisons Centre, ambulatory and primary healthcare) will assist the focused targeting of poisoning efforts and monitoring of poisoning across the spectrum of severity.

A review of opioid-poisoning deaths in New Zealand between 2001 and 2002 found that morphine and methadone were most frequently involved, prompting the authors to suggest restrictions in the availability of these substances alongside increased monitoring of prescription and dispensing.29 Similarly, a study on antidepressant deaths in New Zealand highlighted the need for awareness of toxicity associated with higher doses when prescribing antidepressants.29 Efforts to address unsafe drug use could be strengthened by implementing best practice for treating drug dependence, modifying prescription drugs to reduce their potential for accidental ingestion or abuse,30 and limiting medication pack sizes to reduce ingested doses in self-poisoning.31

**Conclusion**

The majority of intentional poisoning fatalities in New Zealand were ascribed to carbon monoxide poisoning, a finding consistent with international studies.12,19 Regulations relating to minimum approved emission standards for all motor vehicles imported to New Zealand were strengthened in 2007.32 In the United States, similar measures resulted in a decrease in events ascribed to the inhalation of automotive exhaust, although a recent analysis suggests a concomitant increase in carbon monoxide-mediated poisoning by charcoal burning.33 Whether a similar shift is occurring in New Zealand given the nearly universal use of catalytic converters in motor cars and the easy access to charcoal requires further investigation.
Alcohol accounted for almost one-fifth of intentional self-harm hospitalisations and unintentional poisoning fatalities, emphasising the need for a comprehensive public health approach to address this problem. Cost-effective strategies in this domain include increasing minimum price and taxation, restrictions to the physical availability of alcohol, drink-driving countermeasures, brief interventions with at-risk drinkers, and treatment of drinkers with alcohol dependence.

The New Zealand’s suicide prevention strategy goals include the promotion of mental health and well-being, improving care of people experiencing mental disorders associated with suicidal behaviours, reducing access to the means of suicide, and expanding the evidence about associated with suicidal behaviours, reducing access to the means of suicide, and expanding the evidence about the elevated risk of unintentional poisoning especially among older Pacific people and the apparent link to food as a source of poisoning require further study. There is a need to strengthen strategies to prevent poisoning in homes, particularly in low deprivation areas. Investigating and addressing the links to broader social determinants of health (e.g. poverty, access to health information and care) should also be prioritised to reduce socio-economic disparities in poisoning rates. Finally, a comprehensive approach that can monitor fatalities and hospitalisations for poisoning, investigate underlying risks, and implement and evaluate relevant interventions could be facilitated by including acute poisoning in New Zealand’s Injury Prevention Strategy coordinated by a designated lead agency.

References

27. Wong L, Sobrun-Maharaj A. Self-harm in Asians in New Zealand. In:
Examining patients’ preferences for participation in clinical decision-making: the experience in a Latin American chronic obstructive pulmonary disease and cancer outpatient population

P. Jordan,¹ S. Quadrelli,¹ M. Heres,¹ L. Belli,² N. Ruhl² and H. Colt³

¹Buenos Aires British Hospital and Buenos Aires Sanatorio Güemes, ²School of Philosophy, University of Buenos Aires, Buenos Aires, Argentina, and ³Pulmonary and Critical Care Unit, University of California Irvine Medical Center, Irvine, California, USA

Key words

cancer, COPD, preference.

Correspondence

Silvia Quadrelli, Charcas 3319, 10° B, 1425, Buenos Aires, Argentina.
Email: pablod_jordan@yahoo.com.ar

Received 4 February 2013; accepted 16 December 2013.
doi:10.1111/imj.12351

Abstract

Background and Aims: It is generally accepted that patients prefer to be told the truth by their physicians; however, the practice of partial truth-telling is frequent with an existing ‘norm of nondisclosure.’ Our primary objective was to determine what patients wanted to be told about their illness, and whether there might be differences between patients with cancer or advanced chronic obstructive pulmonary disease (COPD). A second objective was to determine how these patients envisioned their participation, or lack thereof, in the treatment decision-making process.

Methods: Subjects were eligible for this prospective study if they were attending the oncology or pulmonary outpatient consultation services at the British Hospital or the Sanatorio Güemes Private Hospital in Buenos Aires, Argentina between June 2009 and May 2010.

Results: Ninety-nine patients were recruited. Forty-four had a diagnosis of COPD, and 55 patients had cancer. Seventeen of the patients expected their health to improve in the future, but a significantly higher proportion of patients with malignant disorders expected to get better in the near future as compared with those with COPD (98.2% vs 62.8%, P < 0.001). Most study participants expressed a desire to receive all the information available about their condition. A majority of the participants expressed a preference for making treatment decisions in collaboration with their physician (40.4%).

Conclusions: While they considered the role of their families relevant and wanted information to be shared so that family members might participate in decision-making, they did not want their families to have a right to withhold information, make final decisions.

© 2013 The Authors

Internal Medicine Journal © 2013 Royal Australasian College of Physicians

281
Introduction

It is generally accepted that patients prefer to be told the truth by their physicians regardless of the patient’s gender, ethnicity and place of residence. However, in some hospitals the practice of partial truth-telling is frequent with an existing ‘norm of non-disclosure’ practised by many physicians, particularly those caring for the elderly or for patients with ultimately fatal disease. Furthermore, results from several studies reveal that many physicians avoid the enumeration of statistics or the declaration of chances for decreased survival when describing disease processes or during discussions of prognosis.1

There may be several reasons for variations in physician truth-telling behaviours, probably related to differences in ethics and values regarding principles of autonomy, obligation, duty, primum non-nocere and recognition of one’s social responsibility to avoid deceptive practices. Variations in patients’ desires for truthful disclosure may depend on patient age, medical history, disease type, severity of illness, likelihood of disease-related death, influence of family members and social behavioural expectations.

Ethnicity, especially in culturally diverse healthcare environments such as the United States, may also contribute to patients’ perceptions of truthfulness. Results from at least one study revealed that elderly Korean Americans and Mexican Americans were less likely to believe they should be told the truth about diagnosis and prognosis in case of serious illness than their European American and African American counterparts.4,5 In Japan, investigators found that only 40% of physicians usually told patients about a cancer diagnosis.6 In a survey of the International Psycho-Oncology Society, oncologists estimated that less than 40% of their colleagues used the word cancer in African countries.7 Similar practices have been described in France, Hungary, Italy, Japan, Panama, Portugal and Spain.6,8 In Latin America, a study among Brazilian physicians showed that in cases of fatal prognosis, 63.1% of physicians told the truth only to families, while 31.6% preferred informing only patients.10 A study from Argentina identified similar behaviours.11

Family member influence and societal expectations might also impact practices of truthful disclosure. In some countries, health is considered a family affair rather than an individual struggle; the family often makes medical decisions when one of its members is ill without always disclosing the whole truth to their loved one.12 In Saudi Arabia, for example, 49% of patients preferred that their families, rather than themselves, be informed of their diagnosis.13 In other regions where societies are traditionally averse to the idea of individual, autonomous decision-making, there is weaker evidence, however, that patients support less than fully truthful disclosures from their physicians or that patients want to be excluded from family-based decisions regarding their medical care.14 In one study of 382 patients and 482 families in China, a large majority of cancer patients were more likely than their families to believe they should be informed of their diagnosis, stating also that the physician-in-charge was the appropriate person to disclose diagnosis.15 Similar results were reported from surveys of patients in Taiwan and Japan.16

Using the terms patient preferences, truth-telling and disclosure, we found no studies regarding patient preferences from the traditionally family-oriented decision-making cultures of Latin America. The purpose of this study, therefore, was to examine physician truth-telling practices and patient preferences regarding truthful disclosure and participation in medical decision-making in Buenos Aires City, a large metropolitan area of Argentina, where physicians have historically been reluctant to first share diagnosis and prognosis with patients rather than with family members. Our primary objective was to determine what patients wanted to be told about their illness and whether there might be differences between patients with either cancer or advanced chronic obstructive pulmonary disease (COPD). A second objective was to determine how these patients envisioned their participation, or lack thereof, in the treatment decision-making process and what role, if any, they preferred be conferred onto their families and physicians.

Methods

Subjects were eligible for this prospective study if they were attending the oncology or pulmonary outpatient consultation services at the British Hospital or the Sanatorio Güemes Private Hospital in Buenos Aires, Argentina between June 2009 and May 2010. Patients needed to be 18 years or older, have a diagnosis of a primary malignancy or severe COPD (Gold III–IV), present with normal cognition, and be able to communicate fluently in Spanish. The study was approved by Institutional Review Boards for both institutions. Written informed consent was obtained from each patient enrolled in the study prior to completion of any of the survey instruments.

Patients were randomly approached by one of the investigators (NR), who in no instance was a treating physician at the time of the patient’s clinic visits. Patients were asked to complete a 30-item survey instrument that had been
pilot tested in 15 patients. Each survey consisted of a questionnaire and cover letter explaining the project and the participant’s role in its completion. The cover letter explicitly stated that the survey was in no way connected to the patient’s diagnosis or reason for seeing a physician. Patients were informed verbally and in writing of their right to refuse to participate in any portion of the survey. They were also informed that their refusal would be without consequences. Surveys were done face-to-face with non-treating physician-investigators so that all responses were recorded by the interviewer. In addition to asking participants to complete the questionnaire about their preferences regarding truth-telling participation in the decision-making process, and desire for information regarding their illness, data were collected pertaining to the patient’s age, ethnicity, level of education, occupation, marital status, living situation, household income, self-perception regarding seriousness of their current disease, time since diagnosis and performance status were collected.

Statistical analysis

All values were described as mean ± standard deviation. Chi-squared statistics test or Fisher’s exact test was used for categorical data and an unpaired Student’s t test for continuous data. In order to examine the effects of independent variables on the odds of wanting to be told about near death, a univariate logistic regression analysis was conducted. All items were treated as categorical variables in the analysis. In a second step, only the subscales significant in the univariate analyses were tested in a multivariate model. Statistical significance was set at P = 0.05. All data were analysed using SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Ninety-nine patients were recruited (47 male, 52 female). Mean age was 60 ± 13.9 years. Forty-four had a diagnosis of COPD, and 55 patients had cancer. Overall, the demographic, social and clinical characteristics of patients with COPD and cancer were similar (Table 1). All but seven of the respondents lived with family or friends. Most (69%) had a secondary school or higher education, and 92% considered their condition serious or very serious. Only six patients felt their illness was not serious. Seventeen of the patients expected their health to improve in the future, but a significantly higher proportion of patients with malignant disorders expected to get better in the near future as compared with those with COPD (98.2% vs 62.8%, P < 0.001).

Most study participants expressed a desire to receive all the information available about their condition, including potential side-effects of treatment, chance for cure, likelihood of disease-related pain or disability, whether the disease had an eventual risk of death or if there was a possibility of dying in the near future, and explanations of treatment alternatives including what might occur should treatment be refused (Table 2). Most patients wanted to receive bad news about your disease (98%). If your disease was incurable, the 92% of patients want that your doctor communicates it (Table 3).

Less than half of the participants wanted their families to remain uninformed about the seriousness of their condition. Logistic regression analysis failed to reveal factors that could predict what patients would not want to be told about a near death, nor who would not want to have bad news shared with their families. A majority of the participants expressed a preference for making treatment decisions in collaboration with their physician (40.4%) or involving both their family members and their treating physician (33.3%) Only four patients wanted their doctors to make decisions on their own, and only one patient preferred that the family and the physician together make therapy-related decisions for them (Table 4). Overall, only 5% of patients wanted to refrain from engaging in the medical decision-making process. In case of a disagreement between physicians and family members regarding treatment choices, most patients (76.6%) preferred to follow the physician’s recommendation, with only 5% considering the family’s choice more relevant (Table 3). Regarding preferences for information provided by their doctor, statistically significant differences between patients with COPD and cancer were noted only for news of potential imminent death (preferred by patients with cancer, Table 3).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients with cancer (n = 55) and COPD (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>COPD patients (n = 44)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 years ± 14 months</td>
</tr>
<tr>
<td>Male</td>
<td>25 (45.4%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Completed primary school</td>
<td>29 (67.4%)</td>
</tr>
<tr>
<td>Lives alone</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Time since diagnosis (months)*</td>
<td>69 ± 117</td>
</tr>
<tr>
<td>ECOG performance status 0</td>
<td>33 (78.6%)</td>
</tr>
<tr>
<td>ECOG performance status 3</td>
<td>1 (2.4%)</td>
</tr>
</tbody>
</table>

* Differences statistically significant (P < 0.05). COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group.
Discussion

Most patients expect and desire truthfulness from physicians who, by practising honest and truthful disclosure of diagnosis and prognosis, respect a patient’s right to receive information about their illness. To refrain from truth-telling, therefore, can severely strain a physician–patient relationship normally based on trust. Truth-telling also honours patient autonomy and allows patients to participate knowingly in the informed consent and medical decision-making process. Several studies suggest that regardless of cultural context, informed patients are more satisfied, less anxious, more likely to comply with treatment and have improved outcomes.

Table 2  Patient preferences regarding information desired from their doctors (n = 99)

<table>
<thead>
<tr>
<th>Question</th>
<th>I absolutely want this information</th>
<th>I would like this information</th>
<th>I do not want this information</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are all possible side effects of treatment?</td>
<td>80 (80.8%)</td>
<td>16 (16.2%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>What effect can I expect from this treatment?</td>
<td>85 (85.9%)</td>
<td>9 (9.1%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Is my disease cancer or not?</td>
<td>85 (85.9%)</td>
<td>9 (9.1%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Is there any chance for cure?</td>
<td>86 (86.9%)</td>
<td>12 (12.1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>What will the treatment exactly do?</td>
<td>78 (78.8%)</td>
<td>14 (14.1%)</td>
<td>6 (6.1%)</td>
</tr>
<tr>
<td>What is the medical name of my disease?</td>
<td>79 (79.8%)</td>
<td>11 (11.1%)</td>
<td>8 (8.1%)</td>
</tr>
<tr>
<td>Is this a hereditary or contagious disease?</td>
<td>85 (85.9%)</td>
<td>13 (13.1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Can I die from this disease?</td>
<td>82 (82.8%)</td>
<td>10 (10.1%)</td>
<td>5 (5.1%)</td>
</tr>
<tr>
<td>What are the chances of dying from this disease?</td>
<td>76 (76.8%)</td>
<td>15 (15.2%)</td>
<td>8 (8.1%)</td>
</tr>
<tr>
<td>If I may die: how much time will I live?</td>
<td>75 (75.8%)</td>
<td>11 (11.1%)</td>
<td>10 (10.1%)</td>
</tr>
<tr>
<td>Can I become disabled from this disease?</td>
<td>76 (76.8%)</td>
<td>13 (13.1%)</td>
<td>9 (9.1%)</td>
</tr>
<tr>
<td>Can this disease cause me pain that treatment does not control completely?</td>
<td>83 (83.8%)</td>
<td>9 (9.1%)</td>
<td>7 (7.1%)</td>
</tr>
<tr>
<td>How effective is treatment in other patients?</td>
<td>74 (74.7%)</td>
<td>18 (18.2%)</td>
<td>7 (7.1%)</td>
</tr>
<tr>
<td>Can you give me examples of treatment effectiveness in other patients</td>
<td>73 (73.7%)</td>
<td>20 (20.2%)</td>
<td>6 (6.1%)</td>
</tr>
<tr>
<td>Can you give me examples of when this treatment was not effective in other patients?</td>
<td>67 (67.7%)</td>
<td>18 (18.2%)</td>
<td>14 (14.1%)</td>
</tr>
<tr>
<td>What will happen if I do not undergo treatment for this disease?</td>
<td>86 (86.9%)</td>
<td>9 (9.1%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>What other treatment options exist and what are their advantages and disadvantages?</td>
<td>86 (86.9%)</td>
<td>9 (9.1%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Who is the most recognised specialist in this disease to provide a second opinion?</td>
<td>68 (68.7%)</td>
<td>17 (17.2%)</td>
<td>14 (14.1%)</td>
</tr>
</tbody>
</table>

Table 3  Patient preferences (yes/no questionnaire) regarding information desired from their doctors (n = 99)

<table>
<thead>
<tr>
<th>Questions</th>
<th>Yes</th>
<th>No</th>
<th>COPD %</th>
<th>Cancer %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>I want my doctor to give me all information, good or bad, about my disease</td>
<td>97 (98.3%)</td>
<td>2 (2%)</td>
<td>95.3</td>
<td>100</td>
<td>0.211</td>
</tr>
<tr>
<td>If something goes wrong I want my doctor to tell me.</td>
<td>97 (98.3%)</td>
<td>2 (2%)</td>
<td>95.3</td>
<td>100</td>
<td>0.211</td>
</tr>
<tr>
<td>If my disease is incurable I want my doctor to tell me</td>
<td>92 (92%)</td>
<td>7 (8%)</td>
<td>90.7</td>
<td>96.0</td>
<td>0.410</td>
</tr>
<tr>
<td>If there is bad news I want my doctor to tell my family first</td>
<td>29 (29.3%)</td>
<td>70 (70.7%)</td>
<td>18.6</td>
<td>30</td>
<td>0.235</td>
</tr>
<tr>
<td>If I have a severe illness I want to know, even if my family does not want to give me that information</td>
<td>94 (94.9%)</td>
<td>5 (5.1%)</td>
<td>90.7</td>
<td>98.0</td>
<td>0.178</td>
</tr>
<tr>
<td>If there is a risk I might die, I want my doctor to tell me</td>
<td>95 (96%)</td>
<td>5 (4%)</td>
<td>90.7</td>
<td>100</td>
<td>0.042</td>
</tr>
<tr>
<td>If I may die in short time, I want my doctor to tell me</td>
<td>89 (89.9%)</td>
<td>10 (10.2%)</td>
<td>88.4</td>
<td>100</td>
<td>0.019</td>
</tr>
<tr>
<td>If I have a serious illness I want my doctor to tell me and not tell my family</td>
<td>45 (45.5%)</td>
<td>51 (51.5%)</td>
<td>51.2</td>
<td>44.0</td>
<td>0.536</td>
</tr>
</tbody>
</table>

*Differences statistically significant (P < 0.05). COPD, chronic obstructive pulmonary disease.*
Current opinions and practices regarding the importance of truth-telling, however, are mostly derived from studies of Anglo-Saxon or migrant patient populations in the United States and may not always take into consideration that truth-telling practices and preferences are a cultural artefact that cannot necessarily be extrapolated to diverse cultural contexts. Truth-telling, however, has been shown to contribute to patient distress, anguish, depression, hopelessness, pain and anger, and does not necessarily result in improved quality of life. \(^{22-23}\) Furthermore, patients with irreversible or ultimately fatal disease such as cancer or advanced COPD are particularly vulnerable to physician behaviours. \(^{26,27}\) Healthcare providers striving to balance their obligation to tell the truth with the do-no-harm imperative of the Hippocratic oath may, therefore, practise paternalistic, selective non-disclosure.

However, in predominantly Anglo-Saxon countries studies show that patients with cancer want to know the nature of their terminal illness, a desire that has also been documented in patients with chronic life-altering diseases such as multiple sclerosis and Alzheimer’s. \(^ {28-30}\)

Our study demonstrates a similar desire for physician truth-telling practices among patients with advanced COPD (GOLD stage III/IV) and cancer, finding that that 98% of all patients wanted to be told the truth regardless of their illness, even if it meant that being told there was a high risk of death.

For those patients aware of their diagnosis, results from studies in the United States, Canada and Japan suggest that preferences regarding the patient’s role in treatment-related decision-making vary. \(^ {31-33}\) Blanchard et al. \(^ {34}\) reported that 92% of hospitalised cancer patients preferred receiving all the information necessary to decision-making, 24.9% preferred that their physician make therapeutic choices. Elkin et al. \(^ {35}\) showed that 52% patients age 70 years and older with a recent diagnosis of metastatic colorectal cancer preferred assuming a passive role in treatment-related decision-making, whereas Benbassat et al. \(^ {36}\) noted that while patients may not want to assume an active role in the doctor–patient relationship, they do not want to be entirely passive either. Patients may actively seek information to satisfy an aspect of psychological autonomy that does not necessarily include participation in decision-making. Sutherland et al. and Katz suggesting that one’s motivation to become informed in order to exercise or not decision-making power, illustrates one’s right to sell determination. \(^ {37,38}\)

We found that almost all respondents sought information and wanted to be knowledgeably engaged. Contrary to the relatively widespread assumption throughout Latin America that families should make medical decisions when one of its members is ill, it seems, according to our investigation, that almost all respondents wanted to be directly engaged in decision-making regarding their own health. We believe this is an interesting finding that deserves further attention. \(^ {39}\)

Motivated by the paucity of literature pertaining to truth-telling practices and patient preferences regarding participation in the treatment decision-making process in Latin America, we designed our study to explore these issues, in addition to potential differences among patients with life-altering disease such as advanced COPD and cancer in patients residing in Buenos Aires, a large, metropolitan region in Argentina. The strong family-oriented culture of Latin America was only modestly apparent. Limiting the generalisability of results, however, is that Buenos Aires is a large city that may not be representative of smaller towns and rural areas of Latin America. In addition, Argentina is a culturally diverse country with descendants from immigrants who may not be representative of the rest of Latin America. \(^ {39}\) Third, the interpretations of quantitative research findings from questionnaires may fail to capture social and psychological phenomena that reflect the true nature of human social behaviour. This is because results often rely on what people say rather than on what they do, seeking to reduce meaning to what is plainly observable. \(^ {40}\)

This variance might be explained by different settings in which studies are performed, patient populations, disease processes, whether or not patients are hospitalised, whether there exists a preponderance of falsely optimistic views of one’s disease, severity of symptoms, and other factors including age, gender, ethnicity and cultural environment. \(^ {41}\)

The data in this paper provide guidelines on what the overall group of patients wish or expect in terms of participation and disclosure of information in decision-making; this does not tell the clinician what the individual would wish, and it is vital that each practitioner establishes this with each patient.

Studies incorporating ethnographic and other qualitative research methodologies are warranted to better

---

**Table 4 Patient preferences regarding treatment-related decision-making (n = 99)**

<table>
<thead>
<tr>
<th>Treatment decisions should be made by</th>
<th>n</th>
<th>COPD (n = 55)</th>
<th>Cancer (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The doctor alone</td>
<td>4 (4%)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Myself alone</td>
<td>10 (10.1%)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Myself and the doctor together</td>
<td>40 (40.4%)</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>The doctor, myself and my family equally</td>
<td>33 (33.3%)</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>The doctor and my family together</td>
<td>1 (1.0%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myself and my family together</td>
<td>11 (11.1%)</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease.
understand the healthcare-related preferences and practices of various groups of people throughout the South and Central American continent.

**Conclusion**

The Latin American patients in our study wanted to be thoroughly informed about their diagnosis and their disease. Regardless of whether they had advanced COPD or cancer, they also wanted to be actively engaged in the medical decision-making process. Our patients wanted to be told the truth, even if their condition entailed a serious risk of death. These findings can have a profound impact on changing physician–patient communication styles and medical decision-making behaviours in Latin America.

**References**


**BRIEF COMMUNICATIONS**

**Hepatosplenic T-cell lymphoma, immunosuppressive agents and biologicals: what are the risks?**

K. Subramaniam,1 D. Yeung,2 F. Grimpen,1 J. Joseph,2 K. Fay,2,4 M. Buckland,3 D. Talaulikar,5 J. Elijah,6 A. C. Clarke,1 P. Pavli1 and J. Moore2

1Gastroenterology and Hepatology Unit, 2Department of Haematology, 3Office of Medicines Safety Monitoring, Therapeutic Goods Administration, Canberra, Australian Capital Territory, 4Department of Haematology and UNSW Clinical School, 5Department of Anatomical Pathology, and 6Department of Haematology, Royal North Shore Hospital, Sydney, New South Wales, Australia

**Key words**
hepatosplenic T-cell lymphoma, immunosuppression, biologicals, inflammatory bowel disease, psoriasis.

**Correspondence**
Kavitha Subramaniam, Gastroenterology and Hepatology Unit, Canberra Hospital, ACT 2606, Australia.
Email: kaviths@hotmail.com; kavitha.subramaniam@act.gov.au

Received 27 April 2013; accepted 14 September 2013.

doi:10.1111/imj.12363

We present three cases of hepatosplenic T-cell lymphoma (HSTCL); review the evidence for an association between HSTCL and immunosuppressive drugs and biologicals (specifically the antitumour necrosis factor agents (anti-TNF)), and argue for improved pharmacovigilance processes to help determine the benefit to risk ratios for the use of these and other new agents.

**Case 1:** A 39-year-old man with a 13-year history of Crohn disease presented with a flare of symptoms, hepatosplenomegaly and neutropenia (platelets $281 \times 10^9/L$, neutrophils $0.5 \times 10^9/L$, haemoglobin 140 g/L). Treatment after diagnosis included bowel resection and mesalazine, followed by a combination azathioprine and prednisone therapy for 4 years prior to presentation.

**Abstract**

We present three cases of the rare hepatosplenic T-cell lymphoma (HSTCL): two patients suffering from Crohn disease who developed HSTCL on azathioprine without exposure to biologicals, and a third patient who had psoriasis treated using etanercept, cyclosporine and methotrexate. The evidence for an association between HSTCL and immunosuppressive drugs and biologicals is reviewed. We argue for improved pharmacovigilance processes to help determine the benefit to risk ratios for the use of these and other new agents.

**Funding:** None.

Conflict of interest: None.
Computed tomography (CT) scan revealed splenomegaly with areas of splenic infarction but no lymphadenopathy. Liver biopsy demonstrated an infiltrate of intermediate to large T cells in liver sinusoids. Immunophenotyping of marrow and liver tissue showed a T-cell monoclonal population (CD2/3/7/16/TCRαβ POS, Vβ12 POS, CD4/8/38/57/HLA-DR NEG). Karyotyping revealed isochromosomes 7q, 8q and Y loss. A diagnosis of HSTCL was made based on the histological appearance and karyotype. The patient was commenced on DHAC (dexamethasone, carboplatin and cytarabine) chemotherapy without a lasting response; this was changed to the SMILE protocol (methotrexate, ifosfamide, l-asparaginase and etoposide). At the end of the second course, he developed neutropenic sepsis, a widespread pulmonary infiltrate, and died. Post-mortem examination revealed widespread malignant lymphocytic infiltration of the pulmonary sinusoids.

Case 2: A 42-year-old man with a 13-year history of Crohn disease presented with weight loss, malaise and upper abdominal pain, and was found to be pancytopenic (haemoglobin 130 g/L, neutrophils 0.7 × 10⁹/L, lymphocytes 0.5 × 10⁹/L and platelets, 47 × 10⁹/L) and had abnormal liver function tests. He had received azathioprine (cumulative dose 440 g) but no other immunosuppressive or anti-TNF agents. CT scans revealed hepatosplenomegaly but no lymphadenopathy. Bone marrow biopsy showed atypical lymphoid cells but no diagnostic features of lymphoma (normal CD4 and CD8 expression, normal karyotype). A few weeks later, he presented with fevers, further weight loss and atypical lymphocytes on blood film. A diagnosis of HSTCL was established on repeat bone marrow and liver biopsy, which showed an infiltrate of neoplastic T cells, which on immunophenotyping were CD2/3/7/56 positive, with relatively low expression of CD4 and CD8/16/HLA-DR negative. Cytogenetics showed isochromosome 7q, addition 17p and Y loss, and molecular studies demonstrated clonal rearrangement of the T-cell gamma delta receptor gene.

He commenced chemotherapy using hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone). A repeat bone marrow after the first cycle of chemotherapy showed progression. The patient declined further chemotherapy and died 2 weeks later.

Case 3: A 30-year-old man with a history of severe psoriasis presented with bruising, lethargy, fever, weight loss, splenomegaly and pancytopenia (platelets 49 × 10⁹/L, neutrophils 1.7 × 10⁹/L, haemoglobin 118 g/L). A history of immunosuppressive use included methotrexate weekly for 12 months, cyclosporine for 4 years and 3 months of etanercept 2 years prior to presentation. Bone marrow examination revealed infiltration of marrow sinususes by intermediate-sized lymphocytes in an intra-sinusoidal distribution (Fig. 1). Immunophenotype by immunoperoxidase staining and flow cytometry was consistent with T-cell lymphoma (CD2/3/7/16/56/TIA-1
positive, CD4/8/38/57/HLA-DR negative), and negative for both gamma-delta and alpha-beta, and cytogenetic analysis found a malignant clone with add(1p), loss of 14 and 20. HSTCL was treated using DHAC (dexamethasone, carboplatin and cytarabine), resulting in complete remission after three cycles. After high-dose intravenous methotrexate administered for central nervous system prophylaxis, an autologous stem cell transplant was performed using BEAM conditioning (carmustine, etoposide, cytarabine and melphalan), resulting in complete cytogenetic remission. He relapsed 7 months post-transplant and died 2 years later after multiple courses of palliative radiotherapy to the spleen.

HSTCL is a rare form of peripheral T-cell, non-Hodgkin lymphoma that was described in 1981 and recognised in the World Health Organization classification of lymphoid malignancies in 1990. It was originally described in γδ T cells; the αβ variant was recognised as a subtype later. Patients tend to be adolescent males, often in the setting of immunosuppression and chronic antigen stimulation. Fever, night sweats and weight loss are common symptoms. The liver, spleen and marrow are usually involved at diagnosis: hepatosplenomegaly and cytopenias, especially thrombocytopenia, are common. Lymphadenopathy is typically absent.

Histologically, cells are monotonous, arranged in and around sinusoids progressing to an interstitial pattern and blast-like with advanced disease. These T cells have a non-activated phenotype, commonly CD2/3/8/38+/56+, CD4/8/5/25/30– and CD7/16+/−. Isochromosome 7q is a consistent cytogenetic finding; trisomy 8 and loss of Y are also encountered. Viral antigens, such as EBER and HTLV-1, are negative. The disease is aggressive, with a median survival of less than a year. There is no established therapy, and there are reports on the lack of efficacy of intermediate-dose chemotherapy regimens like CHOP, with reports of long-term survival with intensive chemotherapy like hyper-CVAD. The use of 2'-deoxycoformycin and other targeted therapies, such as alemtuzumab, anti-γδ TCR monoclonal antibodies and anti-CD44 therapy, has shown promising results in anecdotal reports, but probably the best chance of cure lies in allogeneic stem cell transplantation; long-term survival is approximately 40%.

More than 200 cases of HSTCL have been reported; while the majority of cases occur de novo, about 20–30% were associated with states of altered immunity, including solid organ transplantation, Hodgkin lymphoma, acute myeloid leukaemia, malaria and patients treated for inflammatory bowel disease.

Approximately 36 cases involving inflammatory bowel disease (IBD) patients receiving thiopurines have appeared since 1996. Twenty received concomitant anti-TNF therapy. In the setting of combination therapy, the median time from initiation of thiopurines to the development of HSTCL was 5.5 years. Most patients had been taking thiopurines for at least 2 years and were men younger than 35 years of age.

Parakkal and colleagues reviewed all cases of HSTCL reported to the United States Food and Drug Administration in patients receiving TNF-α inhibitors. Twenty-five cases were identified. Twenty-two patients had IBD. Four cases were in women and four patients were above 65 years of age. Twenty-four cases also received an immunomodulator. There were no cases in IBD patients who received only anti-TNF therapy. The REFURBISH study also concluded that the risk of T-cell non-Hodgkin lymphoma is increased with combination anti-TNF therapy and thiopurines, but not with anti-TNF therapy alone.

We report an additional two patients suffering from Crohn disease who developed HSTCL without exposure to biologicals, and a third patient who had psoriasis treated with etanercept, cyclosporine and methotrexate. This is the first case associated with the use of etanercept therapy to be described, in only the second patient on any anti-TNF agent for disease other than IBD.

HSTCL is associated with a poor outcome, and its incidence may be increased in patients with IBD who are treated with immunosuppressive and/or anti-TNF agents. However, the overall risk is small, and the clinical benefit of these drugs may outweigh the potential risks. We sought to determine the extent of the risk in Australia by interrogating the Adverse Drug Reactions Advisory Committee (ADRAC) database (http://www.tga.gov.au) and surveying over 150 Australian gastroenterologists with an interest in IBD. The population of Australia is approximately 22 million (Australian Bureau of Statistics: http://www.abs.gov.au) and the estimated numbers of Crohn disease and ulcerative colitis patients are 28 000 and 33 000 respectively (Access Economics report: http://www.acca.net.au). The ADRAC database holds details of reports of suspected reactions to drugs submitted voluntarily by Australian doctors, dentists and pharmacists since 1 November 1972: we found only 17 reports of adverse drug reactions associated with the use of azathioprine or 6-mercaptopurine dating back to 1972; there were three reports of ‘pseudolymphoma’ reported in 1977, 1985 and 1993, and two cases of HSTCL reported in 2007 and 2008 (both treated with both azathioprine and infliximab). In contrast, there were 613 reports of adverse drug reactions associated with anti-TNF agents and 10 reports of lymphoma since 2003, two of whom were the same two HSTCL patients treated with azathioprine and infliximab referred to above. Our email survey of Australian gastroenterologists identified one case, which was associated with the use of combined...
anti-TNF and immunosuppressive agents, which has been reported previously and is also present in the ADRAC database. The identification of low-incidence complications of any drug after its marketing depends on pharmacovigilance programmes, which generally involve voluntary reporting of cases or series of adverse drug reactions by the medical community and the collation of Periodic Safety Update Reviews by the pharmaceutical industry. The rarity of HSTCL and the novelty of anti-TNF agents have resulted in a relatively accurate picture of the absolute risk of this condition developing in patients exposed to anti-TNF agents. In contrast, the paucity of reports of adverse drug reactions associated with thiopurine analogues and other immunosuppressive agents precludes an assessment of the relative contribution of the two classes of drugs to the risk of developing HSTCL.

Are the immunosuppressive agents the only factors contributing to the risk of HSTCL? Is the risk increased by concomitant use of anti-TNF? To get a more representative picture of the relative safety of novel therapies, particularly when used in combination with other drugs, it will be necessary to establish more accurate pharmacovigilance programmes using registries, drug event monitoring, sentinel sites and/or other means. Nevertheless, the Australian experience presented above conforms to the literature to date; the only patients who developed HSTCL were treated with immunosuppressive agents alone or in combination with anti-TNF agents, but not with anti-TNF agents alone.

References
Long-term outcomes in patients with restrictive filling following ST-segment elevation myocardial infarction

L. Hee,¹,² X. Brennan,² J. Chen,² C. Allman,¹ G. A. Whalley,³ J. K. French,¹,² C. P. Juergens¹,² and L. Thomas¹,²,⁴

¹Cardiology Department, Liverpool Hospital, ²South Western Sydney Clinical School, The University of NSW, ³Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia, and ⁴Faculty of Social and Health Sciences, Unitec Institute of Technology, Auckland, New Zealand

Key words
diastolic dysfunction, ST-segment elevation myocardial infarction, transthoracic echocardiogram, restrictive filling pattern.

Correspondence
Liza Thomas, Cardiology Department, Liverpool Hospital, Elizabeth Street, Sydney, NSW 2170, Australia.
Email: l.thomas@unsw.edu.au

Received 26 June 2013; accepted 25 November 2013.
doi:10.1111/imj.12360

Abstract
This study evaluated the effect of restrictive filling pattern (RFP) on 5-year outcomes in patients following ST-segment elevation myocardial infarction (STEMI). A hundred STEMI patients treated either by rescue or primary percutaneous coronary intervention with an echocardiogram performed within 6 weeks of STEMI comprised the study group. Creatinine kinase (CK) and left ventricular ejection fraction were independent determinants of RFP, and RFP was an independent predictor of cardiac and all-cause mortality at median follow up of 5 years.

Percutaneous coronary intervention (PCI), for ST-segment elevation myocardial infarction (STEMI), limits myocardial injury and reduces mortality;¹ however, myocardial damage from STEMI results in systolic and diastolic dysfunction (DD). Although elevated left ventricular (LV) end-diastolic pressure is a predictor of adverse outcome after STEMI,² its invasive nature precludes routine clinical use. Non-invasive estimates of diastolic function, particularly Doppler assessment of LV filling and, more recently, left atrial (LA) volume, have been reported to be predictors of outcome following myocardial infarction (MI).³ Previous studies have reported the adverse impact of restrictive filling pattern (RFP) in STEMI patients treated by thrombolysis, demonstrating increased all-cause mortality.⁴ The present study evaluated the impact of RFP on longer term outcomes in STEMI patients treated by PCI. We hypothesised that RFP would remain an independent predictor of longer term outcomes in STEMI patients treated by PCI.

A total of 107 consecutive STEMI patients from Liverpool Hospital, Sydney (January 2003–May 2010), underwent a transthoracic echocardiogram (TTE) (day 3–6 weeks), following STEMI. Patients were excluded for atrial fibrillation (n = 3), severe mitral regurgitation (n = 1) and poor echocardiographic images (n = 3). A total of 100 patients (78 males; mean age: 59 ± 11 years) comprised the study group, and was treated by rescue (n = 40) or primary (n = 60) PCI. All patients were clinically stable when the TTE was performed; none had an intra-aortic balloon pump, were on inotropes or in heart failure (HF). All participants had cardiac enzyme evaluation. The study protocol was approved by the Sydney South West Area Health Service ethics committee (QA2009/046).

A comprehensive echocardiogram was performed using commercial equipment (Phillips Sonos 7500, Philips Co, The Netherlands; GE Vivid 7, Horten, Norway) according to standard recommendations.³ Transmirtal flow was obtained from the apical four-chamber view using pulsed Doppler, and peak E and A velocities, E/A ratio, and deceleration time (DT) were measured. Pulsed tissue Doppler imaging (TDI) from the septal mitral annulus in early diastole (e’) was evaluated when available (n = 59).

LV diastolic function was classified as normal, impaired relaxation, pseudo-normal and restrictive filling based on published criteria;¹ RFP was defined as E/A ratio >2 and/or DT <140 ms.⁶ Patients (n = 10) with indeterminate diastolic grade (i.e. normal vs pseudo-normal filling) were reviewed using A-wave and pulmonary vein A-wave duration and e’ velocity. Left ventricular ejection fraction (LVEF)⁷ was measured using the modified biplane Simpson’s method; biplane maximum

Funding: None.
Conflict of interest: None.
LA volume was measured using the area-length method; and LV mass was calculated using the Penn method. The latter two variables were indexed to body surface area.

Baseline demographic details, cardiac risk factors and discharge medications were obtained from patient records. Duration of ischaemia was measured from symptom onset to establishing TIMI-3 flow. Clinical outcomes, including cardiac death, all-cause death, HF hospitalisation, non-fatal MI, stroke and coronary revascularisation, were tracked for a median of 5 years, from hospital records and/or by telephone follow up from patients or their physicians. Major adverse coronary and cerebral events were a composite of HF, death, MI, stroke or revascularisation.

Analysis was performed using spss 19 (SPSS Inc., Chicago, IL, USA) and Stata 12 (StataCorp, College Station, TX, USA). All statistical tests were two-tailed and a $P$ value $<0.05$ was deemed significant. Cumulative survival was constructed by Kaplan–Meier curves, and groups were compared with the log–rank test. A Cox regression analysis was performed for the primary end-point; variables significant at the bivariate level ($P < 0.05$) or had clinical relevance were included in the model. Multivariate logistic regression analysis was performed to identify independent determinants of RFP.

The study cohort was stratified into restrictive ($n = 24$) and non-restrictive ($n = 76$) groups (Table 1). A higher proportion of patients treated with rescue PCI had RFP (58% vs 34%, $P = 0.035$). Age, gender and cardiac risk factors were similar. A significantly higher percentage in the RFP group was discharged on loop diuretics and/or aldactone (46% vs 19%, $P = 0.011$). Higher levels of cardiac enzymes (TnT, CKMB and CK) were found in RFP than non-RFP group ($P < 0.001$, respectively), whereas indexed LV mass was similar between the groups (Table 1).

Kaplan–Meier analyses demonstrated that both cardiac (1% vs 21%, $P < 0.001$) and all-cause death (9% vs 38%, $P = 0.003$) were higher in RFP patients (Fig. S1). There was no significant difference for other end-points (Table S1). Cox regression analysis was performed to investigate the predictive values of clinical and echocardiographic indices on all-cause and cardiac death. Variables included in the model were age, gender, PCI (rescue vs primary), infarct-related variables (TnT, CK, proximal LAD lesion and duration of ischaemia) and echocardiographic indices (LVEF, indexed LV mass and
patients. However, the majority of these reports, including morbidity and mortality in acute myocardial infarction RFP. 

Analysis, CK and LVEF were independent predictors of larger LA volume and a reduced LVEF. On multivariate patients, those with higher cardiac biomarker levels, a mortality. Restrictive filling was more prevalent in rescue PCI were independent predictors of cardiac and all-cause mor-

dictors of all-cause and cardiac death (Table 2). Independent predictors of RFP determined by multivariate the likely effect of RFP after STEMI.

This study evaluated the impact of RFP on long-term outcomes in STEMI patients treated with PCI. RFP and age were independent predictors of cardiac and all-cause mor-

tility. Restrictive filling was more prevalent in rescue PCI patients, those with higher cardiac biomarker levels, a large LA volume and a reduced LVEF. On multivariate analysis, CK and LVEF were independent predictors of RFP.

RFP has previously been identified as a predictor of morbidity and mortality in acute myocardial infarction patients. However, the majority of these reports, including a meta-analysis from 2008, were performed in the era of thrombolytic therapy where TIMI flow status was not ascertained. Patients were heterogeneous, including both STEMI and non-ST segment elevation myocardial infarction patients. Follow up for the majority was 12–24 months, with only 3/16 studies having longer term follow up (4 years). However, the current study examines the impact of RFP in STEMI patients treated by contempor ary PCI therapy, which has significantly improved size. The definition of RFP has been variable; some defined RFP as E/A ratio >2, while others used a shortened DT. We defined RFP as E/A ratio >2 and/or DT <140 ms in all instances. Although current guidelines for the assessment of LV diastolic function mandates more than E/A ratio and DT, transmitral Doppler is robust for determining RFP and has been used by other investigators, including the MERGE HF group and the European Study Group on Diastolic HF.

Despite the modest size of the group and the low number of events, patients with RFP had increased all-cause and cardiac death. Multivariate analysis showed stable numeric estimates for both hazards ratios and 95% CIs, with significance consistent with univariate analyses results. A previous study demonstrated that RFP at discharge was an independent predictor of mortality. Therefore, echocardiograms performed immediately post-STEMI may reflect transient LV diastolic dysfunction with subsequent improvement. In this study, as the echocardiograms were performed at variable times (3 days–6 weeks), at worst, we would have underestimated the likely effect of RFP after STEMI.

Approximately 30% of HF patients have preserved LVEF and HF due to DD, with an increasing prevalence with age. While RFP did not predict HF occurrence (Table 2, P = 0.578), a higher percentage of RFP patients were discharged on diuretics (Table 1). Cardiac biomarkers (CK, CKMB and TnT) are surrogates of infarct size. Significantly higher CK, CKMB and TnT levels were observed in the RFP group, suggesting that a larger infarct predisposed to the development of RFP. In a multivariate analysis, CK was an independent predictor of RFP, similar to a previous study in STEMI patients that demonstrated a correlation between peak CK and infarct size.

There are several limitations given that this is a single-centre retrospective study with an overall low event rate; nevertheless, we believe our results are clinically important and warrant further study. While the timing of echocardiograms was variable, the percentage of RFP (~20%) was similar to that reported in other studies. Patients with HT and diabetes may have pre-existing DD; however, similar proportions of patients with HT and DM were present in RFP and non-RFP groups. We acknowledge that the modest cohort size increases the likelihood of a type 2 error. However, the weight of previous data on the adverse effects of RFP on cardiac outcomes suggest that this is unlikely.

This study demonstrates that RFP was a determinant of cardiac and all-cause mortality at a median follow up of 5 years post-STEMI treated by PCI. While the evaluation of diastolic function following PCI for STEMI is an evolving area, these preliminary results are interesting but require validation in larger patient cohorts.
Brief Communications

References


Supporting information

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

Figure S1 Cumulative incidence of outcomes among the study patients between RFP and non-RFP groups. Kaplan–Meier survival curves are shown for (A) cardiac death; (B) all-cause death. P values were calculated using log–rank test.

Table S1 Clinical outcomes at 5 ± 2 years follow-up after index STEMI.
Left atrial appendage occlusion with the Watchman device in a patient with paroxysmal atrial fibrillation and intolerance of all forms of anticoagulation due to hereditary haemorrhagic telangiectasia

R. Spina and B. Gunalingam

Department of Cardiology, St Vincent’s Hospital, Sydney, New South Wales, Australia

Key words
left atrial appendage occlusion, Watchman device, hereditary haemorrhagic telangiectasia, secondary stroke prevention, stroke prevention in atrial fibrillation.

Abstract
An elderly woman presented to our attention because of paroxysmal atrial fibrillation and cerebrovascular events requiring systemic anticoagulation and a concomitant, serious bleeding diathesis (the Osler-Weber-Rendu syndrome, or hereditary haemorrhagic telangiectasia). Her risk of suffering a major stroke was significant given a CHA2DS2-VASc score of 6. However, she was unable to tolerate any form of anticoagulation because of torrential epistaxis and previous gastrointestinal haemorrhage on antiplatelet therapy. We proceeded with percutaneous occlusion of the left atrial appendage with a Watchman device. Ten months post-procedure she is well, without recurrence of neurological symptoms, and off all forms of anticoagulation. The current internationally accepted practice post-deployment of the Watchman device mandates warfarin transition for 6 months to allow for endothelialisation of the device. However, there is no evidence in the literature to support left atrial appendage occlusion without any peri-procedural antiplatelet and anticoagulation therapy and therefore our case represents novel and important anecdotal evidence that secondary stroke prevention with left atrial appendage occlusion may be effective and safe even in patients who cannot tolerate any form of anticoagulation at all.

An 82-year-old woman presented to our attention in October 2012 because of paroxysmal atrial fibrillation (AF) and transient ischaemic attacks requiring systemic anticoagulation and a concomitant, serious bleeding diathesis. She suffered from the Osler-Weber-Rendu syndrome, or hereditary haemorrhagic telangiectasia (HHT), an autosomal dominant disease characterised by vascular anomalies, such as telangiectasia and arteriovenous malformations (AVM), affecting multiple organs, including the skin, the lungs, the gastrointestinal tract, the liver and the brain.1,2 Our patient had diffuse cutaneous telangiectasia, frequent episodes of epistaxis, sporadic episodes of gastrointestinal haemorrhage, but no evidence of cerebral, hepatic or pulmonary AVM. As a result, she had developed chronic iron-deficiency anaemia requiring continuous oral iron supplementation and regular three monthly iron infusions. Her father had been diagnosed with the Osler-Weber-Rendu syndrome, but neither of her two children had been affected. Her past medical history included thoracic vertebral osteomyelitis with associated epidural abscess, and hypertension. She was widowed, lived alone with minimal assistance in domestic tasks and mobilised independently.

One month prior, she had presented to a regional hospital with left hand clumsiness of rapid onset, which resolved within 15 min. Two months prior, she presented to medical attention because of transient paraesthesia and numbness in the left arm, which were followed by a brief episode of shaking in the left arm. Magnetic resonance imaging of the brain revealed established infarcts in the right frontoparietal and left frontal lobes, and no evidence of cerebral AVM. She recovered without sequelae from her neurological events, and was discharged home on dual anti-platelet therapy (DAPT) with aspirin and clopidogrel. However, both agents had to be discontinued days after commencement because of torrential epistaxis. Although sinus rhythm was documented on electrocardiography at the time of hospital admission, subsequent Holter monitoring detected paroxysms of AF. A transthoracic echocardiogram demonstrated normal left ventricular size and function, and detected no intracardiac thrombus. Transoesophageal echocardiography excluded the presence of left atrial appendage (LAA) thrombus, patent foramen ovale and...
Our patient underwent percutaneous left atrial appendage occlusion (LAAO) with a Watchman device through the left femoral vein. The procedure was uncomplicated, and satisfactory occlusion of the LAA was achieved on device deployment (Fig. 1). The current standard postoperative anticoagulation regimen mandates warfarin and DAPT cover for 45 days, followed by long-term aspirin. We decided to treat her with aspirin only post-procedure because her bleeding risk on warfarin and DAPT were perceived to be excessively high. However, the aspirin had to be ceased 1 week post-LAAO due to recurrent, disabling epistaxis. Ten months post-procedure, she is well, off all forms of anticoagulation and has not experienced recurrence of her neurological symptoms.

Neurological manifestations of HHT include cerebral haemorrhage associated with ruptured cerebral AVM, and cerebral infarct or transient ischaemia caused by shunting of thrombus or air from the venous to the arterial system through a pulmonary AVM. Screening for pulmonary AVM in HHT is usually accomplished with transthoracic echocardiography with the use of agitated saline contrast. A positive study is followed up by confirmatory high-resolution computed tomography scanning of the chest. Our patient, however, had no evidence of pulmonary AVM on prior chest imaging, and other common causes of non-cardioembolic stroke had been ruled out, thus making cardioembolism the most likely cause of her recurrent neurological symptoms.

Her management was problematic. Given her AF, her previous history of stroke and the increased risk of cerebrovascular events in patients with HHT, she was at significantly increased risk of a future major stroke. Her CHA2DS2-VASc score was 6, giving her an estimated annual risk of stroke of 9.8%. On that basis, long-term systemic anticoagulation was warranted. HHT is generally considered at least a relative, if not an absolute, contraindication to treatment with anti-platelet agents or oral anticoagulant therapy, although two recent studies have suggested that anticoagulation may be well tolerated by a small minority of patients with HHT. In those studies, anti-platelet therapy was associated with an increase in the patient-reported severity of epistaxis, whereas oral anticoagulation was associated with an increase in the patient-reported rate of other haemorrhagic events. However, our patient was unlikely to be able to tolerate long-term anticoagulation because of her propensity to develop severe, recurrent epistaxis on anti-platelet agents alone, and the prior history of gastrointestinal haemorrhage. This led us to consider alternative, non-pharmacological methods of reducing the risk of further cerebrovascular events in the context of AF, such as occlusion of the LAA. The LAA is the source of thrombus in more than 90% of patients with non-valvular AF, and exclusion of the appendage from the systemic circulation has been shown to reduce the risk of stroke in AF. LAAO may be performed through surgical ligation or through a percutaneous, catheter-based intervention.

The PROTECT AF trial has demonstrated the non-inferiority of catheter-based LAAO with the Watchman device compared with warfarin in reducing the risk of stroke in non-valvular AF, with acceptable complication rates. Medium-term follow-up studies have confirmed the non-inferiority and safety findings demonstrated in the original trials.

The inherent thrombogenicity of the implanted occlusion device underpins the rationale for the administration of anti-platelet and anticoagulant therapy following...
endovascular occlusion of the LAA. Device-related thrombosis occurred in 15 patients (3.5%) in the PROTECT AF trial, although only two of those patients experienced an ischaemic stroke as a result of it.6 Autopsy studies of canine and human hearts implanted with the Watchman device have demonstrated that at 45 days post-implantation, endothelial cells cover the device surface. By 90 days, a complete endocardial lining covers the former LAA ostium, and the sealed LAA cavity contains organising fibrous tissue and thrombus.7

Based on those studies, in the Watchman trials, warfarin was continued for 45 days post-procedure to allow for endothelialisation of the device surfaces, and was discontinued if complete seal of the LAA was demonstrated on transoesophageal echocardiography and no device-related thrombus was visualised. Following that, patients received aspirin 100–325 mg daily and clopidogrel 75 mg until 6 months post-procedure, followed by aspirin indefinitely.

However, the optimal anticoagulation strategy post-LAAO is not known and practices are evolving as evidence is accumulated. For example, the strategy described above is not desirable or is contraindicated in patients who cannot tolerate warfarin or anti-platelet therapy, such as the patient described above. A recent multicentre, prospective study has suggested that the Watchman device may be safely deployed without warfarin cover post-procedure, provided DAPT is administered for 6 months.8 However, the latter study is the first in the published literature to report such findings, and therefore the safety of Watchman implantation without warfarin transition needs to be evaluated further. In addition, there is limited evidence that LAAO with other devices may be safe with DAPT cover only in the peri-procedure period. A 5-year follow-up study of the PLAATO system, a device that does not require warfarin transition post-procedure, revealed a 3.8% annual stroke rate when the anticipated CHADS2 annual stroke rate was estimated at 6.6%.9 However, the PLAATO system is no longer commercially available. Experience with the recently developed Amplatzer Plug is still accumulating. Initial analyses suggest that implantation with DAPT cover only appears to be safe.10

However, there is no evidence in the literature to support LAAO without any periprocedural anti-platelet and anticoagulation therapy, and our case therefore represents novel and important anecdotal evidence that secondary stroke prevention accomplished by LAAO with the Watchman device may be effective and safe even in patients who cannot tolerate any form of anticoagulation at all.

References

Method for improving the quality of discharge summaries written by a general medical team

P. Russell,¹ U. Hewage¹ and C. Thompson²

¹Flinders Medical Centre and ²University of Adelaide, Adelaide, South Australia, Australia

Abstract

We developed a writing rubric that assessed the quality of four common errors found in the synopsis of a discharge summary: relevance, accuracy, clarity and presentation (R-A-C-P). We assessed the effect of an intervention that taught the essentials of discharge summary preparation. The intervention reduced the number of inadequate discharge summaries written by medical staff on a busy medical service. Writing the clinical synopsis of a discharge summary is a skill that can be taught quickly.

Written hospital discharge summaries are the most widely accepted practice for summarising patient management while in the hospital and communicating this information to other clinicians. There has been increased focus on this transfer of information, which reveals specific deficiencies.¹⁻³

The monitoring of the quality of information in discharge summaries is regarded as a responsibility of the treating consultant who is expected to scrutinise and correct the discharge summary before its distribution. This quality checkpoint can be variably attended (C. Thompson, pers. comm., 2010), leaving little accountability for this important area of information transfer. The quality of the summary’s content is more difficult to appraise reliably than the timeliness of its dispatch, even though the latter is easy to quantify and compare as a key performance indicator.

Much of the content and structure of a discharge summary can be generated automatically by an electronic medical record (EMR) system. Despite these improvements, significant deficits remain in the presentation, relevance, accuracy and clarity of the summary, which can potentially adversely affect the quality and safety of patient care.³ The aim of this study was to develop a strategy for assessing and improving the quality of discharge summaries.
Table 1 The rubric

<table>
<thead>
<tr>
<th>Category</th>
<th>Good</th>
<th>Acceptable</th>
<th>Unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance</td>
<td>Each problem is followed by a discussion which is limited to that particular subheading. Primary and all secondary diagnoses are active problems.</td>
<td>Each problem is followed by a discussion which is mostly about that particular problem, but strays a bit into discussing other problems. Secondary diagnoses with confusion with medical history.</td>
<td>So much rambling as to render the summary too difficult to understand; almost flight of ideas.</td>
</tr>
<tr>
<td>Accuracy</td>
<td>No inaccuracies</td>
<td>Not much factual information given, but what is present is generally accurate; minor inaccuracies: for example, ferritin listed as 57 is, in fact 45.</td>
<td>Inaccuracy that compromises future care. For example, troponin is listed as normal for the patient admitted for chest pain, when in fact it is grossly abnormal.</td>
</tr>
<tr>
<td>Clarity</td>
<td>All pertinent information included in PIE format: each Problem is discussed in terms of the Investigations, Interventions and End results</td>
<td>All critical information included, although not all secondary diagnoses listed are given a subheading and discussion; for example, peripheral arterial disease (an active disease) listed, but no in-hospital management listed.</td>
<td>It is necessary to read it several times to understand the meaning; crucial information omitted making the document in need of remediation. For example, an abdominal ultrasound to investigate the size of a AAA also discovered splenomegaly not mentioned in the DS; if the primary diagnosis is listed as a symptom (e.g. falls, shortness of breath, collapse, confusion).</td>
</tr>
<tr>
<td>Presentation</td>
<td>Problem-lists in the subheadings and arranged in order of importance, starting with the primary diagnosis.</td>
<td>Problems listed as subheadings, but in no particular order.</td>
<td>Complete disregard for subheadings; synopsis given in narrative format.</td>
</tr>
</tbody>
</table>

How we graded the quality of the clinical synopsis of the discharge summary: Our rubric was created with certain characteristics in mind. First, it must be easy to use; second, it must be memorable; and third, it must satisfy the basic requirements we gleaned from a variety of sources, including a literature search, our own experience reading discharge summaries and consultation with colleagues. We learned that discharge summaries at our hospital are inadequate for four basic reasons: the inclusion of irrelevance, important inaccuracies, the difficulty finding the area of interest in post-discharge follow up, and omission of important details. After perusal of several dozen discharge summaries, we developed the following rubric, which covers these four basic areas: relevance, accuracy, clarity and presentation. At first glance, the grading rubric below might seem clumsy and abstract. Most discussions regarding the quality of a particular discharge summary generally place it in one of three categories: really good; okay (‘it will do’); or substandard and in need of remediation. From this, we decided to give a numerical grade to express what we were qualitatively describing. Three numerical categories to represent these three qualitative distinctions. However, this could be easily modified to a simple pass or fail binary system, especially if the clearest goal of the assessing is to identify those house officers with difficulty communicating.

For each category in this rubric, a score was given: 0 = synopsis requires substantial review from the writer before final distribution of the discharge summary; 1 = meets minimum requirement; and 2 = exemplary standard. A score of 1 or 2 indicated the summary was acceptable for that category.

The intervention consisted of a 30-min training session of five interns during their first week of general medicine service. We emphasised the need (i) for a structured problem-based synopsis rather than one that is a free-ranging narrative; (ii) for a brief discussion of each problem, P-I-E (list the Problem, then discuss the Investigations and/or Interventions, followed by the End result); (iii) to be clear about the principal diagnosis, listing a pathological diagnosis rather than a symptom or clinical syndrome whenever possible (e.g. ischaemic cardiomyopathy is a better diagnosis to list than congestive heart failure; ‘falls’ is not a pathological diagnosis, but Parkinson disease is); and (4) in the list of secondary diagnoses, to list only the problems relevant to this admission, rather than all past problems that the patient has ever experienced. We used examples of poorly written summaries to demonstrate what to avoid, and well-written ones for inspiration.

The hospital charts and corresponding discharge summaries from 80 randomly selected patients admitted during the 12 months before the intervention and from 60 randomly selected patients admitted during the 10 weeks following the intervention were scrutinised. We included any patients whose charts and summaries were written by a general medical team regardless of their possible exposure to the intervention. Cases were...
excluded if: (i) no summary was completed; (ii) patients were admitted to general medicine but discharged from a different service; (iii) patients died during hospitalisation; and (iv) patients were transferred to a different hospital.

Each discharge summary was scrutinised by a single assessor who applied the rubric and scoring method while comparing the summary with the corresponding admission and progress notes in the hospital chart.

In analysing the differences in category scores between the pre- and post-intervention discharge summaries, non-parametric methods were used, Chi-squared for binary data and Mann–Whitney test for continuous data. Statistical significance was denoted by a $P < 0.05$. All calculations were performed with Excel (Microsoft, Redmond, WA, USA). This study was approved by the hospital ethics committee.

Of summaries written prior to the intervention, only 9 of 56 (16%) were considered acceptable (score 1 or 2) in all four categories; the rest should have required remediation to be considered safe. After the intervention, 24 of 50 summaries (48%) were graded as acceptable in all four categories ($P = 0.0001$).

Prior to the intervention, 93% of the summaries were acceptably accurate and 66% were acceptably relevant. Few were acceptable in terms of their clarity (23%) or presentation (18%) (Fig. 1). After the intervention, the percentages of summaries acceptable in terms of accuracy (96%) and relevance (72%) were unchanged, but the percentages acceptable in terms of clarity (62%) and presentation (62%) had improved significantly ($P < 0.001$) for both comparisons.

This study has identified several important issues relating to the creation of acceptable discharge summaries. We have developed a quality rubric and educational intervention for improving and evaluating the quality of discharge summaries written by busy medical staff within a hospital’s general medical service. The intervention was more effective at improving certain attributes of the summary than others. The study has limitations in relation to the following: being a non-blinded, single assessor, single-centre study; potential bias of judging the efficacy of an intervention of our own design; the use of a non-validated rubric; and no assessment of intra-rater reliability.

Our findings have several implications for clinical practice. The desired quality of certain summary attributes may be easier to teach than others using this intervention. The standards regarding presentation and clarity might have been the easiest to understand. The persistence of inappropriate (i.e. irrelevant) diagnoses in the list of secondary diagnoses may have contributed to the relative lack of improvement in relevance, which is a difficult concept to teach. Accuracy was acceptable 93% of the time prior to intervention so there was little room for improvement, which is in contrast to other studies that have reported major deficits in accuracy. The failure to improve this attribute might reflect the limitations of a younger authorship (interns), not always directly involved in the care of the patient.

Although discharge summary completion rates have been used primarily as a measure of patient safety, critically reviewing the discharge summary also provides an opportunity to educate junior doctors and improve their communication skills. Consultant review of the discharge summary provides a quality checkpoint for accuracy as well as a means for assessing the skills of the junior doctor. Our rubric for grading a discharge summary is in line with other assessment tools used in medical education and provides the user with examples in order to make grading easier. Consultant review of the summary can provide the trainee with effective and ongoing feedback about their performance in written communications and understanding and synthesis of clinical problems, and identify those in need of help.

Many of the inputs necessary for creating high-quality discharge summaries have been automated within our
hospital EMR. This automation greatly improves accuracy and completeness in regard to dates of admission and discharge, complications, discharge destination, and medication lists. At the same time, however, the EMR fails to discourage certain practices that can compromise quality, perpetuating errors rather than correcting them. For example, one flaw in the software underpinning our study was the carry-over of secondary diagnoses from one admission to the next without any forcing function that rechecks the relevance or accuracy of such diagnoses. Moreover, much of the data required for the summary are being inserted at the computer terminal based on recorded notes rather than at the bedside based on history-taking.

Another consideration, recently highlighted by Chin et al., is how suboptimal quality of discharge summaries can negatively impact the level of reimbursement for services provided, as a result of incomplete coding of primary and/or secondary diagnoses that are poorly documented in the discharge summary.12

In conclusion, this report shows that the use of a simple rubric and educational intervention targeting common flaws in discharge summary preparation can reduce the number of unsatisfactory discharge summaries.

References
PERSONAL VIEWPOINT

General medicine advanced training: lessons from the John Hunter training programme

D. Jackel,1 J. Attia1,2,3 and R. Pickles1,2

1Division of Medicine, John Hunter Hospital, 2Hunter Medical Research Institute and 3School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia

Key words
internal medicine, physician, specialist, graduate medical education, medical education, general medicine.

Abstract
Recent years have seen a rapid growth in the number of advanced trainees pursuing general medicine as a specialty. This reflects an awareness of the need for broader training experiences to equip future consultant physicians with the skills to manage the healthcare challenges arising from the demographic trends of ageing and increasing comorbidity. The John Hunter Hospital training programme in general medicine has several characteristics that have led to the success in producing general physicians prepared for these challenges. These include support from a core group of committed general physicians, an appropriate and sustainable funding model, flexibility with a focus on genuine training and developing awareness of a systems approach, and strong links with rural practice.

General medicine training in Australia and New Zealand is overseen by the Royal Australasian College of Physicians (RACP) and is now formally called general and acute care medicine, in recognition of the central role of general physicians in acute care medical practice. General medicine is now the largest subspecialty advanced training programme in both Australia and New Zealand, with advanced trainee numbers in Australia increasing from 110 in 2008 to 357 in September 2013, with a further 198 current trainees in New Zealand, compared with 174 in 2008. New Zealand has continued its tradition of having a much higher overall proportion of advanced trainees undertaking general medicine training than Australia.

The recent growth in general medicine training, and the reopening of departments of general medicine in some Australian hospitals, is redressing the decline in general medicine that was evident as greater subspecialisation took place. The 2005 joint position paper between the Internal Medicine Society of Australia and New Zealand (IMSANZ) and the RACP documented this decline and promulgated strategies for restoring general medicine training and practice. These strategies included strengthening hospital departments in general medicine, and formalising a structured programme of training and continuing professional development for general physicians.

Approximately 80% of Australian general medicine trainees are co-enrolled in a second subspecialty, referred to as dual training. In Australia, the largest growth in general medicine training has been in Queensland, Victoria, and South Australia, with New South Wales (NSW) underrepresented compared with its proportion of the Australian population. This growth is beginning to be reflected by a commensurate increase in new Fellows of the RACP qualified as general physicians. The most common dual training programmes currently undertaken by general medicine advanced trainees are in geriatrics, endocrinology, respiratory and sleep medicine, infectious diseases, and gastroenterology.

Trainees in general medicine are required to undertake 2 years of core training, followed by a third non-core year, or the additional core requirements of their second specialty in the case of dual trainees. Dual trainees can complete dual training in a minimum of 4 years, or 5 years in the case of those undertaking dual training in nephrology or cardiology, where core requirements have recently increased from 2 to 3 years.
General medicine core requirements include the following: ²
- 6 months in a general medicine unit
- 6 months ‘A’ rotation (acute medicine unit, emergency medicine, intensive care unit, acute cardiology and acute respiratory units)
- 6 months ‘B’ rotation (most other specialties with inpatient and outpatient focus, e.g., gastroenterology, neurology and nephrology)
- 6 months ‘C’ or further ‘B’ rotation (‘C’ rotations include endocrinology, immunology/allergy, palliative care, research, administration and education)

A problem increasingly experienced by general medicine trainees as trainee numbers have increased is that of access to subspecialty rotations, which are required in order to complete a balanced training programme. The recent change to three core years training by some subspecialties is expected to exacerbate this problem.

The RACP has developed a general medicine working group to consider national registration issues for general physicians in Australia, as well as general medicine training and workforce issues. The RACP, in partnership with the NSW Ministry of Health, has established a western NSW dual training pilot programme to create another structured pathway for dual training in general medicine and a second subspecialty. This pilot is specifically targeting trainees interested in rural practice.

**Description of the John Hunter general medicine training programme**

Hunter New England Local Health District (HNELHD) provides healthcare to the regional city of Newcastle, and the Hunter and New England regions of NSW. It covers an area of 130 000 km² with a population of approximately 880 000. The population is diverse with a broad spread among metropolitan, rural and remote locations. Around 20% of the indigenous population in NSW live within the health district catchment. The HNELHD has the state’s most complex system of hospitals including 10 general practitioner-led community hospitals, 12 district hospitals with occasionally resident medical specialists, and 2 tertiary referral hospitals both of which are in Newcastle. The HNELHD employs around 1500 medical practitioners and has approximately 70 trainees undertaking basic physician training.

The current general medicine advanced training programme in the Hunter region began in 2007. It was initially funded by the local health district, and has more recently utilised Federal Specialist Training Program (STP) funding. The intake for each year since inception has typically been three trainees. Eleven general physicians have gained Fellowship of the RACP, of whom eight also undertook dual training in a second subspecialty. A further 11 trainees are currently undertaking advanced training, two of whom have received RACP Fellowship. The majority of trainees were locally recruited, and most have gone on to practise either within the HNELHD, or in other rural or regional areas of Australia (Table 1).

Our programme is 3 years in duration for pure general and acute care medicine trainees, or 2 years for dual trainees (within four or more total years of advanced training). Trainees have typically completed the first year or two of their advanced training in general medicine, and then undertaken their subspecialty training, although much flexibility has been afforded to enable trainees to access dual training as it becomes available either locally or in other training centres. In most cases, those who have left after the first core year of general medicine to pursue a second subspecialty have returned to complete their second core year; only 2 of 11 so far who have finished training have decided not to complete their general medicine accreditation. The development of prospective dual training enrolment and accreditation, such as that in the western NSW pilot programme, would greatly enhance security for trainees and training networks in this regard.

A requirement of our STP funding is that each trainee spends a minimum of 6 months training in a rural area. This is typically undertaken at one of our medium-sized rural hospitals where admissions are usually with a general medicine model, with subspecialty consulting where required and available.

**Lessons for success**

We believe there are six core features of our training programme that have seen it develop as a successful and sustainable training model for general physicians. We see our success as being reflected by the high completion rates of our trainees in both general medicine and the subspecialty of their choice, and the high retention rates on completion of training. Many of the trainees who have not stayed in our network have settled in rural areas that are well served by physicians with diverse clinical and professional experiences.

1. Ongoing support of a core group of committed general physicians: Our network is fortunate to have a large number of physicians with broad experience in general medicine. Unlike many large hospitals in NSW, Newcastle maintained strong general medicine units at a time when many Sydney hospitals closed theirs. Our physicians are from diverse backgrounds both personally and...
professionally, and most also practise a second subspecialty. There is strong professional commitment to the programme as it is seen as a ‘good fit’ for our patient population, particularly with the demographic trends of ageing and increasing comorbidity levels. There are several ‘champions’ of general medicine, in the past and present, many with active positions in the RACP, who have been strong advocates of general medical practice, helping establish it as a legitimate training choice. This has not been a result of serendipity but may perhaps have been forged as a consequence of numerous attempts to close the general medicine department; the dedicated efforts of key general medicine ‘believers’ over the years lend truth to the aphorism that ‘what doesn’t kill you makes you stronger’.

2 The right funding model: In our programme, funding follows the trainees. This provides security for them and flexibility for the network. Trainee-based funding has specifically enhanced the access of general medical trainees to subspecialty terms. Through bringing their own funding, trainees are extremely attractive to subspecialty departments; difficulties accessing subspecialty rotations are a noted barrier with other general medicine training models in Australia. Additionally, the capacity for some transferability of funding between trainees has enabled trainees to alter the order of their advanced training years, especially where an opportunity for a dual training subspecialty post has arisen. There is a risk that continuity of care of patients, and negative impacts on basic physician trainees, could occur with advanced trainee movements. However, in our hospital, advanced trainees rotate between teams, and at any given time most general medical teams are without an advanced trainee minimising the potential disruption.

3 A genuine training position: Our training programme is grounded in a strong philosophical belief in the value of general medicine and that broad training experiences improve the skill base of our total physician pool. Hence, diverse training experiences have been encouraged and nurtured, whether through enabling subspecialty rotations or dual training, or in the support of more novel training experiences, such as a rotation in East Timor (designed to establish a bronchoscopy service). The importance of providing cost-conscious, high-quality evidence-based care is promoted through a formal programme of evidence-based medicine and clinical epidemiology tutorials during the first year of advanced training. Trainees are strongly supported with their research pursuits and have access to broad basic sciences, epidemiology and biostatistical resources available through the Hunter Medical Research Institute, the third largest medical research organisation in NSW.

<table>
<thead>
<tr>
<th>Year of RACP Fellowship and/ or current training year</th>
<th>Second subspecialty</th>
<th>Further study during advanced training</th>
<th>Completed 2 years of core general medicine training?</th>
<th>Current place of practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Nuclear medicine</td>
<td>—</td>
<td>Yes</td>
<td>Newcastle</td>
</tr>
<tr>
<td>2009</td>
<td>Gastroenterology</td>
<td>—</td>
<td>Yes</td>
<td>Taree, NSW</td>
</tr>
<tr>
<td>2010</td>
<td>Gastroenterology</td>
<td>—</td>
<td>No</td>
<td>Canberra</td>
</tr>
<tr>
<td>2010</td>
<td>Gastroenterology</td>
<td>PhD</td>
<td>No</td>
<td>Canberra</td>
</tr>
<tr>
<td>2011</td>
<td>Endocrinology</td>
<td>—</td>
<td>Yes</td>
<td>Newcastle</td>
</tr>
<tr>
<td>2010</td>
<td>Respiratory and sleep medicine</td>
<td>—</td>
<td>Yes</td>
<td>Newcastle</td>
</tr>
<tr>
<td>2012</td>
<td>Respiratory and sleep medicine</td>
<td>—</td>
<td>Yes</td>
<td>Taree, NSW</td>
</tr>
<tr>
<td>2012</td>
<td>—</td>
<td>PGCertCU‡</td>
<td>Yes</td>
<td>Mackay, Queensland</td>
</tr>
<tr>
<td>2013</td>
<td>—</td>
<td>MPH§</td>
<td>Yes</td>
<td>Newcastle</td>
</tr>
<tr>
<td>2012/Year 5</td>
<td>Respiratory and sleep medicine</td>
<td>GDipClinEpid¶</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>2012/Year 5</td>
<td>Cardiology</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Year 4</td>
<td>Gastroenterology and hepatology</td>
<td>—</td>
<td>Pending</td>
<td>—</td>
</tr>
<tr>
<td>Year 3</td>
<td>Endocrinology</td>
<td>—</td>
<td>Pending</td>
<td>—</td>
</tr>
<tr>
<td>Year 3</td>
<td>Gastroenterology and hepatology</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Year 3</td>
<td>Respiratory and sleep medicine</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Year 2</td>
<td>Endocrinology</td>
<td>MClinEpid††</td>
<td>Pending</td>
<td>—</td>
</tr>
<tr>
<td>Year 2</td>
<td>Geriatrics</td>
<td>—</td>
<td>Pending</td>
<td>—</td>
</tr>
<tr>
<td>Year 1</td>
<td>Cardiology†</td>
<td>MClinEpid††</td>
<td>Pending</td>
<td>—</td>
</tr>
<tr>
<td>Year 1</td>
<td>Neurology</td>
<td>MClinEpid††</td>
<td>Pending</td>
<td>—</td>
</tr>
<tr>
<td>Year 1</td>
<td>Cardiology</td>
<td>—</td>
<td>Pending</td>
<td>—</td>
</tr>
</tbody>
</table>


© 2014 The Authors
Internal Medicine Journal © 2014 Royal Australasian College of Physicians
service provision is recognised as a key component of competency-based development as a consultant physician, trainees are afforded protected time to enable the pursuit of their research and teaching interests. From the initiation of their training, our advanced trainees act as junior consultants in terms of on-call responsibilities. This actively fosters the progression, in a supported environment, from basic training towards professional practice as a consultant physician.

4 Strong links with rural practice: The HNELHD has ample opportunities for rural and regional practice. The formal requirement in our programme for 6 months of rural training exposes trainees to inpatient and outpatient services in rural areas, and also to rural lifestyles. Trainees also participate in drive, or fly-in-fly-out, clinics at several Aboriginal medical services within our region. These clinics offer rurally based indigenous people, often with complex comorbid disease, access to specialist care with a strong focus on a holistic, context-specific approach. Similarly, trainees attend non-indigenous outreach clinics in rural areas promoting resourcefulness in practice and a more nuanced understanding of the difficulties of practice in less resource-intense environments. Trainees typically report strong satisfaction with involvement in these clinics both in terms of the medical challenges and professional development experiences. Indeed, 5 of 11 graduates of our programme have filled positions in rural and regional Australia outside the Hunter region.

5 Flexibility: Every trainee is seen as an individual with different interests and aspirations. Leadership of the programme reflects a belief in diverse, holistic medical practice and has led to the support of a different training experience for each trainee. While many trainees have chosen to undertake dual subspecialty training during their non-core/elective year, others have been supported in the pursuit of further qualifications, such as Master of Public Health, Master of Clinical Epidemiology or Postgraduate Certificates in Clinical Ultrasound. Trainee-based funding means that trainees also have the flexibility to choose from a wide range of clinics and subspecialty rotations, to complement any gaps in their training to date. A supportive departmental attitude towards flexibility for trainees does bring with it the risk of institution service disruption, and at worst the possibility of trainee loss if they failed to return to complete their general medicine training. To date, however, this has not been a major issue, and it is possible that our trainees have repaid us with loyalty in response to the flexibility and support shown to them.

6 Fostering awareness of a systems approach: The IMSANZ and RACP-led refocus of general medicine training to promote acute care exposure has seen the strong involvement of our advanced trainees in local emergency departments where they actively target impending medical admissions, and coordinate acute care for general medical and subspecialty medical patients. Our trainees have become involved in health services research, for example evaluating the impact of recent changes in acute medical units and their own role in these. Advanced trainees have also played a role in helping develop strategies to meet National Emergency Access Targets through adapting the nature of their position to be a potent resource for earlier senior medical decision-making; their involvement has contributed to recent strong performance in this regard by reducing emergency department length of stay for general medical patients. Discussions with trainees have revealed that involvement in these issues during this early stage of their advanced training has raised awareness of the systems of care, and fostered a sense of empowerment and willingness to change processes where necessary, rather than a ‘powerlessness’ or cynicism with ‘bureaucracy’.

Conclusions

In summary, the structure of our general medicine training programme has made it both desirable to trainees and sustainable for our health service; several key features have enabled this. Trainees completing our programme are choosing to practise as general physicians, and often in a second subspecialty, in our region or in other regional or rural areas of Australia. This is taking place as our programme has enabled skills matching between our trainees and the patient mix, and hence specialist medical workforce requirements, across much of Australia. This skills matching is likely to become even more critical in this era of an ageing population, whose health is dominated by non-communicable chronic disease with the associated high levels of comorbidity, demanding broad medical skills for the delivery of excellence in patient care. The capacity of general physicians to deliver equivalent patient outcomes to subspecialty physicians, at lower cost, provides ongoing impetus to foster general medicine training programmes across Australia and New Zealand.

References

1 Internal Medicine Society of Australia and New Zealand and the Royal Australasian College of Physicians.

2 Royal Australasian College of Physicians.


© 2014 The Authors

Internal Medicine Journal © 2014 Royal Australasian College of Physicians

305
LETTERS TO THE EDITOR

Clinical-scientific notes

Lymphangioma: an unusual cause for a non-functioning adrenal mass

Elucidation of the nature of large cystic adrenal masses mandates exclusion of malignancy, in addition to evaluation of secretory function. This case report describes the clinical history, imaging and pathology of a very rare cause of a large cystic adrenal mass, the adrenal lymphangioma.

A 23-year-old woman presented to the emergency room with sudden onset of right upper quadrant abdominal pain and loin tenderness. Physical examination demonstrated normal blood pressure and no features of hypercortisolism or hyperandrogenism.

Computed tomography (CT) showed a lobulated, septated mass arising from the right adrenal measuring $52 \times 25 \times 27$ mm, with fluid attenuation and no enhancement (Fig. 1a). Serum electrolytes and androgens were normal, as were 24-h urinary catecholamines (metanephrine, normetanephrine, adrenaline and noradrenaline) and cortisol levels.

Surgical resection was undertaken using a laparoscopic approach. The multiloculated mass measured $37 \times 27 \times 22$ mm, weighed 12.7 g, with cystic areas filled with clear gelatinous and haemorrhagic material (Fig. 1b). Postoperative recovery was uneventful.

Microscopy demonstrated an adrenal lymphangioma. The adrenal cortex and medulla were distorted by large

Figure 1 (A) Abdominal computed tomography showing a lobulated right adrenal mass arising from the right adrenal gland. (B) Excised mass weighing 12.7 g. (C) Haematoxylin and eosin stained section at ×40 magnification. (D) Haematoxylin and eosin stained section at ×100 magnification.
fibrous-walled cysts, lined by a single flattened layer of attenuated cells (Fig. 1c,d) without evidence of cytological atypia. There were lymphatic vascular channels, separated by fibrous material; some contained aggregates of adrenal cells. Immunoperoxidase staining showed positive staining for factor VIII and D2-40 immunostain; epithelial markers (AE1/AE3, CAM 5.2) and CD34 were negative.

Cystic adrenal masses have an incidence approximating 0.06% of the general population.1 Within the differential diagnosis of these lesions, adrenal lymphangiomas are a very rare cause. Lymphangiomas are benign tumours of the lymphatic system, arising from malformations originating in embryogenesis.2 They are characterised by thin-walled, cystic lesions lined by endothelial cells and filled with lymph fluid.2 The literature suggests that adrenal lymphangiomas are more frequently right-sided, with a female predominance.3

While most adrenal lymphangiomas are clinically asymptomatic,3 patients can present with flank pain, gastrointestinal symptoms or a palpable mass, relating to the size and position of the cyst.4 The lack of distinctive symptoms and laboratory findings make preoperative diagnosis challenging.5 The acute pain presentation of this case may have occurred due to bleeding into a cyst.

Adrenal lymphangiomas on CT imaging are characteristically non-enhancing, hypodense masses with an appearance indistinguishable to other cystic adrenal lesions, including cystic pheochromocytoma and adrenal cortical carcinoma.6 Surgical resection is usually necessary to distinguish these benign lesions from potentially aggressive malignant lesions, in addition to relieving symptoms.3

A possible diagnosis of a lymphangioma should be considered when a hypodense, non-enhancing cystic, non-functioning adrenal mass is found in youth or middle age. Histological diagnosis of non-functioning adrenal masses must be undertaken with care, preferably in a unit specialising in endocrinology or endocrine surgery. As the differential diagnosis of larger non-functioning masses includes adrenal or metastatic carcinoma, excision biopsy is preferred, rather than fine-needle aspiration biopsy.3,4 Due to the rarity of these tumours, their natural history is not known. Whether these tumours may be observed (after evaluation of functional status and exclusion of malignancy) is not known.

Received 24 June 2013; accepted 3 October 2013.
doi:10.1111/imj.12361

E. Blanchard,1 P. Brenner,2 W. Delprado3 and K. Samaras1,4
1Diabetes and Obesity Program, Garvan Institute of Medical Research, Departments of 2Urology and 4Endocrinology, St Vincent’s Hospital and 3School of Medicine Sydney, Notre Dame University, Sydney, New South Wales, Australia

References

Recurrence of Carney complex atrial myxoma causing embolic stroke

Carney complex is a rare genetic disease that can lead to the formation of multiple atrial myxomas. These tumours have the propensity to fragment, causing strokes and other embolic events. We present the case of a patient who suffered a stroke due to recurrence of a Carney complex atrial myxoma.

A 58-year-old woman presented to the emergency department following a collapse with no associated loss of consciousness. In the department, she was confused and agitated, and reported blurred vision. A neurological examination revealed a left-sided motor deficit, visual agnosia and perseveration.

The patient had a known diagnosis of Carney complex. She had previously undergone surgical excision of myxomas of her left atrium, bowel and uterus, as well as
bilateral adrenalectomies for cortisol-secreting tumours. The previous left atrial myxoma had been excised 21 years prior to this presentation. Her last screening transthoracic echocardiogram was performed 2 years prior to this presentation when she underwent excision of her uterine myxoma. This showed no recurrence of cardiac myxoma. Before this, she had been lost to follow up after moving interstate 6 years previously.

Initial non-contrast brain computed tomography showed no acute haemorrhage or gross ischaemia; however, the images produced were noted to be of poor quality due to movement artefact. Over the next day, her symptoms resolved and she was able to undergo brain magnetic resonance imaging. This showed extensive chronic and acute cardioembolic infarcts involving multiple cerebral artery territories (Fig. 1).

Following this, transthoracic echocardiography was performed, which showed a large left atrial mass, suspicious of atrial myxoma. This was confirmed with transoesophageal echocardiography and cardiac magnetic resonance imaging. The patient was then referred to the regional cardiothoracic centre for definitive excision of the tumour.

Carney complex is an autosomal dominant condition that predisposes the affected individual to skin lentigines, myxomas of the heart and skin, and a wide variety of endocrine tumours. It has two known genotypes: a mutation of the tyrosine kinase PRKAR1A gene located at 17q23-24 and several mutations located at 2p16. The phenotypes of these two genotypes are indistinguishable. Carney complex accounts for only a small proportion of all atrial myxomas. Since the condition was first
described in 1995, only around 500 cases have been recorded.\(^1\)

Atrial myxomas, while histologically benign, can nevertheless cause significant morbidity by impairing cardiac output, or by fragmenting and causing embolic events. Diagnosis of intracardiac tumours is with echocardiography with the transoesophageal approach having a sensitivity demonstrated up to 100%.\(^2\)

The patient described in this case report had a primarily histological diagnosis for myxoma as she had tested negative for the PRKAR1A mutation. She is now under ongoing surveillance by the local cardiology team, with her next echocardiogram due in 2 years time. The hereditary nature of the disease was discussed with the patient and her family. They did not want to undergo screening echocardiography at that time but were happy to be referred to a clinical geneticist for ongoing follow up.

Stroke or transient ischaemic attack from cardiac myxoma emboli is a condition that, if incorrectly diagnosed, can lead to inappropriate treatment with anticoagulation as opposed to surgical resection. Despite atrial myxoma being a fleetingly rare condition, with a prevalence estimated at 0.0005–0.015\%,\(^3\) it should be considered in all patients presenting with stroke or transient ischaemic attack without an obvious precipitous cause. Furthermore, for patients with a previous history of Carney complex atrial myxoma presenting with abnormal neurological findings, a diagnosis of recurrence of the myxoma should be considered.

Acknowledgement
Gold Coast University Hospital radiology department for the assistance with radiographs for inclusion in the article.

Received 11 October 2013; accepted 4 December 2013.
doi:10.1111/imj.12365
Gold Coast University Hospital, Southport, Queensland, Australia

References

Ventricular fibrillation storm in a young man with early repolarisation abnormality: the role of isoprenaline and quinidine

A 28-year-old man was admitted to the emergency department with refractory ventricular fibrillation (VF) requiring repeated shocks from an implantable cardioverter defibrillator (ICD).

He originally presented with an out-of-hospital VF arrest 6 years earlier and underwent implantation of a single-chamber ICD. He was otherwise well with no family history of premature sudden cardiac death. The presenting electrocardiogram (ECG) demonstrated 1 mm of J-point elevation in lead III. Transthoracic echocardiogram, stress thallium and flecainide challenge were unremarkable. Over the next 6 years, he received appropriate shocks for VF on three occasions, having trialled atenolol and sotalol.

He presented to the hospital in near-intractable VF having woken feeling not unwell. ECG prior to each VF episode revealed more marked inferior J-point elevation (Fig. 1a) than seen previously.

In the emergency department, VF was recurrent despite amiodarone, magnesium, lignocaine and overdrive pacing through the ICD at 110 b.p.m. VF became incessant with unsuccessful ICD and external defibrillation. Cardiopulmonary resuscitation was commenced, and the patient was intubated and placed on venoarterial extracorporeal membrane oxygenation (ECMO) support.
Figure 1  (A) Marked inferior J-point elevation preceding degeneration into coarse ventricular fibrillation (VF). (B) Electrocardiogram recording immediately following conversion of VF to sinus rhythm (on isoprenaline), with unifocal triggering ventricular premature beat seen.
Next, procainamide was administered, and three more shocks were unsuccessful. While preparations were made for urgent electrophysiology study with a view to targeting the responsible triggers, isoprenaline was tried. Intravenous isoprenaline at a 10-mcg bolus and 4 mcg/min infusion was commenced with a single shock then restoring sinus rhythm. An ECG post-reversion demonstrated unifocal triggering ventricular ectopics, likely originating from the left ventricular posterior Purkinje or papillary muscle (Fig. 1b).

Quinidine was commenced soon after, and within hours only rare ventricular ectopy was present and an electrophysiology study was no longer pursued. Isoprenaline and ECMO were weaned after 48–72 h and the patient was extubated. The patient made a complete neurological recovery and was discharged following ICD generator replacement. There was significant resolution of the inferior J-point elevation on quinidine.

Early repolarisation (ER) is defined as the elevation of the QRS-ST junction (J-point) in at least two leads, manifested as notching or slurring of the terminal portion of the R wave (J wave). While ER is a common finding in 5% of the population, Haïssaguerre made the seminal observation of ER in the inferior or inferolateral leads in 31% of patients with idiopathic VF. Patients with ER and Brugada syndrome are the most vulnerable to events at rest or during nocturnal hours, with the responsible ion channel abnormality involving the transient outward current Ito. Despite its life-saving impact in patients with ventricular arrhythmias, quinidine is of limited availability in Australia.

Short-coupled ventricular ectopics arising from the Purkinje network play a key role in the initiation and perpetuation of VF in these patients. These triggers have been successfully ablated in patients with ‘idiopathic VF’, and catheter ablation would be indicated if VF was recurrent despite quinidine or if it was not tolerated.

This case highlights the variable appearance of ER in a patient with idiopathic VF and the dramatic effects of isoprenaline and quinidine.

Received 15 September 2013; accepted 30 September 2013.
doi:10.1111/imj.12358

A. Voskoboinik, A. J. McLellan and P. M. Kistler
Department of Cardiology, Alfred Hospital, Melbourne, Victoria, Australia

References


© 2014 The Authors
Internal Medicine Journal © 2014 Royal Australasian College of Physicians
General correspondence

Professionalism, patient-centred care and revalidation

Phelps and Dalton suggest that the medical profession must move to a ‘patient-centred’ rather than profession-centred concept of professionalism. They suggest that revalidation of doctors may provide an opportunity to embrace and demonstrate this concept.

Yet revalidation of doctors is inherently profession-centred, and while it may contribute to public protection from a small number of poorly performing doctors, it is unlikely to contribute substantially to improved quality and safety in healthcare systems.

I believe that efforts to embed robust and routine processes into healthcare to measure more systematically quality, and to identify, monitor and investigate safety issues and adverse events, are more likely to be effective in improving healthcare and help it appropriately serve society.

Perhaps a question to be considered in the revalidation debate is the relative value of investment in revalidation of doctors or in robust ‘patient-centred’, outcome-focused measures, which will have the potential to have an impact on the health system for the benefit of all, not just those who need protection from poorly performing doctors.

It is our professional duty, if we are truly ‘patient-centred’, to ask this question.

Received 5 December 2013; accepted 17 December 2013.

doi:10.1111/imj.12355

G. Gabb
General Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia

Reference


Author reply

We welcome Gabb’s comment on our paper. We argue that the purpose of any revalidation process must be to reassure the community that as doctors we are practising at a level that both protects the community and meets both individual (patient-centred care) needs and broader community needs for care, which is effective and sustainable. We believe that demonstrating care that is patient-centred care is a paramount design principle in any process aimed at assessing the performance of doctors.

We are not suggesting that linking our concept of demonstrable professionalism to revalidation is the only mechanism to improve care, and agree that efforts to continually improve care processes are critical, but suggest that doctors taking individual responsibility for demonstrating their own performance in a way which makes sense to the community is a bedrock element of system improvement.

In doing so, we argue that the profession will minimise the risk of individual doctors failing to meet acceptable community and professional standards, but also maximise the likelihood of the profession doing what it can to contribute to the community’s need for a safe, effective and affordable healthcare system.

Received 1 January 2014; accepted 6 January 2014.

doi:10.1111/imj.12368

G. Phelps1 and S. Dalton2
1Deakin University Medical School, Geelong, Victoria and 2The Children’s Hospital at Westmead, Sydney, New South Wales, Australia

References


© 2014 The Authors
Internal Medicine Journal © 2014 Royal Australasian College of Physicians
General Medical Physician

A Specialist opportunity exists for General Medical Physicians with sub-speciality experience in Cardiology and/or Respiratory. Whangarei Hospital is the largest hospital in Northland, providing secondary care services for the region supported by three district hospitals. There are approximately 4,500 general medical admissions per annum with interesting, challenging and varied pathology.

The Department of Medicine has ten Physician positions sharing leadership of 3 teams consisting of 10 Medical Registrars and five House Officers. The department has a coronary care unit with 6 beds, two medical wards with 52 beds and a spacious outpatient facility. Transoesophageal imaging, exercise and pharmalogic stress testing is available, and a CT angiography will be launched March 2014.

For more information on the Consultant Physician vacancy, contact Dr Stephen Jennison, Head of Department Medicine. Email: stephen.jennison@northlanddhb.org.nz

All applicants MUST be eligible to register in New Zealand as a Medical Practitioner, and gain either locum tenens and /or Vocational registration with the Medical Council of New Zealand.

Northland covers an area of 12,600 square kilometres and has a population of 150,000. Excellent schools, affordable housing and exciting scenic coastal areas which offer a mixture of recreational activities awaits you.

Vacancy No: MD13-013

Job Description and Official Application Form are available from our website, www.northlanddhb.org.nz/careers/vacancies.aspx or by contacting Trudi Freer, Recruitment Officer - Senior Medical Officers, Phone: +64 9 430 4101 ext 7402, Email: Trudi.Freer@northlanddhb.org.nz; Postal: c/o Northland District Health Board, Private Bag 9742, Whangarei 0148, New Zealand

www.facebook.com/wileyhealth

Click the LIKE button to reveal your 15% book voucher