Editorial
1249 Pill testing at music festivals: can we do more harm?
J. Schneider, P. Galettis, M. Williams, C. Lucas and J. H. Martin

Review
1252 Management of diabetes in Indigenous communities: lessons from the Australian Aboriginal population
W. D. Niyomen, S. Chatterje and L. J. Maple-Brown

Clinical Perspectives
1259 Alcohol use disorders in Australia
C. N. Fryers, K. G. Merley and P. S. Haber

Original Articles
1269 Clinical trials of medicinal cannabis for appetite-related symptoms from advanced cancer: a survey of preferences, attitudes and beliefs among patients willing to consider participation

1276 The revolving door: antibiotic allergy labelling in a tertiary care centre

1284 Determining the efficacy of the chronic disease self-management programme and readability of ‘living a healthy life with chronic conditions’ in a New Zealand setting
J. F. S. Cheng, A. A. Ahmad and A. J. Broadhurst

1291 Benefit from cytoreductive nephrectomy and the prognostic role of neutrophil-to-lymphocyte ratio in patients with metastatic renal cell carcinoma
D. Day, V. Karapapan, E. Kious, D. Vip, N. Lourtesghal, J. D. Davis, A. A. A. Aliz, S. Wong, M. Rosenfeld, P. Gibbs and B. Y. Yip

1297 Heart failure following cancer treatment: characteristics, survival and mortality of a linked health data analysis
R. A. Clark, N. M. Berry, M. H. Chowdhury, A. L. McCarthy, S. Ullah, V. Versace, J. J. Atherton, B. Koczwara and D. Roder

1306 Utility of surgical lung biopsy in critically ill patients with diffuse pulmonary infiltrates: a retrospective review
L. H. Donaldson, A. J. Gill and M. Hibbert

1318 Detection and clinical significance of glomerular M-type phospholipase A2 receptor in patients with idiopathic membranous nephropathy
H. Liu, W. Liu, S. Gong and K. Ding

1323 Introduction of New South Wales adult subcutaneous insulin-prescribing chart in a tertiary hospital: its impact on inpatient glycaemic control
V. W. Wong, A. H. E. Faden, N. S. Luna and H. Russell

Brief Communications
1328 Rates of neutropenia in adults with influenza A or B: a retrospective analysis of hospitalised patients in South East Queensland during 2015
P. Higgins, N. Bannagan, R. J. Bird and K. A. Markby

1332 Use of computed tomography abdomen and pelvis for investigation of febrile neutropenia in adult haematology patients
H. Y. Lim, M. Ashley, B. Williams and A. Gegg

1336 Beta-blockers are under-prescribed in patients with chronic obstructive pulmonary disease and co-morbid cardiac disease

1340 Pharyngoesophageal dysphagia: an under-recognised, potentially fatal, but very treatable feature of systemic sclerosis
C. Rajarapu

Letters to the Editor
Clinical-scientific notes
1345 Concomitant plasmapheresis and cladribine infusion for the treatment of life-threatening systemic lupus erythematosus
W. P. Delacruz, A. Cap and N. Shumway

1346 Large volume subcutaneous lymphoedema drainage
S. Hynes and J. B. Hardy

1347 Visceral leishmaniasis triggering (mimicking) macrophage activation syndrome in a patient with adult onset Still disease
M. Barotin, G. E. Jenson, K. C. Pawar, E. Zekan and B. Anic

General correspondence
1349 Family escalation of care: well meaning, but where's the evidence
A. Stroth

1350 A hybrid of conventional medical terminology and patient-friendly terminology
P. Regal
RACP CONGRESS 2017

Bringing Specialists Together. Sharing Knowledge. Building Skills

Melbourne 8–10 May 2017

REGISTRATIONS NOW OPEN. VISIT THE CONGRESS WEBSITE
www.racpcongress.com.au

The new shared interest RACP Congress 2017 is an opportunity for you to:

- learn about medical breakthroughs
- hear the latest clinical updates
- join the conversations on the ‘big issues’ that are relevant to all physicians: obesity, disability, ageing and end-of-life issues
- attend high energy, cross-disciplinary think tanks
- network with global thinkers and healthcare leaders, socialise with peers and forge new professional ties.

Congress is a valuable learning opportunity and participation counts towards your annual CPD requirements.

Dates: Monday, 8 May to Wednesday, 10 May 2017
Location: Melbourne Convention and Exhibition Centre

RACP Congress 2017 Secretariat
Email: RACP@saneevent.com.au
Phone: +61 2 9553 4820

Join the conversation #RACP17
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 (General)
Paul Bridgman, Christchurch

Cardiology (Arrhythmias)
Andrew McGavigan, Adelaide

Clinical Genetics
Les Sheffield, Melbourne

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

Continuing Education
( Clinical Perspectives)
Christopher Pokorny, Sydney

Emergency Medicine
Joseph Ting, Brisbane

Endocrinology
Morton Burt, Adelaide
Anthony Russell, Brisbane

Ethics
Paul Komesaroff, Melbourne

Gastroenterology
David M. Russell, Melbourne

Geriatric Medicine
Leon Flicker, Perth

Haematology (General)
Peter Browett, Auckland

Haemostasis/Thrombosis
Claire McIntock, Auckland

Immunology and Allergy
Marianne Empson, Auckland

Infectious Diseases
David Gordon, Adelaide

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 Youssef, 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 Assistant
Aparna Avasarala, 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)
Anywhere Article.  
Any format, any device, any time.

Today, more than ever, we need access to information that is immediate, clear and communicable. As a member of the community we serve, you will know how important it is to have access to that data, whenever you need it, and wherever you are.

What is Anywhere Article?
Anywhere Article is focused on making our online journal content on Wiley Online Library more readable and portable, whilst also allowing rich information to be brought to the surface. It achieves these goals in the following ways:

1. **Readability**
   - Clean design. Superfluous information and unnecessary distractions have been removed so that readers can focus on the article. Figures can be viewed in context or separately, and easily navigated, browsed or downloaded.

2. **Functionality**
   - The new layout and sidebar tray allow readers access to important information, i.e., references, figures, publication history at any point in the reading experience, without losing their place on the main page.

3. **Mobility**
   - Whatever device you use - desktop, tablet, or mobile - the article will be presented to take best advantage of that device, always readable, always easy to use, wherever you are.

When Can I Start Using Anywhere Article?
- **Enhanced Article (HTML)** You can view an article in the new "Anywhere Article" format wherever you see this link. You'll be able to view it easily on the device of your choice, at your convenience.

Visit [www.wileyonlinelibrary.com](http://www.wileyonlinelibrary.com) today and look out for the new links underneath each journal article, try it, and see the difference for yourself.
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

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-0000-2016). 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 © 2016 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)
Keeping readability, discoverability and mobility in mind, Wiley has been working towards improving the PDF reading experience. Partnering with ReadCube, Wiley are proud to announce the launch of ReadCube Enhanced PDFs across our journal content on Wiley Online Library.

Whilst keeping the clear layout and simple design of the standard PDF, PDFs opened in the ReadCube Enhanced PDF format, feature hyperlinked in-line citations, clickable author details, as well as supplementary information, figures and other valuable article data, all just a click away.

Online Library users do not need a ReadCube account to experience the benefits of the enhanced PDFs in their web browser, though additional benefits, like saving highlights or annotations you have made to an article, are available to readers who download the PDF and open it in the free ReadCube Desktop application.

Download the free desktop app to enhance your downloaded PDFs at: www.readcube.com, or visit Wiley Online Library at: www.onlinelibrary.wiley.com, and click on an article PDF link, to try the new, online enhanced PDF yourself.
Editorial
1249 Pill testing at music festivals: can we do more harm?
J. Schneider, P. Galettis, M. Williams, C. Lucas and J. H. Martin

Review
1252 Management of diabetes in Indigenous communities: lessons from the Australian Aboriginal population
H. D. Nguyen, S. Chitturi and L. J. Maple-Brown

Clinical Perspectives
1259 Alcohol use disorders in Australia
C. H. Freyer, K. C. Morley and P. S. Haber

Original Articles
1269 Clinical trials of medicinal cannabis for appetite-related symptoms from advanced cancer: a survey of preferences, attitudes and beliefs among patients willing to consider participation

1276 The revolving door: antibiotic allergy labelling in a tertiary care centre

1284 Determining the efficacy of the chronic disease self-management programme and readability of ‘living a healthy life with chronic conditions’ in a New Zealand setting
J. J.-Y. Cheng, F. Arenhold and A. J. Braakhuis

1291 Benefit from cytoreductive nephrectomy and the prognostic role of neutrophil-to-lymphocyte ratio in patients with metastatic renal cell carcinoma

1297 Heart failure following cancer treatment: characteristics, survival and mortality of a linked health data analysis
R. A. Clark, N. M. Berry, M. H. Chowdhury, A. L. McCarthy, S. Ullah, V. L. Versace, J. J. Atherton, B. Koczvara and D. Roder

1306 Utility of surgical lung biopsy in critically ill patients with diffuse pulmonary infiltrates: a retrospective review
L. H. Donaldson, A. J. Gill and M. Hibbert

1311 Return to sender: the need to re-address patient antibiotic allergy labels in Australia and New Zealand
J. A. Trubiano, L. J. Worth, K. Urbancic, T. M. Brown, D. L. Paterson, on behalf of the Australasian Society for Infectious Diseases Clinical Research Network, M. Lucas, on behalf of the Australasian Society of Clinical Immunology and Allergy and E. Phillips

1318 Detection and clinical significance of glomerular M-type phospholipase A2 receptor in patients with idiopathic membranous nephropathy
H. Liu, W. Luo, S. Gong and X. Ding

1323 Introduction of New South Wales adult subcutaneous insulin-prescribing chart in a tertiary hospital: its impact on inpatient glycaemic control
V. W. Wong, A. Ho, E. Fiakos, N. S. Lau and H. Russell
RACP Specialists. Together

INTERNAL MEDICINE JOURNAL

November 2016, Volume 46, Issue 11

Brief Communications

1328 Rates of neutropenia in adults with influenza A or B: a retrospective analysis of hospitalised patients in South East Queensland during 2015
P. Higgins, N. Runnegar, R. J. Bird and K. A. Markey

1332 Use of computed tomography abdomen and pelvis for investigation of febrile neutropenia in adult haematology patients
H. Y. Lim, M. Ashby, B. Williams and A. Grigg

1336 Beta-blockers are under-prescribed in patients with chronic obstructive pulmonary disease and co-morbid cardiac disease
P. A. Neef, C. F. McDonald, L. M. Burrell, L. B. Irving, D. F. Johnson and D. P. Steinfort

1340 Pharyngoesophageal dysphagia: an under recognised, potentially fatal, but very treatable feature of systemic sclerosis
C. Rajapakse

Letters to the Editor

Clinical-scientific notes

1345 Concomitant plasmapheresis and cladribine infusion for the treatment of life-threatening systemic lupus erythematosus
W. P. Delacruz, A. Cap and N. Shumway

1346 Large volume subcutaneous lymphoedema drainage
S. Heng and J. R. Hardy

1347 Visceral leishmaniasis triggering (mimicking) macrophage activation syndrome in a patient with adult onset Still disease
M. Barešić, G. E. Janka, K. Gjadrov-Kuveždić, Š. Zekan and B. Anić

General correspondence

1349 Family escalation of care: well meaning, but where’s the evidence
A. Tobin

1350 A hybrid of conventional medical terminology and patient-friendly terminology
P. Regal
WILEY Job Network

WE MAKE YOUR RESEARCH EASY. NOW WE MAKE JOB HUNTING EASY.

Let your partners in research energize your career.

Drawing on our expertise and relationships across the research and business communities, Wiley-Blackwell invites you to join Wiley Job Network, the definitive job site for professionals in the sciences, technology, business, finance, healthcare and the arts.

• FIND premium jobs from the most respected names in your industry
• ATTRACT hundreds of recruiters and employers in your field
• 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!

wileyjobnetwork.com
Pill testing at music festivals: can we do more harm?

Recently, there have been calls for pill testing to be introduced at music festivals. Advocates say that this would inform consumers and reduce risks. However, there are a number of technical and laboratory limitations of such an intervention that need to be considered. This editorial will highlight these limitations.

The recent deaths and hospitalisation of young people from illicit drug use has led to calls for the introduction of on-site testing of tablets and capsules containing illicit drugs (‘pills’) at music festivals and events.\(^1\)\(^2\) Pill testing, both on- and off-site, is available in several European countries, with individuals submitting samples for drug identification and purity analysis. These services are aimed at both harm minimisation and providing information on the availability and emergence of new psychoactive substances.\(^3\) Death and morbidity data are unavailable to ascertain the effectiveness or harm of this intervention. Advocates for pill testing argue that by providing information on content, the person can reconsider taking the pill.\(^4\) To support that, an online survey by the Australian National Council on Drugs reported that most young people supported pill testing being available and wanted access to reliable and balanced information so that they would be more equipped to make informed decisions about the risks of using drugs.\(^5\) A field survey of Swiss attendees at dance music events reported that respondents were receptive to harm reduction measures, including pill testing. However, 27.4% responded that they would never use pill testing; 31.1% would use it systematically before taking a pill, and 41.6% would not use unless they did not know the substance, dealer or both.\(^6\)

The introduction of pill testing is perceived as a way to monitor pill composition and encourage information exchange. However, it is possible that information received from this may also be seen as affirming the quality and purity of the pill.\(^7\)

The testing of illicit drug formulations does not guarantee the safety of the product or protect the person consuming the drug from harm. In a research report on ecstasy pill testing, the authors concluded that pill testing at best gave an artificial ‘shine of safety’, and other simpler harm reduction mechanisms were more likely to be effective.\(^7\) Although some would consider some information better than nothing, false reassurance because of false negative results is a concern. Thus, this editorial focuses on the technical and laboratory limitations of such an intervention.

On-site pill testing procedures include pill identification, reagent testing kits and chromatographic techniques. Pill identification relies on visually comparing pills supplied by the consumer with formerly analysed pills. This approach has limited utility if testing is to be performed at different geographically distinct locations. Even if the tablets are similar in appearance, it assumes that each batch contains the same excipients and the same dose and that each tablet in a batch contains a uniform dose or that the same tablet press has not been used to manufacture another batch of tablets containing a different drug.

Reagent testing involves mixing a small sample of powder scraped or removed from the illicit drug formulation with chemical reagents to produce a colour change. The class of drug present is identified by the colour produced. Some kits are labelled semi-quantitative and use colour intensity to classify tablet content from very low to very high. Problems with reagent testing include lack of specificity between similar compounds, cross-reactivity with non-related compounds producing incorrect results and the inability to detect other potentially dangerous compounds that may be present. As the distribution of the illicit drug in the tablet may not be uniform, samples taken from multiple scrapings of the same tablet surface may give results varying from little or no drug to high concentration. In terms of actual dose that will be administered, the interpretation of what low or very high means is variable.

It may be argued that, given the flaws of pill identification and chemical reagent testing, sophisticated techniques, such as liquid or gas chromatography with mass spectrometry, could be employed for on-site pill testing. These techniques involve expensive and technical equipment and highly trained personnel just to undertake the analytical work. For chromatography to be effectively used, there needs to be a previously determined reference library of drugs, likely contaminants and harmful excipients in a tablet or capsule to which test samples can be matched. Any drug testing method needs to know what drug or chemical it is looking for. Therefore, unknown substances in a preparation may not be detected if the testing method is not set up to detect this. The analysis may find the substance it is looking for but miss a dangerous adulterant or, if a new designer drug is present that is not in the assay library, it could be missed...
completely. This testing method also suffers from the fact that a scraping or sample of powder from one tablet or capsule will not accurately reflect either the dose in that particular tablet or capsule or indeed the dose in any of the tablets or capsules from the same batch. Commonly used chromatographic testing will also not determine the ratio of isomers present if the drug is a racemic compound. Different processes used to manufacture the illicit drug may influence the ratio of each isomer present. As different isomers can vary significantly in potency and psychoactive effect, quantifying the total amount of drug present will not be a useful guide to pharmacological effect.7

Time taken for analysis is also a factor. A reagent test takes minutes, but how many potential pill takers would be willing to delay consumption for the still incomplete but more comprehensive chromatography testing, which may take hours depending on sample numbers.

In comparison, production of tablets and capsules in the pharmaceutical industry is highly regulated and subject to strict quality control and safety guidelines to ensure products are safe for the consumer. Any tablet or capsule may contain diluents, disintegrant, binding agents and glidants in addition to the drug. Diluents are added to increase the powder mass. Tablets may also contain a binding agent to help the tablet maintain its shape after compression and a disintegrant so that the tablet breaks into small fragments when swallowed, aiding absorption. A glidant may be added to help powder flow evenly from the machine hopper into the tablet die or capsule shell. This ensures that each tablet or capsule contains the same amount of powder and therefore the same dose. The active ingredient and the excipients must undergo satisfactory mixing to ensure that every tablet or capsule contains the correct dose of drug. Determining the correct manufacturing procedure is in itself a time-consuming process that is strictly controlled. In registered pharmaceutical products, the active ingredient (drug) undergoes identity and purity testing to ensure that no harmful levels of residual ingredients, by-products or other contaminants are present. Excipients are also tested to ensure no effect on drug stability or the performance of the tablet or capsule when administered. During and post-production, tablets and capsules undergo tests, such as uniformity of content and weight, to ensure that each tablet or capsule produced contains the appropriate dose and dissolution and disintegration testing to ensure that the tablet or capsule will disintegrate, and the drug will dissolve at an appropriate rate to produce the desired effect. The stability of the drug in the dosage form over time is also tested to ensure that the drug does not break down to inactive or toxic products.

In distinction, the production of illicit drug formulations is not controlled. Illicit drug dosage forms are not subject to any quality control measures, meaning that whilst a drug may be sold as ‘drug X’, it may in fact contain pure drug, no drug, another drug or a toxic or non-toxic diluent. The stability of an illicit drug in the formulation is not known, and there is less, if any, data on potential toxicity of decomposition products. Even if the product contains the active ingredient, it may also contain dangerous by-products of the drug synthesis process. Mixing of ingredients prior to preparing the tablets and capsules is unlikely to be satisfactory, resulting in uneven distribution of drug through the powder bed. This will result in some tablets from the same batch having very little drug while others have a very high dose. As distribution of drug within a tablet or capsule is usually not uniform, a portion of powder taken from one part of a tablet by scraping the surface of the tablet or by opening the capsule for testing may not be representative of what the entire tablet or capsule contains.

The pharmacological effects of illicit drugs or other excipients also appear to have been forgotten. Even if the likely drug and dose is determined, drugs exhibit inter-individual variability in their pharmacokinetics and pharmacodynamics. The same dose of drug administered to different people may produce markedly different responses. Observed differences may be because of any number of factors, including genetic polymorphism, interaction with other co-administered drugs and physiological factors affecting drug distribution and elimination. Formulations may also influence how much of the illicit drug is absorbed. If a tablet disintegrates rapidly, a rapid rise in plasma drug concentration may occur, whereas if the tablet does not disintegrate in the gastrointestinal tract, the drug may not be released from the formulation. A delayed release of the drug resulting in delayed onset of action may result in the consumer taking additional pills, thinking the pills they have are ‘weak’.7 For many illicit drugs, the full pharmacological spectrum of action is not known. The lack of pharmacokinetic data for many illicit drugs also poses a concern in an emergency situation with illicit drug intoxication. Often, the pharmacological and toxicological effects of other excipients, by-products and contaminants are not known, producing an unpredictable spectrum of effect.

Even reflecting on the small percentage of potential analytical factors discussed here, it is evident that the consumer considering taking an illicit drug may have a false sense of security, particularly if their decision to take the
drug is based only on information provided by quantitative and qualitative on-site pill testing. The failure to detect an agent that could be life-threatening is of great concern. Although the ‘harm reduction’ argument is noted, equally, the many unknown and potentially unidentifiable factors that could cause mortality are noted. On-site testing will thus not solve this problem and could lead to other problems of an unpredictable and tragic nature.

References

5. Lancaster K, Ritter A, Matthew-Simmons F. Young people’s opinions on alcohol and other drugs issues.

© 2016 Royal Australasian College of Physicians
**Management of diabetes in Indigenous communities: lessons from the Australian Aboriginal population**

H. D. Nguyen, S. Chitturi and L. J. Maple-Brown

1Department of Endocrinology, Division of Medicine, Royal Darwin Hospital, Tiwi, and 2Menzies School of Health Research, Charles Darwin University, Casuarina, Northern Territory, Australia

**Abstract**

Type 2 diabetes mellitus and other chronic cardio-metabolic conditions are significant contributors to the large disparities in life expectancy between Indigenous and non-Indigenous Australians. Type 2 diabetes is more prevalent from a young age among Indigenous Australians and is often preceded by a cluster of risk factors, including central obesity, dyslipidaemia, albuminuria and socio-economic disadvantage. Management of type 2 diabetes in Australian Indigenous peoples can be challenging in the setting of limited resources and socio-economic disadvantage. Key strategies to address these challenges include working in partnership with patients, communities and primary healthcare services (PHC, Aboriginal community controlled and government services) and working in a multidisciplinary team. Population prevention measures are required within and beyond the health system, commencing as early as possible in the life course.

**Introduction**

Among Aboriginal and Torres Strait Islander Australians there is both a higher prevalence and earlier age of onset of type 2 diabetes mellitus compared with the non-Indigenous Australian population (Fig. 1). There are regional variations in the prevalence of diabetes, with study estimates ranging between 3.5% and 33.1% due to heterogeneity in many potential risk factors, including body build, socio-economic status, remoteness of community and access to food stores and duration of acculturation as well as differences in study designs. Diabetes remains undiagnosed in up to 50% of the general Australian population, and as such, the population prevalence of diabetes is likely to be underestimated. However, the proportion of undiagnosed diabetes among Indigenous Australian populations has not been characterised in detail and likely varies across different regions of Australia, with one study reporting 29% of Indigenous participants in the Darwin region undiagnosed with diabetes. Diabetes is a major contributor to mortality among Indigenous Australians, being responsible for nearly 8% of all deaths. The higher diabetes-related mortality rate among Indigenous Australians is a major contributor to the 10–20-year difference in life expectancy compared to non-Indigenous Australians and contributes 12% to the total burden of Indigenous health gap.

Key differences in the cardio-metabolic risk profiles of Indigenous Australians likely contribute to higher prevalence of chronic diseases, including diabetes, chronic kidney disease (CKD) and cardiovascular disease (CVD) among Indigenous Australians compared to the general Australian population. Risk factors contributing to higher prevalence and earlier age of onset of this cluster of cardio-metabolic chronic diseases among Indigenous Australians include higher rates of cigarette smoking, central obesity, lower high-density lipoprotein-cholesterol, lower socio-economic status and limited access to fresh food in remote communities, including lack of appropriate storage facilities.

There is growing evidence of the role of factors in utero (foetal origins) in the later development of chronic diseases, particularly among populations in epidemiological transition, such as Indigenous Australians. Thus, earlier age of onset of type 2 diabetes in Indigenous Australians results in rates of type 2 diabetes in pregnancy that are 10 times higher than the general Australian
These high rates of type 2 diabetes in pregnancy in turn may contribute to high rates of youth-onset type 2 diabetes in Indigenous Australians in the next generation, thus contributing to inter-generational cycles of increasing rates and early onset of type 2 diabetes in Indigenous Australians, as has been described in native American populations. Higher rates of diabetes-related complications are reported among Indigenous Australians compared to non-Indigenous Australians, with the exception of diabetic retinopathy where rates are conflicting. There is a two-fold increased risk of peripheral vascular disease and albuminuria among Indigenous Australians compared to the general population. Rates of end-stage renal disease requiring renal replacement therapy are 10-fold greater in Indigenous Australians, and rates of coronary artery event and death are two-fold higher.

As displayed in Figure 2, the greatest disparity in age-specific incidence of end-stage renal disease is in the younger age groups, aged 25–55 years. Earlier diagnosis and prompt diabetes management allows prevention and delays progression of diabetes-related microvascular and macrovascular complications.

### Diagnosis and screening

Screening and diagnosis of diabetes mellitus in remote Indigenous Australian communities can be challenging due to difficulties in obtaining a fasting plasma glucose (FPG) sample and completion of an oral glucose tolerance test (OGTT). Glycosylated haemoglobin A1C (HbA1c) measurement has recently been approved for diagnosis and screening of diabetes. HbA1c has advantages over FPG and OGTT due to convenience, without the need for fasting, and is less affected by hyperglycaemic variability during stress and illness. However, HbA1c is not validated to be used for screening and diagnosis in children, adolescents and in pregnancy. HbA1c must be interpreted with caution in the setting of anaemia and other haemoglobinopathies.

Point-of-care (POC) HbA1c is clinically effective and culturally accepted by Aboriginal Health Practitioners (AHP) and Indigenous patients. POC testing has good concordance with laboratory venous blood HbA1c taken on the same day, allowing for increased case detection and timely diagnosis and management whilst waiting for confirmatory laboratory HbA1c.

Screening for type 2 diabetes is recommended for Indigenous Australians over the age of 10 years (or past the onset of puberty) with any one of the following risk factors: overweight or obese, has a positive family history of diabetes, signs of insulin resistance on examination, dyslipidaemia, receiving psychotropic medication or has been exposed to diabetes in utero. Ongoing periodic retesting and provision of healthy lifestyle education as
determined by the risk of the individual is a crucial component of diabetes prevention and early intervention programmes. Universal screening for gestational diabetes mellitus (GDM) is recommended at 24–28 weeks gestation, with testing at the first antenatal visit recommended for Indigenous women, particularly those with additional risk factors (obesity, prior GDM, family history of type 2 diabetes, polycystic ovarian syndrome, signs of insulin resistance and prior history of obstetric complications). Our experience thus far is that the uptake of the new guidelines in remote primary healthcare services (PHC) has been positive, with increasing GDM screening at the first antenatal visit, including use of HbA1c to screen for undiagnosed type 2 diabetes.

Microvascular complications may be present at the time of diagnosis, even among children and adolescents; therefore, screening for complications and CVD risk factors should be undertaken at the time of diagnosis and annually, with the assessment of absolute cardiovascular risk.1,20 The Central Australian Regional Practitioners Association (CARPA) Guidelines are the standard guidelines used in Aboriginal primary healthcare in the Northern Territory (NT) and beyond. This guideline recommends assessment of absolute CVD risk using the Australian modified Framingham Risk Equation that has been endorsed by the National Vascular Disease Prevention Alliance (NVDPA). The guidelines recognise increased risk and earlier age of onset of CVD in Indigenous Australians and recommend commencement of universal CVD risk assessment in Indigenous Australian adults from 35 years of age (compared to 45 years of age for the general Australian population). Physicians need to be aware that the Framingham Risk Equation may underestimate the risk in Indigenous Australian adults, but screening from a younger age will provide an estimate of minimum CVD risk.21,22 With the early age of onset of type 2 diabetes among Indigenous Australians, it is also important to consider and address issues in youth, including psychosocial and sexual health.20,25

Lifestyle modification

Obesity has been independently associated with the prevalence of type 2 diabetes. Waist-to-hip ratio (WHR) was the index of obesity that was more strongly associated with diabetes among Indigenous participants, followed by waist circumference then body mass index in several studies across varying regions in Australia.2,24 The Australian Institute of Health and Welfare reported that Indigenous women were twice as likely to be obese than non-Indigenous women and Indigenous men 1.5 times more likely to be obese than non-Indigenous men.1 A higher proportion of Indigenous adults were also more underweight than non-Indigenous adults.1

Approximately 75% of Indigenous people living in non-remote areas report a sedentary lifestyle.1 Developing a group- and sports-based intervention can improve metabolic, anthropometric and fitness variables. Development and ownership of interventions by community members can improve adherence and sustainability.25,26 Community initiatives that have been explored with variable degrees of success include regular family walking groups, health promotion in the community with sporting and arts festivals and competitions, regular hunting trips and appointment of a community member as sports and recreation officer.27 Diet plays a vital role in the aetiology of diabetes and related chronic conditions. Packaged foods and drinks that are high in fat and sugar content make up the majority of dietary intake among remote communities due to the limited access to and high cost of fresh fruits and vegetables, including lack of appropriate storage facilities.1,9,28 Temporary reversion to the traditional hunter-gatherer lifestyle among a group of Indigenous Australian adults resulted in significant improvements in cardio-metabolic risk profiles related to diabetes and CVD, including weight reduction. This was likely due to increased physical activity and consumption of a diet low in fat and processed foods.29 Initiatives explored as part of a community healthy lifestyle programme in a remote Australian Aboriginal community included nutrition education, healthy cooking classes, store tours to identify healthy food choices and appointment of a community member as store manager to ensure improvement in quality and quantity of healthy food choices.27 However, major impediments to lifestyle changes are poverty and food insecurity.28 Smoking, alcohol consumption, other drug use and gambling may divert the resources and money, leaving little to spend on healthy food, which is often very costly in a remote community. At times when money is exhausted, it can be challenging to procure food, thus sometimes leading to periods of starvation before the next pay day.

Other cardiovascular risk factors that need to be addressed are the high prevalence of tobacco smoking and CKD among Indigenous Australians compared to non-Indigenous Australians. From 2002 to 2008, the proportion of Indigenous Australians aged 15 years and older who were current daily smokers was more than twice the proportion of current smokers among non-Indigenous Australians.1 The proportion of current daily smokers among Indigenous Australians had decreased from 49% to 45% over that time period.1 Those living in remote areas were more likely to be current smokers than those living in urban areas.1,10 However, healthcare programmes that involve smoking counselling or non-
smoking policy in public areas have not demonstrated change in rates of smoking.\textsuperscript{27,30} Recent work has reported that two thirds of Indigenous Australians who currently smoke want to quit, and more than half have tried to quit at least once in the past.\textsuperscript{30} Existing local tobacco control programmes appear to provide motivation to quit, but this does not overcome the challenges to sustain a quitting attempt. Those who live in remote or disadvantaged areas are equally as likely to be counselled by their health provider to quit but are less likely to use pharmacological therapy.\textsuperscript{30}

**Pharmacotherapy**

The first-line medication of choice for the treatment of type 2 diabetes is metformin due to efficacy, safety (including low risk of hypoglycaemia) and durability of glucose-lowering effect. In our experience, in remote communities, the large pill size and diarrhoea are important reasons for poor adherence with metformin therapy. We usually start with a small dose of metformin and gradually increase the dose as tolerated and preferentially use 500 mg extended release tablets over 1000 mg where pill size is identified as a cause for poor adherence. The high prevalence of CKD in the Australian Indigenous population does impact the prescribing of metformin in this population. Recent guidelines supported by the American Diabetes Association and the European Association for the Study of Diabetes suggest that metformin can be continued in mild-moderate CKD at reduced dose, with cessation of metformin when estimated glomerular filtration rate \(< 30 \text{mL/min/1.73} \text{m}^2\).\textsuperscript{31} This is consistent with the current local guidelines (CARPA).\textsuperscript{31}

The choice of subsequent add-on therapies for glucose lowering and frequency of administration requires consideration of food security, access to appropriate storage in the case of insulin therapy, adherence and acceptability by the individual patient. Follow-up of the patient’s adherence to and tolerability of therapy is essential before intensifying management. In patients with lack of food security, a common reason for poor adherence is anti-hyperglycaemic medication-induced hypoglycaemia on the days of starvation. In such patients, we use the medications that are least likely to cause hypoglycaemia, namely metformin, dipeptidyl peptidase 4 (DPP4) inhibitors and sodium/glucose cotransporter 2 (SGLT2) inhibitors.

Newer oral agents, such as the DPP4-inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and SGLT2 inhibitors, have not been studied among the Indigenous Australians with diabetes. However, DPP4-inhibitors are not uncommonly prescribed in patients with diabetes, either as a second-line or third-line therapy, usually when patients are resistant to commencement of insulin therapy. It is also an attractive option in patients with renal and/or hepatic impairment. GLP-1 agonists (twicedaily regimen or once-weekly regimen for patient adherence) are favoured by some patients, particularly to help in weight reduction, and our experience has been favourable thus far.

From our experience, we have been cautious in use of SGLT-2 inhibitors among Indigenous Australians, particularly people from remote areas, due to the adverse effects from glycosuria, such as increased risk of urogenital infections and dehydration. Infections are frequent in Australian Indigenous patients, and CKD is also common, which limits such oral hypoglycaemic agents. The dehydrating properties of SGLT-2 inhibitors are a potential problem in not only remote Australian Indigenous communities, it is a potential problem for anyone living in a tropical climate and people who work outdoors. Of concern are the reports of ketoacidosis in patients with type 2 diabetes taking SGLT-2 inhibitors.

In addition to treatment of diabetes to achieve good glycaemic control and prevention of microvascular and macrovascular complications, adjunct medications, such as aspirin, statin therapy and renin angiotensin system blockers, are prescribed for primary and secondary CVD prevention as per the recommendation for the general Australian population.\textsuperscript{32} Simple once-daily regimens are usually preferable in the complex and resource-limited setting of remote Aboriginal communities. Polypills may help reduce the pill burden and improve medication adherence, with recent evidence of increased self-reported medication use of a polypill.\textsuperscript{33}

**Surgery**

Bariatric surgery, particularly laparoscopic adjustable gastric banding (LAGB), may be acceptable to Indigenous adults for achieving substantial weight loss and improvement in metabolic parameters, including remission of diabetes mellitus. Cost, scarcity of publicly funded bariatric surgery, long waiting periods and difficulties in accessing follow-up surgical care due to geographic location make it a less frequently used option for Indigenous Australians. The rates of micronutrient deficiencies following irreversible bariatric surgeries in remote community-dwelling populations with limited access to fresh vegetables and fruits are unknown. The safety and efficacy of different bariatric surgeries for Indigenous Australians living in remote communities has not been well studied. A recent pilot study in a rural setting reported a remission rate in type 2 diabetes of 66\% in the 30 participants who underwent LAGB.\textsuperscript{34} In addition,
that study reported on the importance of education of the local community health centre staff and patients and on the need for regular follow-up to monitor for short- and long-term outcomes and adverse events.34

Role of primary healthcare

Primary healthcare services play the key role in implementing interventions for health promotion, disease prevention, screening, diagnosis and management of chronic conditions, such as diabetes. Resource and funding availability is a barrier to successful and sustainable implementation of interventions. Building on and ensuring compatibility with existing systems and processes is crucial.35 Other factors that influence the success of implementation and sustainability of interventions include high turnover of staff in remote and regional communities, lack of AHP, leadership and involvement of the local community. Funding may also be required to provide incentives for retention of healthcare staff in the area to maintain continuity of care.35

We as healthcare providers need to understand the importance of competing demands and priorities of patients that may impact their care. It is important to engage, educate and partner with patients when formulating care plans in order to empower and enable patients to take the lead in their chronic condition management. Education needs to be delivered in a culturally safe and friendly healthcare environment.

Electronic clinical support systems provide evidence-based guidelines, scheduling services for individual patients and a reminder and recall system for identification of patients due for scheduled health check-ups. However, electronic systems have limited use with variable sustainability over time if they are not incorporated in a culturally safe and friendly healthcare environment.35,36 Electronic systems supported by trained staff, including local AHP, allow for structured care that can improve control of cardio-metabolic parameters. Any systems introduced require regular auditing and feedback systems for quality control.36,37

Creating dedicated chronic disease positions with clarity in roles and responsibilities will ensure that healthcare workers have sufficient time to dedicate to chronic disease management in a busy primary healthcare clinic. A dedicated referral coordinator will assist with bridging the gaps in referral processes to allied professionals and specialist services when needed. Employment and training of local people in different roles across the primary healthcare setting allows integration of the local community and reinforces partnership between local community and health services providers.35

Role of multidisciplinary teams

Aboriginal health practitioners

AHP play a crucial role in delivery of healthcare by facilitating culturally safe communication between healthcare providers and patients, thereby improving delivery of diabetes services and diabetes care.38,39 AHP engage in regular patient home visits and are involved in provision of diabetes care, such as scheduled clinical reviews of blood pressure and blood tests. They also engage with families, provide counselling and support the use of local and relevant resources for effective patient self-management.39 However, AHP require support to participate in patient decision-making processes and to carry out their work.39 The number of AHP per patient population as well as accessibility to AHP of the same gender may impact the delivery of diabetes care and achievement of scheduled assessment of cardio-metabolic risk.38 We have mentored and supported AHP to complete successfully postgraduate certification in diabetes education, and non-Indigenous staff of our multidisciplinary team have benefited enormously from exchange of information and learnings with AHP. The learnings are two-way. It is also important to involve Indigenous community members and AHP in the design process of any healthcare system changes to ensure that any proposed intervention is culturally acceptable to the wider community.

Role of specialist services

Indigenous Australians, particularly from rural and remotes areas, have higher hospitalisation rates, higher rates of clinic appointment cancellations or non-attendance and are more than twice as likely to discharge from hospital against medical advice.40 Barriers faced by Indigenous Australians include dislocation from family, unfamiliarity of urban centres, time limitation in consultations, lack of appreciation by health professionals for the need of interpreters, lack of communication by hospital staff with remote community health clinics and access to transportation and culturally appropriate accommodation.41 Appropriate primary healthcare as well as access to specialist services can help reduce the need for hospitalisation for acute complications of chronic diseases.41,42 It is also important to provide transport and accommodation for patients from rural and remote regions to facilitate management of chronic diseases in urban healthcare centres. There is an increasing role for telehealth consultation combined with other sustainable outreach models that have minimised the need for patient travel from remote communities to attend specialist services.
Specialist outreach

Specialist outreach services reduce the distance barrier and promote equity of access to specialist care for patients living in rural and remote communities. Specialist clinics conducted in the primary healthcare setting have been shown to improve patient satisfaction and access to specialist care.41 This translates into improved numbers of annual specialist consultations and reduced cost due to reduction in transportation and accommodation costs if patients were brought to urban outpatient clinic appointments.41 However, only some of these outreach services have been sustained over time. Factors that impact sustainability of outreach services include adequate number of specialist staff, access to hospital base and coordination and prior planning of visits to ensure regularity and predictability. Other important factors include integration of outreach services into the pre-existing multidisciplinary framework of the local primary healthcare setting, integration with remote communities, being responsive to individual community needs and accountability to the referring practitioner and community with effective correspondence.41

Telemedicine

Telemedicine has reduced the need for specialist outreach travel to remote communities. There is reliable concordance between assessments performed through telemedicine compared to face-to-face assessments.42 Telemedicine has been successful as it addresses the distance barrier faced by remote Indigenous patients and the difficulties with coordinating a regular specialist visit to remote communities with the associated costs.43 We, along with others in regional and remote Australia, increasingly use telemedicine in conjunction with a hub and spoke outreach model in order to increase access to specialist services for remote Australians.

Telemedicine may also play an important role in the management of diabetic retinopathy. Teleophthalmological medicine allows for increased screening in patients in remote regions, is cost-effective with decrease in need for transportation, has flexibility in timing of review, allows avoidance of pupil dilatation and can be culturally acceptable. The Joslin Vision Network programme is a teleophthalmological programme that has been validated and clinically implemented with significant improvement in diabetes-related health outcomes.44 A similar programme to this is currently being assessed and modified for use in remote Indigenous Australian health (currently within a research programme).

Relationships

Patient–provider relationships are essential, and communication needs to be culturally safe. Relationships develop over long periods of time and add enormous depth to the interaction and patient and provider satisfaction.23,35 Relationships between the specialist multidisciplinary teams and primary healthcare (both government and Aboriginal Community Controlled Health Services (ACCHS)) are also of vital importance. Clinics in partnership with PHC services, performed as outreach to urban and remote ACCHS and government PHC clinics, all help develop and build relationships that are sustainable and valued by both parties.

Conclusion

Management of type 2 diabetes mellitus in Australian Indigenous peoples can be challenging in the setting of limited resources and socio-economic disadvantage. Key strategies to address these challenges include working in partnership with patients, communities and PHC services (Aboriginal community controlled and government services) and working in a multidisciplinary team. We need population prevention measures from a young age in order to reduce the risk of diabetes and other chronic cardio-metabolic conditions in the high-risk population of Indigenous Australians. Interventions need to occur within and beyond the health system (including education, employment and nutrition), through government and non-government agencies, and need to commence as early as possible in the life course.

Acknowledgements

The authors thank colleagues at Royal Darwin Hospital Diabetes team, NT Department of Health Remote Primary Health Care services and Aboriginal Community Controlled Health Services within the NT. The views expressed in this publication are those of the authors and do not reflect the views of the NHMRC.


32 National Vascular Disease Prevention Alliance. Guidelines for the...
Alcohol use disorders in Australia

C. H. Freyer,¹ K. C. Morley² and P. S. Haber¹,²

¹Drug Health Services, Royal Prince Alfred Hospital, and ²NHMRC Centre for Excellence in Mental Health and Substance Use, Discipline of Addiction Medicine, The University of Sydney, Sydney, New South Wales, Australia

Key words
alcohol use disorder.

Abstract

Alcohol use disorders are common in Australia and are often unrecognised. Alcohol places a significant burden on our healthcare system by increasing the risk of injuries as well as many chronic medical conditions. Diagnosis requires a high index of suspicion and can be aided by the use of specific questionnaires, such as the Alcohol Use Disorder Identification Test-C. The current available laboratory tests are of limited sensitivity and specificity, but can nevertheless aid in the diagnosis in some circumstances. Newer tests, such as ethyl-glucuronide and phosphatidylethanol, are more sensitive and specific but are costly and not widely available. The effective management of alcohol use disorder entails psychosocial or pharmacological treatments or a combination of both. In those who cannot reduce alcohol consumption, harm reduction strategies can be applied to reduce the burden of harm to the drinkers as well as the community at large.
Introduction

The consumption of alcohol is widespread in Australia and is integrated into many of our social activities. Most Australians consume alcohol at safe levels, but a substantial proportion of people drink excessively, and indeed, the bulk of alcohol is consumed in a hazardous manner. In 2013, the proportion of people aged 14 years or older who drank any alcohol in the past year was 80%. The rates of daily consumption have been declining, with the level falling from 8% in 2007 to 6.5% in 2013. However, recent publications in this journal have reported that the number of hospital admissions for alcohol use disorders (AUD) and for alcoholic liver disease have been increasing in Australia, suggesting that we are seeing increasing alcohol-related harm. Excessive intake of alcohol increases the risk of traumatic incidents, multiple chronic diseases and leads to negative social and financial sequelae. The 2009 National Health and Medical Research Council guidelines state that drinking more than four standard drinks in one sitting increases the risk of injury or accident, and drinking more than an average of two standard drinks a day increases the risk of lifetime harm related to alcohol. In Australia, one standard drink equates to 10 g of ethanol, but this definition varies between countries. The safe drinking recommendations are now the same for men and women. Around 20% of Australian adults drink at levels that put them at risk of lifetime harm, and 45% drink at levels that place them at risk of injury at least once per year.

Alcohol use disorder

AUD is a diagnosis described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). It replaces the diagnostic labels of alcohol abuse and alcohol dependence described in DSM-4. The main reason cited for the change is that the DSM-4 criteria assumed that ‘abuse’ was a milder disorder than ‘dependence’. However, outcomes of those with alcohol abuse are not different overall from those with dependence. The spectrum of severity is better captured by grades of severity within a single diagnosis. The presence of an AUD indicates the existence of physiological, psychosocial or behavioural stress secondary to alcohol excess and the severity is rated based on the number of criteria present (Table 1). An estimated 50% of alcohol-related harm occurs in patients with an AUD. The other 50% is related to episodes of alcohol use that results in accidents, suicide or violence in persons without an identifiable AUD. Comorbid mental health disorders are common, with 42% of AUD patients suffering from one or more additional mental health disorders over a 12-month period. Addressing substance use prior to further psychiatric evaluation is recommended as AUD can exacerbate or mimic mental health conditions. A younger age of first drink and hazardous drinking in adolescence increases the risk of developing AUD later in life. People without AUD tend to reduce their drinking in their early-to-mid 20s, whereas those with AUD often escalate during this period. By the age of 70, only a minority of patients still meet the criteria for an AUD; roughly 50% will have died, up to one-third will be abstinent, and a small proportion will have achieved controlled drinking. Overall, alcohol use is a major health risk, and in 2010 caused 2.7% of the total burden of disease in Australia.

<table>
<thead>
<tr>
<th>Table 1 Alcohol use disorders – diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Alcohol taken in larger amounts or over a longer time than intended</td>
</tr>
<tr>
<td>2. Persistent desire or unsuccessful attempts at cutting down</td>
</tr>
<tr>
<td>3. Great deal of time obtaining, using or recovering from alcohol</td>
</tr>
<tr>
<td>4. Craving for alcohol</td>
</tr>
<tr>
<td>5. Important activities given up due to alcohol use</td>
</tr>
<tr>
<td>6. Ongoing drinking despite knowledge of harm</td>
</tr>
<tr>
<td>7. Failure to fulfill major role obligations at work, school or home</td>
</tr>
<tr>
<td>8. Continued drinking despite alcohol-related interpersonal or social problems</td>
</tr>
<tr>
<td>9. Recurrent drinking in hazardous situations</td>
</tr>
<tr>
<td>10. Tolerance</td>
</tr>
<tr>
<td>11. Withdrawal or using alcohol to avoid withdrawal</td>
</tr>
</tbody>
</table>

Disorder severity:

- Presence of two to three symptoms: mild
- Presence of four to five symptoms: moderate
- Presence of six or more symptoms: severe

<table>
<thead>
<tr>
<th>Table 2 Relative risk for diseases by number of standard drinks per day, Modified from National Health and Medical Research Council (NHMRC) 2009 Australian guidelines to reduce health risks from drinking alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
</tr>
<tr>
<td>Cirrhosis of the liver</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Oesophageal cancer</td>
</tr>
<tr>
<td>Liver cancer</td>
</tr>
<tr>
<td>Lip, oral and pharyngeal cancer</td>
</tr>
<tr>
<td>1.33</td>
</tr>
</tbody>
</table>

Risk for both genders given as single figure (where no significant gender difference exists). Where gender difference is present, male relative risk given on top, female on bottom.
Alcohol has been linked to more than 60 chronic medical conditions. The relative risk of developing medical sequelae depends on the level of consumption (Table 2). Alcohol is one of the leading causes of chronic liver disease; however, the amount needed to induce cirrhosis varies widely. Other gastrointestinal manifestations include acute pancreatitis, chronic pancreatitis, oesophagitis and gastritis. Heavy intake can result in hypertension, alcoholic cardiomyopathy, atrial fibrillation and sudden cardiovascular death. All causes of stroke are increased by heavy alcohol intake. Alcohol consumption has been shown to increase the risk of developing numerous types of malignancies, including those of the oral cavity, pharynx, larynx, oesophagus, colorectal, liver and breast. Neuropsychiatric conditions associated with alcohol include depression, anxiety, cognitive impairment, cerebellar degeneration and peripheral neuropathy. Foetal alcohol spectrum disorder is an underrecognised and important cause of preventable congenital anomaly. The latter may be seen as an important example of harm to others in that the mother consumes the alcohol, but the non-drinking infant experiences the harms. Low to moderate alcohol intake has previously been reported to have health benefits, including decreased cardiovascular disease and all-cause mortality. However, a recent re-evaluation of previous meta-analyses has brought these findings into question and suggests no benefit in moderate levels of drinking.

Pharmacology
Ethanol is water soluble and rapidly crosses cellular membranes. It is rapidly absorbed in the upper gastrointestinal tract. After consumption, peak blood alcohol concentration (BAC) is reached within 30–45 min. Alcohol elimination follows zero order kinetics; hence, a fixed amount is cleared per unit time. Regular consumption induces cytochrome P4502E1, leading to increased alcohol elimination, oxidative stress and altered drug metabolism. It readily crosses the blood–brain barrier and interacts with multiple neurotransmitters. It potentiates the effects at the GABA<sub>A</sub> receptor, which mediates sedation. Alcohol also increases nicotinic and serotoninergic transmission and inhibits the effects of glutamate. Alcohol increases dopamine release as well as endogenous opioids and cannabinoids, which may explain its pleasurable and addictive effects.

Screening and assessment of AUD
Patients with unhealthy drinking patterns may present in a myriad of ways in the community or hospital setting. They often present with comorbidities associated with their drinking, but infrequently present seeking help specifically for their alcohol use.

Clinicians should obtain a quantified alcohol history from all new patients and use structured questionnaires to screen for AUD as clinical judgement alone misses around 50% of patients. There are numerous screening tests available, of which the Alcohol Use Disorder Identification Test-C can be recommended (Table 3) as it has just three questions and performs well in comparison to the others. Others include the CAGE questionnaire and the Alcohol Use Disorder Identification Test. Patients who screen positive should undergo further assessment.

History taking should focus on the patient’s past and present pattern of alcohol consumption, their most recent drinking episode as well as previous periods of abstinence. Clinical assessments rely on self-report and are not objective, which may result in an underestimation of alcohol intake. Collateral reports and laboratory markers become important where clinical discrepancies are found. Details of previous or current treatments should be sought, as well as triggers for ongoing drinking and any concurrent mental health disorders. A detailed substance use history should include use of other licit, illicit, prescription and over-the-counter drugs. Previous physical, social, legal and financial harm due to alcohol should be clarified. Assess insight into their alcohol problem and motivation to cut down or cease drinking. Finally, look for any long-term sequelae from alcohol abuse.

Physical examination should initially focus on eliciting the signs of alcohol intoxication and withdrawal (see below). Specific signs of long-term complications of AUD

Table 3 Alcohol Use Disorder Identification Test-C (AUDIT-C)

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often do you have a drink containing alcohol?</td>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Monthly or less</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2–4 times per month</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2–3 times per week</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4+ times per week</td>
<td>4</td>
</tr>
<tr>
<td>How many standard drinks containing alcohol do you have on a typical day?</td>
<td>1–2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7–9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>10+</td>
<td>4</td>
</tr>
<tr>
<td>How often do you have six or more drinks on one occasion?</td>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Less than monthly</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Monthly</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Weekly</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Daily or almost daily</td>
<td>4</td>
</tr>
</tbody>
</table>

Interpretation:
Score 0–3: low risk of harm
Score 4–7: medium risk of harm
Score 8+: high risk of harm
should also be sought by a complete physical examination. Neurological examination for signs of Wernicke
encephalopathy, including ataxia, ophthalmoplegia, nystagmus and confusion is essential. Peripheral neuropathy
and cerebellar ataxia can also occur in isolation. An assessment of nutritional status should be made, including
body mass index, signs of muscle wasting, loss of subcutaneous fat and evidence of micronutrient deficien-
cies. A mental state examination is indicated as concurrent mental health disorders are common. Formal
cognitive testing can be performed if deficits are suspected; however, the results should be interpreted with
care if the patient is intoxicated or in withdrawal. Cognitive function appears to improve over 4-6 weeks
of abstinence, and hence, delaying assessment until after this time is appropriate. A Montreal Cognitive Assess-
ment is a readily available screening tool.

Biochemical markers

The most specific marker is to measure alcohol itself in breath or blood. Confirmation of consumption and the
level of intoxication may be diagnostically important. Blood levels quickly fall to zero, so a negative test does
not exclude an AUD. Breath alcohol concentration is highly accurate as a BAC proxy. Full blood count and
liver function tests can provide objective markers for problematic alcohol use, but these are neither sensitive
nor specific. Patients may have a raised y-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), ala-
nine aminotransferase (ALT) and a raised mean corpuscular volume (MCV). GGT elevation generally
requires sustained heavy drinking. It is of the most value in obese patients as levels rise more readily following
alcohol consumption. Sensitivity and specificity vary widely according to the population and level of drinking
studied. One study found that sensitivity is as low as 20% for detecting heavy drinkers in primary care. Sensi-
tivity increases in medical inpatients to 30-83%. Isolated AST and ALT levels are non-specific indicators of
liver disease; however, an AST/ALT ratio greater than 2.0 is >90% specific for alcoholic liver disease. MCV
only becomes elevated after sustained high levels of intake (>60 g/day for 2 weeks), and it has low sensitivity and specificity, 52–75% and 74–85% respectively. The MCV can remain elevated for up to 4 months after
becoming abstinent. Newer biomarkers are more sensitive and specific, but are not widely available due to
cost. Carbohydrate-deficient transferrin levels rise after alcohol consumption and can remain elevated for up to
6 weeks. It has a sensitivity of 60–70% and a specificity of 80–95%. Ethyl-glucuronide is a non-oxidative
metabolite of ethanol and remains in the blood for up to 8 h and the urine for up to 80 h after ingestion of alco-
hol. Urine ethyl-glucuronide detected by enzyme immunoassay has a sensitivity and specificity of 89.3 and
98.9% respectively. This test is commercially available, but remains costly as it is not covered by Medicare. Phos-
phatidylethanol is a phospholipid formed only in the presence of ethanol, with a sensitivity of 94.5–100% and
specificity of 100%. The serum half-life of phosphati-
dylethanol is 4 days. However, the current detection methods are difficult and costly.

Acute intoxication

The clinical effects of alcohol are dependent on the BAC. BAC is measured in g/100 mL and, in common usage, is
expressed without units, for example, a BAC of 0.05. A low BAC (<0.05 g/100 mL) leads to mild intoxication
with relaxation, loss of fine motor skills and increased talkativeness. A moderate BAC (>0.1 g/100 mL) leads to
slurred speech, ataxia and impaired judgement. A higher BAC (>0.2 g/100 mL) can lead to a depressed level of
consciousness, amnesia, dysarthria, diplopia, nausea and vomiting. Markedly elevated BAC (>0.4 g/100 mL) can
eventually lead to respiratory depression, coma and death. In alcohol-dependent patients with tolerance,
these effects may be blunted, and clinical features of intoxication may be absent despite a high BAC. The
partition coefficient of BAC to breath alcohol concentration is 2100:1 in nearly all cases, and after this adjust-
ment, breath and blood alcohol correlates very closely, with a high correlation coefficient (r = 0.98). Manage-
ment of the intoxicated patient usually occurs in the emergency department. Ensuring airway patency and
preventing aspiration are priorities. Patients may rarely require mechanical ventilation. Intravenous rehydration
as well as correcting electrolyte disturbance and hypogly-
caemia should be carried out. An aggressive and agitated
patient may require sedation. Severely intoxicated patients should be monitored until intoxication resolves and
comorbidities are excluded, such as head injury or co-ingestion of other drugs. They can be discharged if
there is a return to acceptable level of consciousness, and
no marked withdrawal syndrome develops. Appropriate follow up should be arranged.

Withdrawal and initial management

Withdrawal occurs when there is abrupt cessation or a
considerable decrease in the amount of alcohol con-
sumed. Importantly, withdrawal can arise before blood
alcohol levels reach zero. Whether a patient is intoxi-
cated or in withdrawal should be evident from their
symptoms and signs. Minor withdrawal symptoms
include tremors, diaphoresis, insomnia, anxiety, palpitations, gastrointestinal upset and headache. These will usually resolve within 24–48 h of ceasing drinking. The optimal setting of withdrawal management depends on the severity and the patients’ specific history of previous withdrawal episodes, comorbidities and social situations. Generally, a patient without previous complicated withdrawal, who is otherwise well and with good social supports, can be managed in the outpatient setting. The inpatient setting is required for those with a history of moderate to severe withdrawal or the presence of serious comorbidities. This is based on guidelines rather than firm evidence management. Detoxification facilities are ideal for those unsuitable for ambulatory care yet at low risk of serious complications. Risk stratification may be complex, and to maintain patient safety, such services may adopt a low threshold for referring patients to general hospitals for treatment. An Alcohol Withdrawal Scale (AWS) or a Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) can be used to monitor the patient’s progress. Care must be taken to avoid over-treating alcohol withdrawal as many of the features on the withdrawal scale can be due to comorbid conditions. Over-treating patients can result in excessive sedation, with potential adverse outcomes such as aspiration pneumonia or respiratory failure. Furthermore, excessive sedation may delay discharge. No withdrawal scale has been validated in hospitalised patients with concurrent comorbidities. Treatment with benzodiazepines may be needed, and diazepam is the agent of choice for most patients. Oxazepam is preferred in patients with hepatic dysfunction given its lack of active metabolites. Benzodiazepines can be given in fixed dose, symptom triggered or front-loading regimens. A common fixed dosing regimen can be seen in Table 4. Alcohol withdrawal seizures generally occur within 24 h of cessation. They tend to be singular and respond to benzodiazepines, but not to phenytoin. Prolonged seizures should prompt investigation into secondary causes. Alcoholic hallucinosis is the presence of hallucinations, usually occurring 12–24 h after cessation of drinking, and is not synonymous with delirium tremens. These patients tend to have visual hallucinations, which are ego-dystonic, and otherwise have no altered consciousness. Delirium tremens is a severe form of withdrawal and is defined by the presence of an agitated delirium. Key features are tachycardia, agitation, visual and tactile hallucinations, disorientation, hyperthermia and diaphoresis. Patients with delirium tremens are often dehydrated and have electrolyte disturbances, including hypomagnesaemia and hypokalaemia. Onset usually occurs around 48–96 h post-cessation of drinking. Approximately 5% of patients suffering from untreated alcohol withdrawal will develop delirium tremens. If untreated, the condition can rapidly lead to cardiovascular collapse and death. Mortality is usually due to cardiac arrhythmias, concurrent infections, refeeding syndrome or from an unrecognised illness, such as pancreatitis. Treatment is based on judicious sedation with benzodiazepines for agitation, fluid and electrolyte replacement, treatment of hallucinations using an antipsychotic, such as risperidone or olanzapine and addressing concurrent illness.

Wernicke encephalopathy occurs in the setting of a thiamine deficiency. It is common and often under-diagnosed in patient with AUD. The classical triad of confusion, oculomotor dysfunction (nystagmus, lateral rectus palsy and conjugate gaze palsy) and ataxia is rarely seen, and it is common for patient to present with only one or two of these signs. Other associated signs include peripheral neuropathy, vestibular dysfunction and hyperthermia. If Wernicke encephalopathy is suspected, prompt treatment with intravenous thiamine, 500 mg three times daily for 3–5 days, followed by oral thiamine, 300 mg daily for 1–2 weeks is indicated. Prophylaxis should be given to all alcoholic patients. Healthy patients with good dietary intake can be given 300 mg oral thiamine daily for 3–5 days, followed by 100 mg daily for 10 days. Chronic alcoholics with poor dietary intake have impaired absorption of oral thiamine, and intravenous or intramuscular thiamine should be given, 300 mg daily for 3–5 days followed by 100 mg daily orally for 2–4 weeks. The above recommendations are based on expert opinion as strong evidence is lacking to guide treatment dose and duration.

### Table 4 Dosing of diazepam† for the management of alcohol withdrawal

<table>
<thead>
<tr>
<th>Dosing schedule</th>
<th>Typical indication</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed dosing</td>
<td>Mild–moderate withdrawal</td>
<td>Day 1, 10 mg QID</td>
</tr>
<tr>
<td></td>
<td>Limited monitoring (e.g. outpatients, inexperienced wards)</td>
<td>Day 2, 10 mg QID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 3, 10 mg BD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 4, 5 mg BD</td>
</tr>
<tr>
<td>Symptom triggered‡</td>
<td>All severities of withdrawal</td>
<td>AWS &lt;4, no dose</td>
</tr>
<tr>
<td></td>
<td>Hospital inpatient with capacity for close monitoring</td>
<td>AWS 4–7, 5–10 mg</td>
</tr>
<tr>
<td>Front loading</td>
<td>Hospital inpatient with Severe withdrawal, closely monitored environment</td>
<td>10–20 mg hourly until AWS &lt;4, or lightly sedated</td>
</tr>
</tbody>
</table>

†Contraindications to diazepam: liver failure, respiratory failure, depressed consciousness. ‡Can be used in addition to the fixed dose regime if moderate to severe withdrawal. AWS, Alcohol Withdrawal Scale; BD, twice daily; QID, four times daily.

© 2016 Royal Australasian College of Physicians
psychosis is a disabling complication of untreated We- 
nicke encephalopathy, characterised by markedly 
impaired anterograde and retrograde memory. Confabu-
luration is a striking, but not universal feature.29,30

**Brief interventions**

Brief interventions are recommended for all patients 
with unhealthy patterns of alcohol intake. These inter-
ventions are effective in reducing alcohol consumption 
in the primary care setting.31 Evidence for efficacy in 
emergency department and hospital inpatient settings is 
less robust. A systematic review showed a small effect in 
emergency patients, and a meta-analysis suggests that 
multiple sessions are required for the intervention to be 
effective in hospital inpatients.32,33

Brief interventions can vary in time, from 5 to 30 min. 
They should focus on the following: feedback on the 
potential harms of the patients’ drinking pattern, advice 
regarding safe drinking levels, emphasising patient 
responsibility for changing habits and providing strategies 
on how to reduce consumption. Follow up should 
be arranged at this stage, and further treatment can be 
discussed/implemented.

**Developing a long-term treatment plan**

Australian data demonstrate an 18-year delay, on aver-
age, before treatment for an AUD, so earlier engagement 
in treatment should be a priority.34 The stigma associated 
with AUD is a major barrier to treatment. The aim of 
management is to maintain abstinence or to reduce 
drinking to safe levels. Addiction medicine is a new spe-
cialty, but there is limited evidence for which patients 
reach the threshold for referral to a specialist. In general, 
referral is appropriate if a patient fails to respond to man-
agement from a general physician or if their AUD is 
complex or severe. The most important part of manage-
ment is engaging patients in evidence-based treatment, 
be it psychosocial, pharmacological or both.35 Most 
patients will benefit from a combination of these 
approaches, which, together, address the neuropharma-
cological and psychological aspects of addiction. The full 
range of treatment options should be discussed with 
patients, and an individualised treatment plan should be 
devised. The various pharmacotherapies and psychoso-
cial therapies available for AUD are outlined below. A 
chronic disease management model has been shown to 
be effective, comprising regular follow up with repeated 
brief intervention, monitoring of any pathological find-
ings and consideration of treatment options.

**Pharmacotherapy**

Three medications are currently approved by the TGA 
for the treatment of AUD and recommended in the 
National Treatment Guidelines,36 acamprosate, naltrex-
one and disulfiram. Only acamprosate and naltrexone 
are available on the Pharmaceutical Benefits Scheme. 
These medications are summarised in Table 5.

Acamprosate is a GABA-like compound and is thought 
to modulate neuronal hyperexcitability. Acamprosate 
is moderately effective in maintaining abstinence.37 Adher-
ence is a potential problem given the thrice daily dosing. 
The main side-effects are diarrhoea and fatigue. It is safe 
to use in patients with hepatic dysfunction, but avoided 
in advanced cirrhosis and in moderate to severe renal 
impairment.38

Naltrexone is mu-opioid receptor antagonist that 
decreases the pleasurable effects of drinking alcohol. It is

<table>
<thead>
<tr>
<th>Table 5 Currently approved medications for alcohol use disorder (AUD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acamprosate</strong></td>
</tr>
<tr>
<td><strong>Action</strong></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td><strong>Indications and patients likely to respond</strong></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
</tr>
</tbody>
</table>

© 2016 Royal Australasian College of Physicians
taken as a tablet once daily, at a dose of 50 mg. Naltrexone has efficacy in maintaining remission as well as decreasing intake in patients who relapse.37 A number of studies has shown that a polymorphism of the mu-opioid receptor gene (OPRM1) predicts response to naltrexone treatment. The most recent and prospective trial failed to confirm this finding,39 so it appears premature to recommend this approach to personalised treatment. It is contraindicated in anyone using long-term opioid analgesics as it may induce opioid withdrawal, as well as patients with liver function tests more than three times the upper limit of normal. Side-effects include nausea, headache, fatigue and hepatotoxicity. Liver function tests should be checked prior to commencement and then every 3 months. Other side-effects, including headache, nausea and dysphoria, typically occur early in the treatment.38

While there has been some suggestion that acamprosate is more beneficial for achieving abstinence, whereas naltrexone is more effective in preventing a relapse to heavy drinking, the most recent meta-analysis found no difference between the two medications for return to any drinking or heavy drinking.37 Combining naltrexone and acamprosate may be more efficacious,40 however, not all studies show a benefit over mono-therapy.41

Disulfiram inhibits the enzyme aldehyde dehydrogenase, which leads to the accumulation of acetaldehyde after alcohol consumption. Acetaldehyde induces unpleasant side-effects, and hence, this drug acts as a deterrent to drinking. These effects include diaphoresis, palpitations, flushing, headache, nausea and vomiting. Severe reactions have been reported, including seizures, coma and death. Patients can be exposed to alcohol from unknown sources, such as perfume, aftershave and alcohol-containing medicines, and they should be educated to avoid these. Side-effects may occur in the absence of concurrent alcohol ingestion and include drowsiness, nausea, altered taste, psychosis, irreversible peripheral neuropathy and rarely fulminant hepatitis. Liver function tests should be monitored fortnightly initially as fulminant hepatitis tends to occur in the first 2–3 months of treatment. Disulfiram is suited to patients who are highly motivated and agree to supervised dosing,37 but is ineffective without supervision. Contraindications include coronary artery disease, psychosis and advanced liver disease.

Several other medications have shown promise for treating AUD. The evidence base is growing but none is presently listed for this indication. Baclofen is a GABA\textsubscript{B} agonist, and some studies,42,43 but not all, have shown it to be efficacious in maintaining abstinence, including in cirrhotic patients and those with comorbid anxiety.44 More trials are needed. Dosing commences at 5 mg daily, with gradual escalation to a range of 10–25 mg three times daily. Baclofen is dangerous in overdose, leading to prolonged coma, and hence should be avoided in patients who have a history or are at high risk of self-poisoning. A common side-effect is drowsiness, and patients should be cautioned not to drive or operate machinery if they experience this. The drug should not be stopped abruptly as this can lead to a withdrawal delirium and seizures.46 Topiramate is widely used in the USA and has proven efficacy for the treatment of alcohol dependence.45 Others include nalmefene, ondansetron and gabapentin.

The choice of medication will be dependent on patient factors, such as underlying physical and psychiatric comorbidities, as well as their social situation, for example, the presence of a reliable person to supervise disulfiram. Pharmacotherapy should be continued for at least 3–6 months, and all patients commenced on treatments require follow up as AUD are chronic persisting disorders. Despite proven efficacy, pharmacotherapy for AUD remains under-utilised in Australia.

**Psychosocial treatments**

Psychological interventions can be effective in reducing drinking or maintaining abstinence, alone or in combination with pharmacotherapy.3 Motivational interviewing is a counselling strategy that aims to address and resolve patients’ ambivalence to changing their behaviour. Motivational interviewing can be conducted by any healthcare professional with brief training, including physicians. These skills are applicable to any health-related behaviour and therefore valuable for the physician to acquire. There is evidence to support its use in AUD,46 and a brief version can be delivered during a consultation by a physician.47 Cognitive behavioural therapy is a form of psychotherapy that is structured and explores how thought patterns lead to maladaptive behaviours, such as alcohol misuse. It aims to equip patients with the ability to identify reasons and triggers for drinking in addition to improving their self-coping strategies. It is efficacious in a large range of substance abuse settings, including alcohol.48 Evidence is growing to support the use of newer psychological approaches, including acceptance and commitment therapy, mindfulness therapy and others.49

Mutual help groups, such as Alcoholics Anonymous (AA) and Self Management and Recovery Training (SMART) groups, are widespread. Most groups place an emphasis on sharing and supporting members to achieve and maintain abstinence. AA meetings emphasise the ‘12 steps of recovery’ that link recovery to
acceptance of powerlessness over alcohol and belief in a higher power. The evidence for AA is mixed as many studies have been flawed in design. Other non-religious programmes demonstrated the effectiveness of AA or 12-step facilitation (TSF) approaches for reducing alcohol dependence. A Cochrane review of eight trials involving 3417 participants concluded that no experimental studies unequivocally demonstrated the effectiveness of AA or 12-step facilitation (TSF) approaches for reducing alcohol dependence or problems. Other non-religious programmes exist, such as the SMART recovery programme. Residential rehabilitation programmes range from 1 to 12 months, aiming to develop skills and attitudes required for long-term abstinence. There is a paucity of effectiveness data.

Harm reduction

Strategies to prevent harm should be considered in those who are unwilling or unable to control alcohol use. Administration of thiamine in the long term and maintenance of nutrition are standard practice. Others strategies involve the protection of family and community and seek to reduce the burden of alcohol-related harms to non-drinkers. An active AUD precludes a patient from holding an unconditional driver’s licence according to the Austroads Guidelines. These guidelines stipulate that a conditional private licence can be considered if a patient is in remission and in a treatment programme for more than 1 month and not suffering from cognitive impairment or end-organ damage that may otherwise impair the ability to drive. The duration of remission and engagement in treatment extends to 3 months for conditional commercial licences. Patients should be informed of their legal obligation to inform the driver’s licensing authority. Reporting of patients who are deemed unfit to drive is not mandatory, except in South Australia and the Northern Territory. In the remaining states, it is up to the discretion of the practitioner, and legally, there is no liability in terms of breaching confidentiality if the reporting is done in good faith out of concern for the patient’s and public’s safety.

Other potential risks include occupational injuries and risk of child abuse or neglect. Medical practitioners may have a duty to report such risks to the relevant authorities even without patient consent and should seek expert advice in such cases.

References

Alcohol use disorders in Australia

46 Smedslund G, Berg RC, Hammerstrøm KT, Steiro A,


Clinical trials of medicinal cannabis for appetite-related symptoms from advanced cancer: a survey of preferences, attitudes and beliefs among patients willing to consider participation


1Centre for Cardiovascular and Chronic Care, Faculty of Health, University of Technology Sydney, 2Discipline of Addiction Medicine, Central Clinical School, Sydney Medical School, 3Drug and Alcohol Services, South East Sydney Local Health District, NSW Health, 4School of Psychology and 13Department of Psychopharmacology, Faculty of Science, The University of Sydney, 5Palliative Care, Concord Repatriation General Hospital, 6Palliative Care, Liverpool Therapy Centre, Liverpool Hospital, 11Sacred Heart Supportive and Palliative Care, St Vincent's Hospital, 12Northern Clinical School, Sydney Medical School, 14The Ingham Institute of Applied Medical Research, and 15South Western Sydney Clinical School, University of New South Wales, Sydney, 7Department of Clinical Pharmacology, School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, and 9Palliative and Supportive Services, Flinders University, Adelaide, South Australia, Australia

Key words
Cannabis, cancer, clinical trial, attitude, anorexia.

Abstract
Background: Australian clinical trials are planned to evaluate medicinal cannabis in a range of clinical contexts.
Aims: To explore the preferences, attitudes and beliefs of patients eligible and willing to consider participation in a clinical trial of medicinal cannabis for poor appetite and appetite-related symptoms from advanced cancer.
Methods: A cross-sectional anonymous survey was administered from July to December 2015 online and in eight adult outpatient palliative care and/or cancer services. Respondents were eligible if they were ≥18 years, had advanced cancer and poor appetite/taste problems/weight loss and might consider participating in a medicinal cannabis trial. Survey items focused on medicinal rather than recreational cannabis use and did not specify botanical or pharmaceutical products. Items asked about previous medicinal cannabis use and preferences for delivery route and invited comments and concerns.
Results: There were 204 survey respondents, of whom 26 (13 %) reported prior medicinal cannabis use. Tablets/capsules were the preferred delivery mode (n = 144, 71 %), followed by mouth spray (n = 84, 42 %) and vaporiser (n = 83, 41 %). Explanations for preferences (n = 134) most commonly cited convenience (n = 66; 49 %). A total of 82 % (n = 168) of respondents indicated that they had no trial-related concerns, but a small number volunteered concerns about adverse effects (n = 14) or wanted more information/advice (n = 8). Six respondents volunteered a belief that cannabis might cure cancer, while two wanted assurance of efficacy before participating in a trial.
Conclusion: Justification of modes other than tablets/capsules and variable understanding about cannabis and trials will need addressing in trial-related information to optimise recruitment and ensure that consent is properly informed.

Introduction
Legislative frameworks for medicinal cannabis provision are the focus of much current debate among Australian healthcare professionals and the general public, with the Federal government announcing changes to the Narcotic Drugs Act (1967) in February 2016. More than
two-thirds of Australians support the use of medicinal cannabis,\textsuperscript{3} despite limited evidence for many indications.\textsuperscript{4} Australian clinical trials (complemented by laboratory research) are planned to evaluate medicinal cannabis in a range of clinical contexts, including management of poor appetite and appetite-related symptoms in advanced cancer. These trials aim to provide important new information about the net benefits of medicinal cannabis, assessing both efficacy and adverse effects. As with any clinical trial, success will depend on patients’ willingness to participate based on the acceptability of the intervention and methods.

Internationally, several studies have surveyed people with chronic health conditions who have used medicinal cannabis,\textsuperscript{5–13} but older studies may not reflect changing views on cannabis, and none has focused on cancer patients or canvassed perspectives on clinical trials. Findings suggest that medicinal cannabis users perceive a range of symptom benefits, including pain, appetite, sleep and nausea, and also a range of psychological benefits and enhanced well-being.\textsuperscript{5,13,14}

Survey results concerning delivery routes for self-administering medicinal cannabis in the community have tended to be dominated by smoking,\textsuperscript{8,10,13} a route associated with carcinogenicity and respiratory toxicity both to the smoker and those in proximity that cannot be used in healthcare and other environments where smoking is banned. Tablets or capsules are the most commonly used delivery mode for medicines, but a broader range needs to be considered for medicinal cannabis to enable tailoring to the indication and optimisation of pharmacokinetic and pharmacodynamic properties of specific products. For example, some cannabinoids have low oral bioavailability and variability in pharmacodynamic effects. A range of delivery routes is also needed because oral and inhalation modes may not be feasible for people with swallowing and respiratory problems. For use in clinical trials, cannabis plant-derived products will also need to meet Australian Therapeutic Goods Administration’s (TGA) standards for Good Manufacturing Processes (GMP).\textsuperscript{15} The standardisation of dosage is important for both clinical trials and (if a benefit is demonstrated) subsequent therapy. Future clinical trials will also require stringent documentation of the major cannabinoid content of agents tested in view of evidence for differing effects and risks associated with the content of tetrahydrocannabinol and cannabidiol.\textsuperscript{16}

Failing to align the drug delivery route with patient preferences may impact trial feasibility, recruitment and retention rates and therefore study completion. Research with other medications has shown mode of administration to be an important predictor of adherence and outcomes for cancer patients.\textsuperscript{17} Preferences for the mode of delivery of analgesics has been found to vary according to patient characteristics (e.g. gender), previous experience and perceived differences in efficacy and side effects.\textsuperscript{18} For this reason, a better understanding of the perspectives of potential participants regarding Australian medicinal cannabis trials is important for informing the choice of delivery mode, the content of trial-related patient information and optimising recruitment, adherence and retention.

A study was designed to explore the preferences, attitudes and beliefs of people with advanced cancer who self-identified as willing to consider participating in a clinical trial of medicinal cannabis for poor appetite and appetite-related symptoms.

**Methods**

A cross-sectional survey design was used. The study was approved by the South Western Sydney Local Health District Human Research Ethics Committee (HREC number LNR/15/LPOOL/185).

**Patient selection**

Patients were eligible if they self-reported as: (i) being ≥18 years of age; (ii) having advanced cancer and poor appetite, taste problems and/or weight loss; and (iii) being willing to consider participating in a medicinal cannabis trial for these problems. Appetite and appetite-related symptoms are among the most common and serious problems in advanced cancer that may benefit from medicinal cannabis\textsuperscript{19} and are the focus of a planned trial.

The volunteer effect expected from open surveys was considered likely to support the study’s aims by biasing selection towards patients likely to participate in future trials. Surveys were administered electronically online and through hard copies in the waiting rooms of eight adult outpatient palliative and/or cancer services, seven in NSW and one in South Australia, between July and December 2015. Participant anonymity was protected by approval from the HREC to assume that the completion of the survey constituted informed consent without this needing to be collected via reference to name and address. Online data collection did not record Internet Protocol addresses or other information that could be used to identify respondents, and surveys completed in waiting rooms were returned through ballot-style boxes rather than directly to clinical or research staff. To minimise response bias associated with a reticence to disclose illegal activity, survey questions focused on medicinal, not recreational, cannabis use. Study information highlighted exemption from
Surveys were developed by a multidisciplinary team of cannabis and clinical trials experts, palliative care physicians and nurses, and was reviewed by consumers (see Box 1 for items). Experts were scientific committee members and site investigators of the Palliative Care Clinical Studies Collaborative (PaCCSC). Item suggestions were circulated via email; responses were collated, and revised items were circulated iteratively until consensus was reached.

Box 1. Items used in the survey on medicinal cannabis use and related clinical trials

1. Age (in years) 18/25–26/40–41–60/61–75/76–85/85+
2. Sex: Male/Female
3. What kind of cancer do you have?_____________________
4. If you were to take part in a clinical trial of medicinal cannabis for improving loss of appetite, taste problems and weight loss, how would you prefer to take the medication? (Tick all that apply)
   - Oral – tablets or capsules
   - Oral mouth spray
   - Oral – eating (cookies)
   - Oral – drinking (tea)
   - Inhaled using a special vaporiser
   - Suppositories (inserted into the rectum)
   - Topical (applied to the skin)
   - Other (please describe):__________________________
5. Would you have any concerns with using medicinal cannabis in a clinical trial? Yes/No/Unsure
   a. If ‘yes’ or ‘unsure’, please describe any concerns you may have.
6. Have you ever used cannabis medically for any health problem(s)? Yes/No (if no, please skip to question 7)
   a. If yes, what health problem(s) have you used cannabis for?
   b. How have you usually used cannabis for health problems?
      (Tick all that apply)
      - Smoked with tobacco in joint or cone
      - Smoked alone in joint or cone
      - Vaporiser
      - Oral forms/edibles (e.g. cookies, biscuits)
      - Other (please describe):__________________________
   c. If you enrolled in a clinical trial, you would be asked to stop your usual use of medicinal cannabis so that measures could more clearly tell whether any benefits were due to the product being used in the trial. Would this prevent you from taking part? Yes/No/Unsure
7. Regardless of whether you have used medicinal cannabis, please use the space below to make any other comments you would like to about future cannabis clinical trials.

Quantitative data were summarised descriptively using SPSS V23.0 (SPSS, Chicago, IL, USA) statistical software. Medicinal cannabis users and non-users were compared for age (<60 years), gender and trial-related concerns (yes or unsure/no). These variables were also used to compare groups expressing particular preferences with regards to route/mode of cannabis delivery. Age <60 years was chosen because people in the younger age group might have been more likely to use cannabis recreationally during their early adulthood and therefore have different views on cannabis than older patients. For this reason, we were also interested in finding out whether patients who took part in the survey (and therefore were willing to consider taking cannabis in a clinical trial) were younger than the national average. Bivariate analyses were used to identify unadjusted relationships, with a significance level of P < 0.10 used to select variables for inclusion in multiple logistic regression analyses of adjusted relationships, with the calculation of 95% confidence intervals (CI). A type I error of 5% was adopted for all analyses. Comments were coded inductively by two researchers.

Results

Respondent characteristics

A total of 211 respondents completed the survey. Seven surveys were removed because participants reported diagnoses other than cancer, leaving 204 for inclusion in analyses. Of these, 175 (86%) completed the survey at participating services, and 29 (14%) completed it online. The median number of surveys collected at each outpatient service was 21 (range: 3–50). Variability in numbers of surveys per site was due, in part, to some sites commencing later than others. See Table 1 for a summary of respondent characteristics.

Previous use of medicinal cannabis

A total of 26 (13%) respondents reported prior use of medicinal cannabis. The most common indications were pain and appetite loss (n = 9 each), followed by psychological problems (n = 5), insomnia (n = 4) and nausea (n = 2). The majority of users reported smoking cannabis either on its own (n = 18) or with tobacco (n = 15), while 12 had consumed it orally, and 10 had used a vaporiser. Of the 25 users who answered the question, 21 indicated that being asked to stop their current medicinal use would not prevent them from participating in a trial, three indicated it would prevent them, and one indicated that she was unsure. Compared with
of the likelihood of having trial-related concerns (P = 0.07) or the likelihood of aged less than 60 years (P = 0.001) but did not differ significantly with regards to gender (χ² = 3.24, P = 0.07) or the likelihood of having trial-related concerns (χ² = 1.92, P = 0.17).

### Preferences for route/mode of delivery

Of the seven modes of medicinal cannabis delivery offered, respondents identified a median of two preferences (range: 0–7), with nine (4%) indicating a willingness to use any mode (Table 2). Reasons for preferences were offered by 134 (66%) respondents and were most commonly related to perceived ease/convenience (n = 66, 49%) followed by considerations relating to taste, nausea or lack of appetite (n = 17, 13%); a familiarity with the mode for taking other medications (n = 11, 8%); perceived faster speed of action (n = 11, 8%); control over dose (n = 7, 5%); enjoyment (n = 5, 4%); and perceived advantages in efficacy (n = 4, 3%) and unobtrusiveness (n = 3, 2%) and adverse effects (n = 2, 1%). Reasons given for preferences against certain modes included a wish not to take any more tablets (n = 6, 4%) and reduced capacities to swallow (n = 7, 5%), inhale (n = 2, 1%) or use suppositories (n = 2, 1%). A further four (3%) patients indicated a general distaste for suppositories. A small number (n = 14, 11%) reported preferences for alternative (n = 4, 3%) or additional (n = 10, 8%) modes, including smoking (e.g. in a ‘joint’ or ‘glass pipe’) (n = 7, 6%), percutaneous endoscopic gastrostomy (n = 4, 3%) and oil (n = 3, 2%).

Given the sample’s strong preference for tablets/capsules and the limited range of cannabinoid-based products deliverable through this mode, inferential analyses were focused on characteristics and attitudes of respondents citing this as an exclusive preference (Table 3). The logistic regression model found female gender to be significantly and positively associated with an exclusive preference for tablets/capsules (odds ratio (OR) = 1.86 (95% CI 0.96–3.61)) and previous experience of medicinal cannabis to be negatively associated (OR = 0.23 (95% CI 0.05–1.03)); there was no evidence of interaction between the variables.

### Trial- and cannabis-related attitudes and beliefs

Of the 204 respondents, 168 (82%) said they had no trial-related concerns, 12 (6%) indicated they did, and 25 (12%) indicated they were unsure. Concerns elucidated in comments included potential adverse psychological effects (n = 14); a need for more information/advice to help them decide about participating (n = 8); and concerns regarding addictiveness (n = 3), compatibility with other medications (n = 2) and legal issues (n = 2). Five respondents perceived a need to limit access or expressed concern about a ‘slippery slope’ to legalisation for recreational use, and three expressed a belief that cannabis would be unlikely to benefit everyone. Two respondents said they would need to be reassured of evidence for efficacy before participating in a clinical trial. Factors highlighted by single respondents as influencing their decision to participate included the dose required, trial duration, risk of allergy to cannabis and tolerability in the context of poor liver function.

General comments (n = 122) frequently went beyond poor appetite to refer to symptoms in general or specific others, such as pain or nausea. A total of 16 (13%)...
respondents believed that there was sufficient evidence for medicinal cannabis without further clinical trials. Four (3%) respondents reported being in favour of clinical trials because of their potential to facilitate legalisation and so improve access to cannabis. A total of 11 (9%) reported first-hand anecdotal evidence for the efficacy of cannabis in managing symptoms, 8 (6%) reported hearing others report such benefits, and 3 (2%) reported being influenced by positive reports in the media or medicinal cannabis advocates. Five (4%) compared cannabis favourably with other medications in terms of side effects, and one (1%) indicated that he was unable to use alternative medications for symptoms, leaving cannabis as his only option. Six (5%) respondents reported a belief that cannabis might have the potential to cure cancer.

**Discussion**

This study is the first to survey people with advanced cancer willing to consider participation in a clinical trial of medicinal cannabis. It therefore yields new insights into related preferences, attitudes and beliefs, with important implications for future trials.

Tablets/capsules were by far the most preferred mode of delivery for reasons of ease/convenience and familiarity, although a small minority were opposed to tablets/capsules on the grounds that they were already taking large numbers for other medications or had problems with swallowing. Univariate analyses suggested that women and those with no experience of medicinal cannabis were more likely to express an exclusive preference for tablets/capsules. However, these variables showed reduced association in multivariate analysis, with results suggesting that the more common preference for tablets/capsules reported by women was largely accounted for by their lesser experience with medicinal cannabis. This finding may suggest that attitudes vary between people who are considering taking medicinal cannabis for the first time because they are newly conceptualising it as a sanctioned medication and those who have used cannabis outside the auspices of medical care.

After tablets/capsules, the most preferred modes of delivery were mouth spray and vapouriser. In Australia, nabiximols (a Schedule 8 medication) is currently the only pharmaceutical on the Australian Register of Therapeutic Goods that delivers cannabinoids through the oro-mucosal route, although other oral pharmaceutical products (nabilone, dronabinol) have been accessible through the TGA Special Access Scheme. There is an emerging interest in the vapourisation of cannabis for the management of symptoms, including neuropathic pain. A recent study has provided evidence of vapouriser acceptability among a large national sample of US cannabis users (n = 2,910), suggesting that it may represent a satisfactory alternative to smoking for people used to that mode of delivery.

Comments offered by respondents to the current survey are consistent with findings from a previous survey and qualitative studies on medicinal cannabis use. Cannabis users have consistently reported anecdotal evidence for symptom improvement, although the proportion reporting benefit has varied widely. The only previous Australian survey (n = 128) found that around a quarter of medicinal cannabis users across a variety of health conditions used it for appetite loss, and nearly all reported ‘great’ or ‘good’ relief. Compared with efficacy, previous studies have paid less attention to the side effects of medicinal cannabis use. Only a small proportion of respondents have tended to report side effects, with the exception of a German study, which found almost a third of respondents rating these as ‘moderate’ or ‘strong’. Results from qualitative studies suggest that the low emphasis placed on side effects by survey respondents may, in part, reflect a perception that these are favourable compared to other medicines, a perception also voiced by a small number in the current survey.

Small numbers of respondents also appeared unclear that the primary purpose of clinical trials is to test...
efficacy, and held beliefs that cannabis has the potential to cure cancer. This suggests that information associated with a clinical trial aimed at evaluating symptom control needs to describe its purposes using language that potential participants can understand, and also highlights the need to balance the rationale for clinical trials with emphasis on equipoise.

Finally, respondents’ requests for further information and advice from the medical community is consistent with previous survey results26 and of special interest given evidence that health professionals themselves hold varying views on medicinal cannabis and report an unmet need for guidance on how best to advise patients.27,28

**Limitations**

Our study’s focus on people willing to consider participating in clinical trials of medicinal cannabis means the results are unlikely to be representative of people with advanced cancer more generally. The services participating in the study served diverse metropolitan communities but did not represent regional and rural patient perspectives. Furthermore, the survey measured patient attitudes rather than behaviours, and the latter cannot be assumed always to follow from the first.29 Also, some respondents may not have reported previous cannabis use because they regarded this to be recreational rather than medicinal. Prior research suggests that users may vary in the degree they distinguish recreational and medicinal use, especially with regards to perceived psychological benefits, which may be seen as falling in both categories.9,13,14 We did not ask about previous recreational use because the study aims were focused on cannabis in a medicinal context, and we sought to minimise ethical issues and response bias associated with the discussion of illegal activity. More research is needed into the relationship between recreational and medicinal use of cannabis in people with chronic illness to understand better related health beliefs and how these influence use over time.

The low prevalence of previous or current medicinal cannabis use within the sample limited analyses regarding the relationship between experience and various perspectives. However, it also provides encouragement for the feasibility of future trials to accrue participants willing to try cannabis for the first time as well as current or previous users. The fact that our sample was somewhat younger than population estimates for Australian cancer patients at diagnosis26 is consistent with the possibility that younger people may be more willing to consider participation in medicinal cannabis trials because societal attitudes have become more sympathetic over time.

Finally, differences in the recruitment strategy used for our survey vis-à-vis those typical of a clinical trial mean the numbers taking part should not be used to estimate likely accrual rates.

**Conclusion**

Future trials of medicinal cannabis for advanced cancer symptoms may be more likely to attract and retain patients if preferences for an oral delivery route can be accommodated or alternative routes justified. People with advanced cancer may have varying understanding about both cannabis and trials. This should be addressed in trial-related participant information and public communication strategies to optimise recruitment, adherence and retention and to ensure that consent is properly informed.

**Acknowledgements**

This study was conducted using existing infrastructure at the PaCCSC and Centre for Cardiovascular and Chronic Care at the University of Technology Sydney. The authors acknowledge Linda Devilee from PaCCSC for her contribution to survey design. We also acknowledge the contributions to data collection made by investigators and/or research nurses at the following sites who have not met all criteria for authorship: Calvary Mater Newcastle (Prof Katherine Clark and Naomi Byfield), Crown Princess Mary Cancer Centre (Dr Christopher Pene), Greenwich Hospital (Bronwyn Raymond), Liverpool Hospital (Robin O’Reilly), Sacred Heart Hospice (Frances Bellemore and Penelope West), St George Hospital Sydney (Dr Caitlin Sheehan) and Southern Adelaide Palliative Services (Dr Peter Allcroft and Aine Greene).

**References**


The revolving door: antibiotic allergy labelling in a tertiary care centre

B. Knezevic,1 D. Sprigg,1 J. Seet,2 M. Trevenen,2,3 J. Trubiano,4 W. Smith,6 Y. Jeelall,6 S. Vale,7 R. Loh,8,9 A. McLean-Tooke1,9 and M. Lucas1,9,10,11

Departments of 1Clinical Immunology, and 2Research, and 10Clinical Immunology, Sir Charles Gairdner Hospital, 11Centre for Applied Statistics, University of Western Australia, 3School of Medicine and Pharmacology, Harry Perkins Institute of Medical Research, 4Department of Clinical Immunology, Princess Margaret Hospital, 5Pathwest Laboratory, Queen Elizabeth II Campus, and 11Institute for Immunology and Infectious Diseases, Murdoch University, Perth, Western Australia, 6Department of Immunology, University of Western Sydney, 7Drug Allergy Working Party, Australasian Society of Clinical Immunology and Allergy, Sydney, New South Wales, Australia

Key words
antibiotic, allergy, hypersensitivity, delabelling, penicillin.

Correspondence
Brittany Knezevic, Department of Clinical Immunology, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, Perth, WA 6009, Australia.
Email: brittany.knezevic@health.wa.gov.au

Received 25 March 2016; accepted 18 July 2016.
doi:10.1111/imj.13223

Abstract

Background: Patients frequently report antibiotic allergies; however, only 10% of labelled patients have a true allergy.
Aim: We investigated the documentation of antibiotic ‘allergy’ labels (AAL) and the effect of labelling on clinical outcomes, in a West Australian adult tertiary hospital.
Methods: Retrospective cross-sectional analysis of patients captured in the 2013 and 2014 National Antimicrobial Prescribing Surveys was carried out. Data were collected on documented antibiotic adverse drug reactions, antibiotic cost, prescribing appropriateness, prevalence of multi-drug resistant organisms, length of stay, intensive care admission and readmissions.
Results: Of the 687 patients surveyed, 278 (40%) were aged 70 or above, 365 (53%) were male and 279 (41%) were prescribed antibiotics. AAL were recorded in 122 (18%) patients and the majority were penicillin labels (n = 87; 71%). Details of AAL were documented for 80 of 141 (57%) individual allergy labels, with 61 describing allergic symptoms. Patients with beta-lactam allergy labels received fewer penicillins (P = 0.0002) and more aminoglycosides (P = 0.043) and metronidazole (P = 0.021) than patients without beta-lactam labels. Five patients received an antibiotic that was contraindicated according to their allergy status. Patients with AAL had significantly more hospital readmissions within 4 weeks (P = 0.001) and 6 months (P = 0.025) of discharge, compared with unlabelled patients. The majority (81%) of readmitted labelled patients had major infections.
Conclusions: AAL are common, but poorly documented in hospital records. Patients with AAL are significantly more likely to require alternative antibiotics and hospital readmissions. There may be a role for antibiotic allergy delabelling to mitigate the clinical and economic burdens for patients with invalid allergy labels.

Introduction

Up to 20% of patients report one or more antibiotic allergies (antibiotic ‘allergy’ labelled).1–3 However, the majority of antibiotic allergy labels (AAL) are invalid.4–6 Drug allergy specialists can assist clinicians by delabelling many patients with alleged antibiotic allergies. For example, almost 90% of beta-lactam labels can be safely removed after thorough assessment.5,6

Beta-lactams, which comprise penicillins, cephalosporins, monobactams and carbapenems, currently account for 60% of antibiotic prescriptions in Australian hospitals.7 Avoiding beta-lactam or other antibiotics in patients with alleged allergy often necessitates prescription of second-line antibiotics which may be less effective, more expensive and lead to higher rates of adverse effects and multi-drug resistance pathogens.4,8,9 International observational studies have shown that patients with AAL have increased hospital utilisation and poorer clinical outcomes.10,11 Unverified antibiotic allergy labelling is a significant and growing public health problem resulting in unnecessary adverse outcomes. Whether

Funding: None.
Conflict of interest: None.

© 2016 Royal Australasian College of Physicians
systematic antibiotic allergy delabelling can mitigate these clinical and economic burdens remains to be seen.

These issues have not been broadly addressed in an Australian context, apart from case series focusing on specific patient groups.12–14 We sought to investigate the frequency of reported AAL, the accuracy of allergy documentation, appropriateness of antibiotic prescribing and the effect of labelling on clinical outcomes in an adult tertiary hospital in Western Australia.

Methods

We performed a retrospective single-centre cross-sectional analysis of 775 inpatients in a 600-bed adult tertiary care teaching hospital in Perth, Western Australia. All patients were captured in the 2013 and 2014 National Antimicrobial Prescribing Survey (NAPS), which was performed during ‘Antimicrobial Awareness Week’ in November. NAPS is a voluntary annual audit of Australian health services, led by The Australian Commission on Safety and Quality in Health Care, which provides a point prevalence of hospital inpatient medication charts to assess volume and appropriateness of antimicrobial prescribing.15

NAPS data were collected from patients’ medication charts by ward pharmacists. The audit captured data on all patients admitted to hospital wards (including all medical and surgical specialties, intensive care unit, psychiatry and rehabilitation wards, but excluding the emergency department and day admission wards). Data collected included patient demographics, antibiotics prescribed (at time of audit) and documented AAL. AAL is a blanket term to denote any antibiotic recorded in the ‘allergies and adverse drug reaction’ section of the patient’s medication chart. Patients were excluded from the study if there was no NAPS documentation to indicate either the presence or absence of antibiotic adverse drug reactions. For AAL, the culprit medication and alleged symptoms (if documented in the medication chart) were captured. Documented AAL symptoms were classified as (i) anaphylaxis, (ii) angioedema, (iii) rash or unspecified swelling, (iv) gastrointestinal upset, or (v) non-specific symptoms (e.g. headache). Groups 1–3 represent allergic-type symptoms (graded according to severity) and groups 4 and 5 represent probable non-immunological intolerances. The daily costs of antibiotics were calculated, per patient, using the hospital pharmacy formulary. NAPS prescribing scores are graded based on the degree of appropriateness (1: optimal; 2: adequate; 3: suboptimal; 4: inadequate; 5: not assessable) of antibiotic choice as assessed by an infectious diseases pharmacist or physician using an internally validated scoring system.15 For the purposes of this study, scores of 1 or 2 were considered appropriate and 3 or 4 as inappropriate. Patient allergies were accounted for in the appropriateness scoring algorithms. Indications for each antibiotic prescription were classified as bacterial infection (specified), prophylaxis, or indication unclear.

NAPS data were supplemented with electronic records and discharge summaries to record principal diagnosis of admission, admitting specialty unit, intensive care admissions, death during admission, hospital length of stay and readmissions within 4 weeks and 6 months of discharge. The overall follow-up period for each patient was 6 months from inclusion (NAPS audit) date. Direct hospital transfers, day procedures and review in the emergency department were not considered readmissions. Patient electronic microbiology records were reviewed to capture any Clostridium difficile toxin, methicillin-resistant Staphylococcus aureus and/or vancomycin-resistant Enterococcus (VRE) positive screening or diagnostic microbiological samples.

Study groups were classified based on the presence or absence of an AAL in the medication chart. We further classified patients with an AAL into ‘beta-lactam’ and ‘non-beta-lactam’ labels. We sub-classified ‘beta-lactam’ labels as ‘penicillin group’, ‘cephalosporin’, ‘carbapenem’ or ‘monobactam’ labels. Patients were classified as non-allergic (no antibiotic allergy label; NAAL) if they had no known AAL or an allergy to a non-antibiotic drug or non-drug allergen. This study was approved through the Sir Charles Gairdner Group Human Research Ethics Committee (quality activity #8380).

Statistical analysis

Data were analysed using the R environment for statistical computing.16 Medians and interquartile ranges are presented for continuous variables whilst counts and percentages are presented for categorical variables, unless otherwise stated. Chi-squared tests (Fisher’s exact tests where appropriate) were used to compare specific antibiotics prescribed and infections between beta-lactam allergic-labelled patients and non-beta-lactam allergically labelled patients. Initially, binary logistic regression was used to analyse the relationships between demographic patient variables and any allergy label (event = ‘Yes’). Subsequently, multivariate models were conducted to investigate the effect of antibiotic allergy labelling on the prevalence of highly resistant bacteria, intensive care admission, patient death in hospital and 4-week readmission rate (logistic regression; event = ‘Yes’); the number of readmissions within 6 months and NAPS prescribing score (ordinal logistic regression); hospital
length of stay (Cox proportional hazards regression; event = ‘leaving hospital’ where those who died during their hospital stay are censored at their date of death); cost of antibiotics (linear regression, log-transformed response) and the number of antibiotics prescribed (Poisson regression). Patient age, gender, admitting team, antibiotic use and audit year were adjusted for in all models and backwards model selection was performed such that variables significant at a 5% level were retained for the final models.

Results
A total of 775 patients was captured in the NAPS database (374 in 2013, 401 in 2014). Based on the maximum available overnight hospital beds, the capture rate was 79% in 2013 (374 out of 476 beds) and 89% in 2014 (401 of 453 beds). This is likely to be an underestimate, as not all beds were occupied at the time of the NAPS audits. There were 38 instances where the same patient was recaptured due to ward transfer during the audit period. The earliest capture date was used for these patients and an additional 50 patients were excluded because allergy status was not recorded in NAPS documentation. The final cohort of 687 patients reflected the expected demographics in the tertiary care centre. From 2013 to 2014, the mean age of all hospitalised patients was 61 years and 53% of patients were male. In the final cohort of 687 patients, the mean age was 62 years, 278 (40%) patients were aged 70 or above, 365 (53%) were male and 279 (41%) were prescribed antibiotics at the time of the audit (Table 1). The major indications for antibiotics were pneumonia (n = 74, 28%), genitourinary (n = 44; 17%), skin and soft tissue (n = 42; 16%), intra-abdominal or gastrointestinal infections (n = 34, 13%), and prophylaxis (n = 26; 10%) (Table 2). Prescribing scores were judged as appropriate for 176 of 279 prescriptions (63%), inappropriate for 84 (30%) and indeterminate for 19 (7%).

Females and older patients were significantly more likely to have an AAL (gender: odds ratio (OR) = 2.54, 95% confidence interval (CI) = 1.69–3.82, P < 0.001; for a 1 standard deviation (19.6 years) increase in age: OR = 1.31, 95% CI = 1.06–1.60, P = 0.007). The same was also true for beta-lactam AAL alone (gender: OR = 2.28, 95% CI = 1.46–3.54, P < 0.001; for a 1 standard deviation increase in age: OR = 1.33, 95% CI = 1.07–1.67, P = 0.011). Patient admitting team (by individual specialities), audit year and prescription of antibiotics at the time of audit were not significantly associated with presence of AAL or, more specifically, beta-lactam AAL.

Antibiotic allergy labels
One or more AAL were recorded in 122 (18%) patients, with NAAL recorded for the remaining 565 (82%) patients. The majority of AAL were beta-lactam labels (n = 101; 83%), of which most were in the ‘penicillin group’ (n = 87; 71% of ‘allergic’ cohort; 13% of whole cohort). The specific AAL comprising the beta-lactam group was ‘penicillin (not otherwise specified)’ (n = 76; 75%), ‘cephalexin’ (n = 7), ‘amoxicillin’ (n = 5), ‘amoxicillin/clavulanic acid’ (n = 3), ‘piperacillin/tazobactam’ (n = 2) and ‘cephazolin’ (n = 2). The majority of non-beta-lactam labels comprised the sulfamethoxazole/trimethoprim (n = 11), macrolide (n = 7) and glycopeptide (vancomycin) (n = 7) groups. In the AAL group, 108 (89%) patients had a single allergy, 10 (8%) had two documented AAL and 4 (3%) had three or more labels.

Descriptions of reactions to the culprit antibiotic were documented for 80 of 141 (57%) individual AAL. For the remaining 61 (43%) labels, there was no documentation of symptoms. Of the 80 AAL with documentation, 61 described symptoms consistent with allergy and 19 were non-specific (non-allergic) intolerances (Fig. 1). Non-specific symptoms were more frequently recorded for non-beta-lactam labels.

Five patients, among a group of 33 penicillin-labelled patients prescribed with antibiotics (6% of the 87 penicillin-labelled patients in total), were receiving an antibiotic that would be considered contraindicated according to their allergy status. Two patients with a history of unspecified penicillin-induced anaphylaxis received a penicillin (piperacillin/tazobactam; amoxicillin/clavulanic acid). One patient with unspecified penicillin-induced ‘rash’ received piperacillin/tazobactam. Two patients with AAL documented as ‘unknown reaction’ (one to an unspecified penicillin, the other to amoxicillin/clavulanic acid), received amoxicillin. There were no adverse events captured as a result of these prescriptions, although this study was not designed to assess outcomes of prescribing errors.

Impact of antibiotic allergy label on choice of antibiotics
The impact of AAL on antibiotic prescriptions is summarised in Table 2. As expected, patients with beta-lactam AAL were prescribed significantly fewer penicillins (P = 0.0002) and significantly more alternative antibiotics, such as aminoglycosides (P = 0.043) and metronidazole (P = 0.021), than non-beta-lactam-labelled patients. Although there was increased use of third and fourth generation cephalosporins, quinolones,
clindamycin, fusidic acid and daptomycin, among beta-lactam-labelled patients, this did not reach statistical significance.

### Impact of antibiotic allergy label on hospital outcomes

Of the 663 discharged patients (excluding 24 patients who died in hospital), 129 (19.5%) were readmitted within 4 weeks. Patients with an AAL were significantly more likely to be readmitted within 4 weeks than NAAL patients (OR = 2.16, 95% CI = 1.34–3.46, P = 0.001) (Table 3). Of the 35 AAL patients readmitted within 4 weeks, 29 (81%) had infections in the first and/or second admission (captured as principal diagnosis or NAPS antibiotic prescription). Five patients (14%) were readmitted with recurrence of the same infection (urosepsis, pneumonia, wound and ocular infections). Limiting the cohort to patients with a principal diagnosis of infection, 9 of 30 (30%) AAL patients were readmitted within 4 weeks, compared with 24 of 136 (18%) NAAL, although this did not reach statistical significance, and was therefore not included in the final multivariate model.

Patients with an AAL also had significantly more readmissions within 6 months compared with NAAL patients (OR = 1.51, 95% CI = 1.00–2.27, P = 0.049). Thirty of 101 (30%) beta-lactam AAL patients had two or more readmissions within 6 months compared with 106 of 562 (19%) non-beta-lactam AAL patients.

Further analysis focusing on beta-lactam-labelled patients yielded corresponding results. Beta-lactam-labelled patients were significantly more likely to require readmission within 4 weeks with 29 of 101 (29%) beta-lactam AAL patients readmitted compared with 100 of 562 (18%) of non-beta-lactam AAL patients (OR = 2.03, 95% CI = 1.23–3.35, P = 0.006). The length of readmissions ranged from 2 to 22 days. Beta-lactam AAL patients also had significantly more readmissions within 6 months (OR = 1.51, 95% CI = 1.00–2.27, P = 0.049). Thirty of 101 (30%) beta-lactam AAL patients had two or more readmissions within 6 months compared with 106 of 562 (19%) non-beta-lactam AAL patients.

These results were adjusted for patient age, gender, admitting team and intensive care admissions and no specific chronic diseases (e.g. cystic fibrosis, malignancy, transplant patients) appeared overrepresented among readmitted allergy-labelled patients. There were no significant differences in the following variables between patients with and without any AAL: antibiotic costs, appropriateness of antibiotic prescribing, prevalence of multi-drug-resistant organisms on microbiological follow up, hospital length of stay, patient death in hospital and intensive care admissions (Table 3).

### Discussion

This study provides a snapshot of antibiotic allergy labelling in a metropolitan tertiary care centre. Eighteen percent of hospitalised patients reported at least one AAL, the majority to penicillin (72%). This equals the national average (18%) and is towards the upper range of reports in the international literature.1–3

Documentation of ‘allergic’ symptoms was frequently missing from patient medication charts, despite inpatient status and ward pharmacist review. Furthermore, five (6%) penicillin-labelled patients received antibiotics which would be considered contraindicated, according to their allergy status. A recently published Australian study reported a similar rate of inadvertent antibiotic rechallenge (7%) in a general medical cohort.14 This is of concern in light of reports of increasing medication-related anaphylaxis and mortality in adult Australian hospitals.17–18 The Australian Commission on Safety and Quality in Health Care medication safety standards state such medication errors are ‘highly preventable’ through effective use of allergy alert systems.19 However, allergy alert systems rely on accurate allergy documentation and correct clinical decision-making: deficits in both areas have been highlighted in previous studies.20,21 None of

### Antibiotic allergy labelling

#### Table 1 Counts and percentages of patient demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Any antibiotic allergy label</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 122)</td>
<td>No (n = 565)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 years</td>
<td>9 (18%)</td>
<td>41</td>
</tr>
<tr>
<td>30–49 years</td>
<td>14 (10%)</td>
<td>121</td>
</tr>
<tr>
<td>50–69 years</td>
<td>37 (17%)</td>
<td>187</td>
</tr>
<tr>
<td>70–89 years</td>
<td>54 (22%)</td>
<td>187</td>
</tr>
<tr>
<td>&gt;90 years</td>
<td>8 (22%)</td>
<td>29</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>80 (25%)</td>
<td>242</td>
</tr>
<tr>
<td>Male</td>
<td>42 (12%)</td>
<td>323</td>
</tr>
<tr>
<td>Admitting team</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>77 (20%)</td>
<td>301</td>
</tr>
<tr>
<td>Surgical</td>
<td>32 (12%)</td>
<td>187</td>
</tr>
<tr>
<td>ICU/Psychiatry</td>
<td>13 (14%)</td>
<td>77</td>
</tr>
<tr>
<td>Principal diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>30 (17%)</td>
<td>142</td>
</tr>
<tr>
<td>Other (not infection)</td>
<td>92 (18%)</td>
<td>423</td>
</tr>
<tr>
<td>Prescribed antibiotics at time of audit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>74 (18%)</td>
<td>334</td>
</tr>
<tr>
<td>Yes</td>
<td>48 (17%)</td>
<td>231</td>
</tr>
</tbody>
</table>

© 2016 Royal Australasian College of Physicians
the five patients had adverse reactions following penicillin rechallenge. Multiple factors (including loss of IgE-mediated allergy reactivity over time and labelling non-immunological adverse drug reaction (ADR) or viral-induced exanthems) explain why many labelled patients tolerate future penicillin use.4–6 However, appropriate risk stratification is essential to avoid preventable prescribing errors and harm to truly allergic patients. It is not clear whether further (undocumented) history guided clinical decision-making for the five patients highlighted in this study.

Drug allergy specialists can safely investigate IgE-mediated (Type I) allergy labels through thorough clinical assessment with skin-prick/intradermal testing, and observed oral challenges for selected cases.22,23 This enables confirmation or, in most cases, exclusion (i.e. delabelling) of AAL. There is evidence supporting the safety of supervised graded oral amoxicillin challenges for children with historical immediate or non-immediate reactions to penicillin, but this approach remains to be fully investigated in the adult population.24

In the acute setting, desensitisation may be indicated to Table 2  Counts and percentages of specific antibiotics prescribed, and documented bacterial infections, broken down by antibiotic allergy label (note some patients received more than one antibiotic prescription or had more than infection)

<table>
<thead>
<tr>
<th>Antibiotics prescribed at time of audit</th>
<th>Any antibiotic allergy label</th>
<th>No antibiotic allergy label (n = 231)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins (penicillin V and G)</td>
<td>Any beta-lactam allergy label (n = 41)</td>
<td>Other antibiotic allergy label (n = 7)</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin ± clavulanic acid</td>
<td>0 (0.0%)</td>
<td>1 (14.3%)</td>
<td>9 (3.9%) NS</td>
</tr>
<tr>
<td>Flucloxacin</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>14 (6.1%) NS</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>5 (12.2%)</td>
<td>2 (28.6%)</td>
<td>68 (29.4%) 0.022</td>
</tr>
<tr>
<td>All penicillins (all above)</td>
<td>9 (22.0%)</td>
<td>4 (57.1%)</td>
<td>122 (52.8%) 0.0002</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>3 (7.3%)</td>
<td>0 (0.0%)</td>
<td>9 (3.9%) NS</td>
</tr>
<tr>
<td>First generation cephalosporins</td>
<td>8 (19.5%)</td>
<td>2 (28.6%)</td>
<td>41 (17.8%) NS</td>
</tr>
<tr>
<td>Third/fourth generation cephalosporins</td>
<td>6 (14.6%)</td>
<td>1 (14.3%)</td>
<td>13 (5.6%) NS</td>
</tr>
<tr>
<td>All beta-lactams (all above)</td>
<td>26 (63.4%)</td>
<td>7 (100.0%)</td>
<td>185 (80.1%) 0.013</td>
</tr>
<tr>
<td>Macrolides</td>
<td>3 (7.3%)</td>
<td>0 (0.0%)</td>
<td>25 (10.8%) NS</td>
</tr>
<tr>
<td>Quinolones</td>
<td>7 (17.1%)</td>
<td>0 (0.0%)</td>
<td>27 (11.7%) NS</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>7 (17.1%)</td>
<td>0 (0.0%)</td>
<td>14 (6.1%) 0.021</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>10 (4.3%) NS</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>9 (3.9%) NS</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>5 (2.2%) NS</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>2 (4.9%)</td>
<td>0 (0.0%)</td>
<td>4 (1.7%) NS</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>3 (7.3%)</td>
<td>0 (0.0%)</td>
<td>3 (1.3%) 0.043</td>
</tr>
<tr>
<td>Rifaxim</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>2 (0.9%) NS</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.4%) NS</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.4%) NS</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2 (4.9%)</td>
<td>0 (0.0%)</td>
<td>21 (9.1%) NS</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>3 (7.3%)</td>
<td>0 (0.0%)</td>
<td>6 (2.6%) NS</td>
</tr>
<tr>
<td>Fusidic acid or daptomycin</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>2 (0.9%) NS</td>
</tr>
<tr>
<td>Anti-mycobacterial agents</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>4 (1.7%) NS</td>
</tr>
<tr>
<td>Documented bacterial infections</td>
<td>12 (29.3%)</td>
<td>1 (14.3%)</td>
<td>61 (26.4%) NS</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (9.8%)</td>
<td>1 (14.3%)</td>
<td>40 (17.3%) NS</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>10 (24.4%)</td>
<td>0 (0.0%)</td>
<td>33 (14.3%) NS</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>3 (7.3%)</td>
<td>0 (0.0%)</td>
<td>20 (8.7%) NS</td>
</tr>
<tr>
<td>Osteomyelitis/joint</td>
<td>2 (4.9%)</td>
<td>0 (0.0%)</td>
<td>19 (8.2%) NS</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3 (7.3%)</td>
<td>0 (0.0%)</td>
<td>8 (3.5%) NS</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>7 (3.0%) NS</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (4.9%)</td>
<td>0 (0.0%)</td>
<td>5 (2.2%) NS</td>
</tr>
<tr>
<td>CNS</td>
<td>0 (0.0%)</td>
<td>1 (14.3%)</td>
<td>3 (1.3%) NS</td>
</tr>
<tr>
<td>Other infection</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>8 (3.5%) NS</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>4 (9.8%)</td>
<td>1 (14.3%)</td>
<td>22 (9.5%) NS</td>
</tr>
<tr>
<td>Indication unclear</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>14 (6.1%) NS</td>
</tr>
</tbody>
</table>

†Fisher’s exact test: comparing beta-lactam-labelled patients with all other patients. NS, not significant.
induce temporary drug tolerance for patients with true IgE-mediated antibiotic allergy, where no acceptable alternative antibiotic exists. Testing strategies for delayed T-cell mediated (type IV) reactions include patch testing (which is only available at selected drug allergy clinics in Australia) and oral challenges on a case-by-case basis. To our knowledge this is the largest Australian-based study to show that hospitalised patients carrying an AAL have poorer clinical outcomes, compared with unlabelled patients. Our study is strengthened by the unbiased selection criteria (based on the NAPS) which provided a ‘real life’ snapshot of documentation and antibiotic prescribing for patients with AAL at the time of their admission. Limitations of our study include the reliance on documentation in medical records to collect additional data. However, we used objective clinical outcomes, such as in-hospital mortality, length of stay and readmissions, which are accurately reflected in medical records. Due to the cross-sectional retrospective study design it was not possible to determine the validity of reported AAL (by patient interview or specific allergy testing) to classify further through a strict immunological basis. Furthermore, we could not capture every infection or antimicrobial prescription during admission, which limited sub-analyses in these groups. Nevertheless, the same trend towards frequent readmissions was seen when limiting the cohort to patients with a principal diagnosis of infection, or those with prescribed antibiotics. Our results may have been biased by the large proportion of beta-lactam AAL patients. However, this reflects the usual composition of AAL in the hospital setting, and encouragingly, delabelling strategies have been well validated in this cohort.

We propose that the association between AAL and hospital readmissions is best explained by necessary reliance on second-line antibiotics in labelled patients with infections. Our data (Table 2) highlight the differences in antibiotic prescribing patterns between AAL and NAAL groups, with greater reliance on alternative antibiotics for AAL patients. Second-line therapies have less favourable safety profiles and can be resistance and C. difficile generating, all of which may necessitate hospital readmissions. An alternative interpretation is that patients prone to readmissions for other reasons (such as more severe disease states requiring more frequent...
repetitive courses or high dose parenteral antibiotics) accumulate more drug allergy labels over time. Although it is not possible to discount the latter, our statistical analysis indicated that patient age, gender, admitting specialty, intensive care admission and chronic disease states did not affect the results.

This study adds to a growing international body of literature highlighting the significant public health implications of (frequently invalid) AAL. Our study complements findings from two recently published studies. A Dutch study reported a higher risk of readmissions within 12 weeks among penicillin allergy-labelled patients. An Australian study reported poor AAL documentation, and inappropriate antibiotic prescriptions for some AAL patients. Both studies reported increased use of broad-spectrum antibiotics (including third generation cephalosporins, quinolones and macrolides) for AAL patients. Similar findings have been reported in the United States; Macy and Contreras reported that patients with penicillin allergy labels spend significantly more time in hospital, with exposure to more broad-spectrum antibiotics and higher rates of C. difficile, methicillin-resistant S. aureus and vancomycin-resistant Enterococcus. Another large American study reported increased lengths of stay, intensive care admission rates and higher mortality rates for patients with AAL. Economic modelling suggests that delabelling strategies could lead to significant healthcare savings. In our study, there were no significant differences in antibiotic costs, hospital length of stay and intensive care admissions. This may be due to the smaller sample size and the broad inclusion of all patients rather than the higher risk patient groups.

Conclusion

Clinicians face two conflicting issues when managing patients with AAL. In the acute setting, clinicians must pay respect to AAL by carefully documenting labels and prescribing antibiotics safely. However, in the long term, over-labeling can set up a negative cycle of restricted access to antibiotics, poorer clinical outcomes and increased hospitalisation – the ‘revolving door’. Given that the majority of AAL are in fact, invalid, many patients may be unnecessarily suffering adverse outcomes. Clinical education in both primary care and hospital settings could lead to considerable improvements in diagnosis and management of patients with suspected drug allergy. Optimal drug allergy management relies on contemporaneous, detailed ADR reporting, to differentiate immunological (types I-IV) and non-immunological ADR at the outset. Patients who carry a historically plausible allergy label (particularly beta-lactam labels), can be further assessed by a drug allergy specialist to confirm true allergy labels and remove invalid labels. Ultimately, a collaborative effort to improve system-wide antibiotic allergy management could lead to significant healthcare savings and provide patients with more timely, safe and effective care.

References


Determining the efficacy of the chronic disease self-management programme and readability of ‘living a healthy life with chronic conditions’ in a New Zealand setting

J. J.-Y. Cheng,1 F. Arenhold2 and A. J. Braakhuis1

1Faculty of Medical and Health Sciences, Discipline of Nutrition/Dietetics, The University of Auckland, and 2ProCare Health, Patient Services, Auckland, New Zealand

Abstract

Background: Self-management programmes are an increasingly popular way of treating chronic diseases.

Aims: This study aims to determine the efficacy of the Stanford Chronic Disease Self-Management Programme (CDSMP) in a New Zealand context by assessing course outcomes and readability of the accompanying reference guide Living a Healthy Life with Chronic Conditions, 4th Edition.

Methods: This is a cross-sectional pre–post study conducted in Auckland between August 2009 and September 2015, using CDSMP participants’ baseline and follow-up Health Education Intervention Questionnaire (heiQTM) data. Readability of the guide was assessed using the Gunning Fog Index, Coleman Liau, Flesch Reading Ease, Flesch Kincaid Grade Level and Simplified Measure of Gobbledygook scores.

Results: Significant evidence of improvement (P ≤ 0.001) was observed in seven of the eight domains measured by the heiQTM (Deakin University, Centre for Population Health Research, Melbourne, Vic., Australia). The greatest improvements were seen in skill and technique acquisition (mean change score 0.25, P ≤ 0.001) and self-monitoring and insight (0.18, P ≤ 0.001). There was little evidence of improvement in health service navigation (0.04, P = 0.17). Readability analyses indicate that a person needs to be reading at a minimum of U.S. 8th grade level in order to understand the text, and possibly up to 11th grade.

Conclusions: The CDSMP is effective for improving patient self-efficacy in the New Zealand setting. However, adaptation of the programme to support better health service navigation is warranted. The readability of the reference guide is not suitable for this setting and requires further improvement.

Introduction

Chronic diseases are rapidly increasing globally, contributing to significant morbidity and mortality rates, causing a large burden on healthcare resources. In response to this growing predicament is a rising popularity of self-management courses.1 One of the most popular versions is the Stanford Chronic Disease Self-Management Programme (CDSMP), developed by Stanford University.1 The CDSMP is a 6-week, small-group intervention attended by people with different chronic conditions. It is taught largely by peer instructors from a highly structured manual. The programme is based on self-efficacy theory and emphasises problem solving, decision-making and confidence building. The primary intended outcome is to improve participant health behaviour, self-efficacy (confidence in ability to deal with health problems), health status and healthcare utilisation, assessed by self-administered questionnaires. The programme aims to provide individuals with the skills and knowledge to manage their condition confidently and effectively.

There is an abundance of both randomised controlled trials (RCT) and longitudinal studies on the efficacy of the CDSMP, most of which have been overwhelmingly positive. Of these RCT, participants suffered chronic conditions that included depression, type 2 diabetes, heart disease or stroke, or participants were from rural or lower socioeconomic backgrounds.2–5 The literature on
the efficacy of the CDSMP has reported reduced fatigue, pain, healthcare costs, improved medication adherence, healthcare service utilisation, health behaviour and quality of life. However, a large proportion of the relevant literature is associated with the programme developers, leading to potential bias. There is also possible negative publication bias, whereby studies showing no effect have not been published. Nevertheless, it is a fact that the vast majority of studies have been conducted in the United States and United Kingdom. Thus, we believe it is important to assess its efficacy in the New Zealand setting.

In New Zealand, the primary health organisation ProCare has been contracted by the local district health boards as a provider of these programmes in the Auckland region. These programmes have been run by ProCare since 2008. The CDSMP involves attending 2.5 h sessions at a community location every week for 6 weeks. The programme is led by trained health professionals or peers or laypeople (members of the community trained for the role rather than health professionals). To ensure the reliability of consistent programme content, leaders are instructed to adhere strictly to the provided programme manual. The benefits of using laypeople as leaders are increased relatability for patients as well as the decreased financial cost of employing health professionals, often compounded by a shortage of health professionals.

The programme attempts to achieve its aims through strategies such as weekly action planning, skills mastery (e.g. mindfulness, decision-making), role modelling (by facilitators and peers) and peer persuasion. It also tries to increase participant knowledge. Often forgotten is the important role of the social support provided by regular meetings. Participants are encouraged to exchange contact details and engage outside of weekly meetings, as well as stay in touch after the course ends.

Aside from the aforementioned aspects, another key aspect of the CDSMP is a participant reference guide, *Living a Healthy Life with Chronic Conditions, 4th Edition*. During sessions, leaders direct participants to specific sections that are relevant to the session content. Participants are encouraged to read it during the week to extend and reinforce their knowledge beyond the basics covered during the session. However, there are concerns about the user friendliness of this guide. These concerns are because of the (perhaps) excessive length of the guide at 343 pages, the amount and complexity of text and the scarcity of non-text components. It is important to remember that these programmes are targeted to the high needs population, and thus, the guide needs to be comprehensible and accessible to people with significant health literacy barriers.

### Methods

#### Participants

All patients attending South Auckland ProCare CDSMP sessions were asked to complete a baseline Health Education Impact Questionnaire (heiQ™) at the first and last session, 6 weeks apart. Responses from August 2009 to September 2015 were included in this study. Participants in the ProCare CDSMP either self-refer after reviewing advertisements in local libraries, community venues, newspapers or practice waiting rooms or are referred by their GP or nurse. The referral criteria include those over 18 years old with a long-term health condition or a caret/ family member of someone with a long-term health condition. Self-referral is usually by phone call or text message. Referral from general practice is by fax or electronic referral system. Total number of referrals that does not result in attendance of the ProCare CDSMP is not captured in this audit. The underlying medical condition of the participant was not recorded. For the purposes of characterising the group, we have data on a small, random subset of the group (n = 76), for which ethnicity and age is presented. If the participant was also seeing a ProCare-registered medical professional at the time of the self-management programme, clinical data were collected. Unfortunately, only four to six participants fall in this category.

#### Questionnaires

The heiQ™ allows for the evaluation of the effects of education interventions provided to patients with chronic diseases. The heiQ™ is a validated psychometric tool designed for the reliable evaluation of self-management and/or health education programmes widely used throughout the world. It covers eight domains: (i) positive and active engagement in life; (ii) health-directed behaviour; (iii) skill and technique acquisition; (iv) constructive attitudes and approaches; (v) self-monitoring and insight; (vi) health service navigation; (vii) social integration and support; and (viii) emotional well-being and negative affect. Each domain is assessed by between four and six questions, with 40 questions in total. Responses are marked on a 4-point Likert scale using the end-points *strongly disagree*/*strongly agree*. A higher score indicates better self-efficacy, except in the emotional well-being and negative affect domain, which is negatively scored.

#### heiQ™ data extraction

The domain score for each section of the heiQ™ was calculated as the mean of the responses to the individual
questions comprising the domain. Some questionnaires were incomplete. For incomplete questionnaires, the domain score was calculated as the mean of the completed items. If no questions for a specific domain were answered, mean substitution was utilised to generate a domain score (i.e., the sample mean domain score was used as the participant’s domain score). A total of 25 domain scores for 16 participants was calculated using this substitution method. Mean change scores for each domain were calculated so that positive scores reflect an improvement in self-efficacy. Thus, for domains (1)–(7), mean change score = sample mean follow-up score – sample mean baseline score. However, as domain (8) is negatively scored, mean change score = sample mean baseline score – sample mean follow-up score.

### heIQ™ data analysis

Statistical analysis was undertaken using SPSS (SPSS Statistics, version 20; IBM, Chicago, IL, USA). A paired t-test was used to compare the pre- and post-intervention heIQ™ scores for each domain and to generate confidence intervals for mean change scores.

Effect sizes (ESs) were calculated for each domain by dividing the mean change score by the sample standard deviation of the baseline domain scores. The ES was calculated to support the interpretation of the magnitude of the outcomes beyond significance or otherwise. Using Cohen’s ES interpretation, an ES of <0.2 is small; an ES of 0.2–0.8 is moderate; and an ES of >0.8 is large.10

### Readability

The CDSMP incorporates the use of a key participant reference guide.8 The reference guide is 343 pages long and written by authoritative experts in the field. In order to give a representative sample of the entire book, readability analysis was conducted on one page from each of the 19 chapters. The fifth page of each chapter was selected (or last full page of the chapter in one case because chapter fourteen was only four pages in length). This was to avoid the introductory passages at the beginning of each chapter, which may have resulted in the underestimation of readability scores. Individual scores for each chapter were then averaged to yield mean readability scores for the entire reference guide, and standard deviations for the mean were generated using Microsoft Excel.

We determined the readability using the Gunning Fog Index, Coleman Liau, Flesch Reading Ease, Flesch Kincaid Grade Level (F-K) and Simplified Measure of Gobbledygook (SMOG) scores. This was achieved by inputting the text of each excerpt into a publicly accessible web-based tool. A brief description and the formula used to generate each score are provided below and in Table 1.

The Gunning Fog Index assesses readability and describes it on a reading grade level, representing how many years of formal education is required for comprehension of a passage11 In contrast, the Coleman Liau index focuses on the number of letters in words.12 The Flesch Reading Ease (FRE) score is widely used by the U.S. government12 and derives a reading level for a given document. The FRE produces a score between 0 (very difficult to read) and 100 (very easy to read). A modification of the FRE, the Flesch Kincaid Grade level (F-K) also allows readability to be described in terms of a reading grade level. Finally, the SMOG determines the reading grade level and is commonly used in analysis of health literature.11 Multiple scores were calculated as any one score has limitations.

### Plain language checklist

To complement the readability analysis, an additional analysis using a Plain Language Checklist11 was undertaken. The checklist contains 60 criteria, of which 58 were applicable to the participant reference guide. The criteria are grouped into categories of vocabulary, sentences, paragraphs, organisation, tone, inclusive language and accessible resources, design concept, font, typeface, space, colour and finish and graphics.
**Results**

**Participants**

We acquired ethnicity and age data on a subset of the population; of the 76 participants, 23 were Maori; 23 were NZ European; 3 were Samoan; 3 were Cook Islanders (other); 3 were European; 2 were Indian; and 2 were Pakistani. The remainder did not specify ethnicity. The average age of the subset was 52 years, with a standard deviation of 15 years as not all participants recorded their age or had their age entered electronically into the ProCare database. ProCare staff (author FA) involved with the self-management programme have stated that this is reflective of the population that participates in the CDSMP (unpublished data). An unpaired t-test showed no evidence of differences in baseline scores between participants that completed the course and those that did not.

**Response rates**

In total, 471 baseline and 317 follow-up heiQ were completed. Only patients who had completed both baseline and follow-up heiQ were included in the analysis (n = 273). Excluded data was a factor of participants not completing the programme (i.e. attending less than four sessions, n = 198) or starting at a later session (n = 44). Data on those invited to participate but did not were not captured.

**Questionnaires**

For each domain, at least 30% of patients had an improved follow-up score compared to their baseline scores. Only 11 patients (4%) did not show an improvement in at least one domain. The heiQ™ results are summarised in Table 2 below. Using Cohen’s ESs, our analysis suggested the CDSMP has a moderate effect on all domains, except health service navigation, for which a small effect is suggested.

Figure 1 shows the mean change score and confidence interval for each domain. For all domains except health service utilisation, there was significant evidence that domain scores differed between baseline and follow-up heiQ. For health service utilisation, there was no evidence that baseline and follow-up domain scores differed.

**Readability**

Using the Gunning Fog Index, the mean readability score for the entire reference guide was 10.32 years (SD = 2.49), indicating that over 10 years of formal education is required for a person to understand the text easily. The mean readability score calculated using the Coleman Liau Index was 9.30 (SD = 2.10), using the F-K grade level was 8.76 (SD = 2.11) and using the SMOG grade level was 10.79 (SD = 1.81). These results indicate that a person needs to be reading at a minimum of U.S. 8th grade level in order to understand the text, and possibly up to 11th grade. The mean FRE score was 57.31 (SD), indicating that it is fairly difficult to read and can be considered easily understood only by those above the 9th grade.14

**Plain language checklist**

The participant reference guide met 47 of the 58 applicable criteria. It scored most highly in the organisation, tone, colour and finish and graphics categories, meeting 92–100% of the criteria in these categories. Important criteria that were not met were ‘use of simple, familiar words that reflect the intended audience’s common language’, keeping all sentences and paragraphs short, providing alternative accessible formats (such as large print, Braille, audiotape, electronic versions), reasonable length overall, sufficient white space around text blocks and simplicity of tables/charts.

**Clinical outcomes**

Participants for whom clinical data were collected (n = 6) are presented in Figure 2. Whilst results for blood

---

### Table 2: Summary of heiQ™ outcomes for each domain

<table>
<thead>
<tr>
<th>heiQ™ domain</th>
<th>n improved (%)</th>
<th>n no change (%)</th>
<th>n worsened (%)</th>
<th>Mean change score effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Positive engagement with life</td>
<td>144 (53)</td>
<td>57 (21)</td>
<td>72 (26)</td>
<td>0.36</td>
</tr>
<tr>
<td>2. Health-directed behaviour</td>
<td>152 (56)</td>
<td>51 (19)</td>
<td>70 (25)</td>
<td>0.28</td>
</tr>
<tr>
<td>3. Skill and technique acquisition</td>
<td>149 (55)</td>
<td>75 (27)</td>
<td>49 (18)</td>
<td>0.50</td>
</tr>
<tr>
<td>4. Constructive attitudes and approaches</td>
<td>136 (50)</td>
<td>62 (23)</td>
<td>75 (27)</td>
<td>0.24</td>
</tr>
<tr>
<td>5. Self-monitoring and insight</td>
<td>154 (56)</td>
<td>51 (19)</td>
<td>68 (25)</td>
<td>0.41</td>
</tr>
<tr>
<td>6. Health service navigation</td>
<td>105 (38)</td>
<td>91 (33)</td>
<td>77 (28)</td>
<td>0.08</td>
</tr>
<tr>
<td>7. Social integration and support</td>
<td>125 (46)</td>
<td>60 (22)</td>
<td>88 (32)</td>
<td>0.20</td>
</tr>
<tr>
<td>8. Emotional well-being and negative affect</td>
<td>146 (53)</td>
<td>33 (12)</td>
<td>94 (34)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

© 2016 Royal Australasian College of Physicians
pressure and HbA1c look promising, the sample size is too small to make conclusions.

Discussion

This study is the first investigation into the efficacy of the CDSMP in New Zealand. Our results suggest that the CDSMP appears to be effective in those who complete the programme. While the CDSMP has been widely used in many countries, most of the efficacy research has been conducted in the United States and United Kingdom. Furthermore, the developers of the programme have been involved in a large proportion of the existing published research, leading to potential conflicts of interest.

The heiQ™ is a questionnaire specifically designed to assess an education intervention for those with chronic conditions. It has been assessed for validity both in Australia and in Germany, where factorial elements were examined in about 1200 rehabilitation patients with a variety of chronic conditions. Although using a sample that included different chronic conditions, this study suggested remarkably stable psychometric properties of the heiQ™ over time.

Our results suggest the CDSMP was effective in improving self-management behaviours, as shown by the heiQ™ results. Health service navigation was the only domain that did not definitively show an improvement; all other domains had some degree of effect. To elaborate, the health services navigation domain measures the understanding and ability of an individual to interact with health organisations and professionals and the ability to have their health requirements met by the healthcare system. To improve the effect on the health navigation domain, we recommend incorporating more information and skills regarding navigating the New Zealand health system and raising awareness of relevant publicly accessible resources. Given that the programme was developed overseas and that facilitators are recommended to stick closely to the material, we recommend further adaptation in order to educate about the New Zealand health service system – similar to what has already been done to incorporate New Zealand nutrition guidelines into the manual.

The heiQ™ is a validated tool for assessing the effect of self-management programmes. A limitation of the questionnaire is the 4-point scale as it may not have sufficient sensitivity to detect smaller effects. Conversely, it could also cause overestimation of effects as a 1-point change in score (the smallest change possible in the questionnaire) indicates a 25% improvement. Fortunately, the data presented in this research are the culmination of grouped data.

While attendance of the CDSMP is associated with improvements in self-efficacy, it is also possible that the benefits have arisen from the supportive social environment of attending group sessions (i.e. perhaps the actual content of the course has little beneficial effect). Social support is widely accepted as being a strong indicator of both physical and psychological health and is crucial for patients living with chronic diseases. It is also important to consider other possible confounding factors, such as participation in other care planning or case management programmes that may have caused the change scores we observed.

An area of concern is participants who have worsened scores following the CDSMP; depending on the domain, this ranges from 18% to 34% of participants (Table 2). Further investigation is required to determine whether the CDSMP is contributory to this and, if so, to develop screening methods to identify those likely to worsen and prescribe an alternative intervention for these individuals. Further studies should also control for possible confounders.

As previously mentioned, the accompanying participant reference guide is a key component of the programme. It is designed to facilitate patients’ exploration of concepts taught in the sessions in more depth and provide support outside of sessions. However, because of its length and wordiness, we had concerns about its readability and approachability. Following our investigation, the readability scores proved our concerns correct. The scores indicated that a reading level of at least U.S. 8th grade is required, and possibly up to 11th grade.

The recommended reading level for health education information varies greatly between sources. Multiple authorities (including the U.S. National Institutes of...
Health, American Medical Association, U.S. National Cancer Institute and American Medical Center Cancer Research Group recommend that a reading level of 4–6th grade is ideal for the comprehension of health education materials. As literacy levels in New Zealand are similar to the United States, these same recommendations should apply for health education programmes in New Zealand. Overall, the New Zealand population has poor health literacy, with skills also varying greatly between ethnicities; this is important because of New Zealand’s multi-cultural composition. The Māori have significantly poorer health literacy than the non-Māori, with four out of five Māori males and three out of four Māori females having poor health literacy. Pacific Islanders and other ethnic minority groups also have higher levels of poor literacy than the general population. We recommend that future studies should also investigate the health literacy of the participants attending CDSMP sessions in order to gain more insight into the suitability of the reference guide.

Furthermore, there was large inter-chapter variability in readability, as indicated by the large standard deviations. We believe this may be due to chapters being written by different authors as the guide has six authors in total. This is important as while some chapters were deemed comprehensible at a 5th or 6th grade level, others ranged up to a 12th grade level, or even up to 2nd or 3rd year university levels. We suggest that the guide is revised in the next edition to improve the overall readability and consistency between chapters.

Additionally, readability formulae are frequently criticised because of their focus on number of the words per sentence or the number of letters or syllables per word. They do not take into account the comprehensibility of sentences or the vocabulary that is being used, which is particularly relevant when assessing health education information. Nor do they consider the overall length of each passage or the entire text itself. They also do not consider the layout, presence/absence of graphics, logical flow or, crucially, the ability to invoke interest in the reader. However, as long as we do not forget the limitations of the formulae, they can still be helpful.

The plain language checklist allowed a more holistic assessment of the reference guide. The checklist identified the need to use simpler and more familiar words that are common in the everyday language of our target audience, providing alternative formats (electronic versions are particularly welcomed in this digital era), shortening of the overall length and simplifying some of the tables in the guide. The use of more diagrams or illustrations may also aid with improving its ability to interest and engage the reader. The plain language checklist also

![Figure 2 Individual change pre- to post-self-management intervention for Weight (kg) (A), HbA1c (B), Systolic blood pressure (C) and Diastolic blood pressure (D)](image-url)
assesses the overall presentation of the document, including graphics and pictures, of which the CDSMP manual rates well.

**Conclusion**

The results of this study suggest that CDSMP is beneficial for improving the self-efficacy of chronic disease patients. Further studies assessing outcomes over a longer period of follow up, in addition to studies on the effects on clinical outcomes, are recommended. Improvements to the reference guide may also increase the effectiveness of the CDSMP.

**Acknowledgements**

The authors thank ProCare for providing access to the participant questionnaires and reference guide and the University of Auckland for funding the audit.

**References**

Benefit from cytoreductive nephrectomy and the prognostic role of neutrophil-to-lymphocyte ratio in patients with metastatic renal cell carcinoma


1Department of Medical Oncology, and 8Biogrid Australia, The Royal Melbourne Hospital, 3Department of Urology, Austin Health, 4Monash University Eastern Health Clinical School, 5Department of Medical Oncology, Olivia Newton-John Cancer and Wellness Centre, Austin Health, 6School of Clinical Sciences, Monash University, 7Department of Medical Oncology, Western Health, and 9Walter and Eliza Hall Institute, Melbourne, Victoria, and

2Department of Medical Oncology, The Canberra Hospital, Canberra, Australian Capital Territory, Australia

Key words
cytoreductive nephrectomy, renal cell carcinoma, neutrophil-to-lymphocyte ratio.

Correspondence
Ben Tran, Department of Medical Oncology, The Royal Melbourne Hospital, Grattan Street, Parkville, Vic. 3050, Australia. Email: ben.tran@petermac.org

Received 9 May 2016; accepted 27 July 2016.
doi:10.1111/imj.13202

Abstract

Background: The role of cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma (mRCC) in the era of targeted therapies is currently undefined. In recent years, neutrophil-to-lymphocyte ratio (NLR) has emerged as a prognostic marker in several cancers, including mRCC. In this multicentre retrospective study, we aim to assess the impact of CN in mRCC and the value of NLR in risk stratification and patient selection.

Methods: Retrospective data from patients with de novo mRCC from four large Australian hospitals were collected. Survival analyses were performed using the Kaplan–Meier method and compared using the log-rank test. Multivariate analyses were performed using the Cox proportional hazards method.

Results: Our study identified 91 de novo mRCC patients. Patients who underwent CN (n = 46, 51%) were more likely to be younger (59.0 years vs 64.6 years, P = 0.019) and to have received systemic therapy (91% vs 76%, P = 0.043). Median overall survival (mOS) was significantly improved in patients who underwent CN (23.0 months vs 10.9 months, hazard ratios (HR) 0.33, 95% confidence interval (CI) 0.20–0.55, P < 0.0001). Patients with NLR ≥ 5 also had inferior mOS (6.2 months vs 16.7 months, HR 1.94, 95% CI 1.14–3.29, P = 0.014). CN was associated with substantially improved survival in patients with both NLR < 5 (mOS 31.1 months vs 7.0 months, HR 0.41, 95% CI, 0.18–0.64, P = 0.0009) and NLR ≥ 5 (mOS 10.9 months vs 2.3 months, HR 0.33, 95% CI, 0.11–0.69, P = 0.009). Significant survival benefits associated with CN were maintained in multivariate analyses (HR 0.39, 95% CI 0.22–0.70, P = 0.0014).

Conclusions: CN is associated with significantly improved overall survival in de novo mRCC. The incremental survival benefit associated with CN was seen irrespective of NLR.

Introduction

Approximately 20% of patients diagnosed with renal cell carcinoma (RCC) will develop distant metastatic disease. Despite substantial advances in the surgical and medical management of metastatic RCC (mRCC) over the last 30 years, the optimal treatment of these patients remains controversial.

Two randomised trials established the advantage of cytoreductive nephrectomy (CN) in the cytokine era in mRCC.1,2 A combined analysis demonstrated that CN followed by interferon-alpha therapy improved survival...
by 5.8 months (hazard ratios (HR) 0.69; 95% confidence interval (CI) 0.55–0.87; \( P = 0.002 \)) compared with interferon-alpha alone.\(^1\) In recent years, improved knowledge of molecular pathways in RCC has led to the successful introduction and approval of multiple molecular-targeted agents, including vascular endothelial growth factor and mammalian target of rapamycin inhibitors. Since 2005, the United States Food and Drug Administration has approved eight novel agents for use in mRCC, with substantial improvement in patient survival and treatment outcomes.\(^2–7\)

Due to the lack of randomised evidence, the role of CN is not well defined in the targeted therapy era. Indeed, the rate of CN has declined since 2005, coinciding with the introduction of targeted therapies.\(^8–9\) However, retrospective series have suggested a survival benefit associated with CN in the targeted therapy era, although the degree of benefit may differ depending on clinical prognostic characteristics.\(^5,10,11\) Additionally, CN carries a higher risk of surgical mortality and complications compared with nephrectomy in non-mRCC.\(^12\) These studies underscore the importance and challenges of appropriate patient selection for CN.

It is well established that inflammation plays an integral role in tumorigenesis and metastatic progression and that systemic inflammation is associated with changes in circulating white blood cells, including relative neutrophilia and lymphopenia.\(^13\) In recent years, the neutrophil-to-lymphocyte ratio (NLR) has been found to be an independent prognostic marker in a number of solid tumours.\(^14,15\) In RCC, elevated NLR has been associated with inferior outcomes after curative nephrectomy in early disease and in patients treated with sunitinib in metastatic disease.\(^1,6–20\) As NLR is an objective, readily available and inexpensive parameter, we evaluated its prognostic role in mRCC patients and hypothesised that it may assist with patient selection for CN.

In this multicentre, retrospective analysis, we aimed to assess the impact of CN in patients with mRCC and the value of NLR in risk stratification and patient selection.

**Methods**

Patients with mRCC treated between 1 January 2006 and 31 December 2012 were identified from four academic centres in Australia (Royal Melbourne Hospital, Austin Hospital, Western Hospital and Canberra Hospital) using electronic databases. Patients who had received systemic therapy before 1 January 2006 were excluded. Patients with metastatic disease at diagnosis (de novo mRCC) and with complete information on survival and treatment data, NLR and other preoperative variables were included for this analysis. Our study was approved by the local institutional human research ethics committees. Patterns of care from this cohort have been previously reported.\(^21\)

Demographic and clinicopathological data were collected, including age, Eastern Cooperative Oncology Group performance status, histological diagnosis and information pertaining to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification.\(^22\) Neutrophil and lymphocyte counts at the time of metastatic diagnosis were collected, and NLR was calculated. NLR \( \geq 5 \) was used as the cut-off for statistical analyses; a systematic review found that a threshold of 5 was most consistently used in published literature.\(^14\) The International mRCC Database Consortium (IMDC) risk classification was unable to be calculated as additional data points, such as platelet count, were not collected.\(^23\) Chart review was undertaken to collect data regarding systemic therapy use, and CN data collection was completed by three clinician-researchers. Data were recorded onto detailed, standardised and pre-tested forms and subsequently collated onto a single electronic database.

Descriptive statistics were used to summarise patient characteristics. Survival analyses were performed by calculating hazard ratios using the Cox proportional hazards model. Median survival was determined using the Kaplan–Meier method. Comparisons between groups were made using Fisher’s exact test. Multivariate analyses included all variables with statistically significant findings in the univariate analysis. \( P \)-values less than 0.05 were considered statistically significant.

Our study used data collected as part of a Pfizer Australia-funded, retrospective, non-interventional study aimed at determining the prescribing patterns for sunitinib in mRCC patients treated in Australian centres. Pfizer was not involved in the collection, analysis, interpretation or reporting of the data.

**Results**

**Patient characteristics**

Our study initially identified 212 consecutive patients treated for mRCC between 2006 and 2012.\(^21\) Overall, 72% (\( n = 153 \)) had a recorded nephrectomy. Patients who had a nephrectomy prior to the diagnosis of metastatic disease were excluded. A total of 115 (54%) patients had metastatic disease at diagnosis and were therefore candidates for CN. Of this group, 91 patients had complete data and were included in the final analysis.

Among this cohort, 46 (51%) patients underwent CN, and 45 (49%) did not. All patients had CN within 3 months of diagnosis of metastatic disease. Patients who underwent CN were more likely to be younger (median age 59.0 vs 64.6, \( P = 0.019 \)), have clear cell histology (80% vs 60%, \( P = 0.02 \)) and have received systemic therapy (91% vs 76%, \( P = 0.043 \)). Sunitinib was the most common
treatment prescribed. There was a trend towards better MSKCC status and a trend towards NLR < 5 in CN patients. Table 1 outlines the baseline patient characteristics.

**Univariate analysis**

Median overall survival (mOS) for the entire study cohort was 11.3 months. With a median follow-up of 87 months, 68 deaths were recorded.

**Multivariate analysis**

All significant prognostic factors from univariate analyses (CN, MSKCC risk classification, NLR, histology and systemic treatment) were included in the multivariate analysis.

---

**Table 1** Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>CN (n = 46)</th>
<th>No CN (n = 45)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>59.0</td>
<td>64.6</td>
<td>0.02</td>
</tr>
<tr>
<td>MSKCC risk classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favourable</td>
<td>10 (22%)</td>
<td>4 (9%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Intermediate</td>
<td>25 (54%)</td>
<td>27 (60%)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>7 (15%)</td>
<td>12 (27%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (9%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>NLR &lt; 5</td>
<td>36 (78%)</td>
<td>28 (62%)</td>
<td>0.11</td>
</tr>
<tr>
<td>NLR ≥ 5</td>
<td>10 (22%)</td>
<td>17 (38%)</td>
<td></td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>42 (91%)</td>
<td>34 (76%)</td>
<td>0.04</td>
</tr>
<tr>
<td>First-line treatment regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>33 (72%)</td>
<td>34 (76%)†</td>
<td></td>
</tr>
<tr>
<td>Pazopanib</td>
<td>4 (9%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>0 (0%)</td>
<td>4 (9%)†</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Interferon</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Best supportive care</td>
<td>4 (9%)</td>
<td>11 (24%)</td>
<td></td>
</tr>
<tr>
<td>Clear cell histology</td>
<td>37 (80%)</td>
<td>27 (60%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-clear cell histology</td>
<td>6 (13%)</td>
<td>5 (11%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (7%)</td>
<td>13 (29%)</td>
<td></td>
</tr>
</tbody>
</table>

†Four patients were enrolled in a trial using alternating everolimus and sunitinib as first-line treatment. CN, cytoreductive nephrectomy; MSKCC, Memorial Sloan-Kettering Cancer Center; NLR, neutrophil-to-lymphocyte ratio.

Figure 1 demonstrates that CN is significantly associated with improvement in overall survival (OS) (median 23.0 months vs 10.9 months; HR 0.33; 95% CI 0.20–0.55; P < 0.0001). When we assessed patient outcomes in different subgroups according to MSKCC risk groups, clear cell histology and systemic therapy use, CN remained significantly associated with improved survival (Table 2).

MSKCC risk classification was also a statistically significant prognostic factor. Median OS for MSKCC favourable, intermediate and poor risk groups were 83.0, 11.0 and 7.0 months respectively. Both intermediate and poor risk groups had significantly poorer survival when compared with the favourable risk group (Table 3).

Patients with NLR ≥ 5 had statistically significant poorer survival compared with NLR < 5 (median 6.2 months vs 16.7 months; HR 1.94; 95% CI 1.14–3.29; P = 0.014) (Fig. 2). In patients with a NLR < 5, median survival was 31.1 months in those who underwent CN versus 7.0 months in those who had no nephrectomy (HR 0.41; 95% CI 0.18–0.64; P = 0.0099; Fig. 3A). In patients with a NLR ≥ 5, a survival advantage was also observed for patients who underwent CN (mOS 10.9 months vs 2.3 months; HR 0.33; 95% CI 0.11–0.69; P = 0.009; Fig. 3B).

Systemic therapy and clear cell histology were both significantly associated with better OS, while age had no impact on this end-point (Table 3).
analysis. Table 3 describes the results from the multivariate analysis. Significant survival benefits associated with CN were maintained in MVA (HR 0.39; 95% CI 0.22–0.70; \(P = 0.0014\)). A NLR \(\geq 5\) also remained as a significant poor prognostic factor (HR 2.17; 95% CI 1.00–4.68; \(P = 0.049\)). Additionally, clear cell histology and MSKCC risk classification remained significant prognostic factors, while the use of systemic therapy was no longer significant.

**Discussion**

Over the last decade, vascular endothelial growth factor- and mammalian target of rapamycin pathway-targeted therapies have largely supplanted cytokine therapy and have substantially improved treatment outcome in mRCC.\(^7\) The role of CN in the era of targeted therapy, however, is undefined, and two prospective randomised clinical trials are currently being conducted to investigate this question (NCT00930033 and NCT01099423).

Large retrospective analyses using the Surveillance Epidemiology and End Results (SEER) database recognised a peak in CN utilisation at 39% in 2004 and a subsequent modest decline of 0.6% a year in the post-cytokine era, beginning in 2005.\(^8\)\(^9\) The reasons for this trend may include concerns related to surgical morbidity and that surgery may delay initiation of effective systemic treatment. In a population-based study, the rate of in-hospital mortality and complications following CN were 2.4% and 26.5% respectively.\(^1\)\(^2\) Interestingly, SEER data demonstrated that mOS among patients receiving CN increased in the targeted therapy era compared with the cytokine era (19 months post-2005 vs 13 months pre-2005), while the OS among patients not receiving CN changed very little (4 months vs 3 months).\(^6\) In a large retrospective series, Heng et al. also found that a survival benefit was associated with CN (20.6 months vs 9.5 months, \(P < 0.0001\)). The HR for death in this study was 0.60 after adjusting for IMDC prognostic criteria. However, patients with four or more IMDC risk factors did not derive benefit from CN, and those with an expected survival of less than 12 months only derived marginal benefit. In their incremental

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR (95% CI)</th>
<th>P-value</th>
<th>Multivariate HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytoreductive nephrectomy</td>
<td>0.33 (0.20–0.55)</td>
<td>&lt;0.0001</td>
<td>0.39 (0.22–0.70)</td>
<td>0.0014</td>
</tr>
<tr>
<td>NLR (\geq 5)</td>
<td>1.94 (1.14–3.29)</td>
<td>0.014</td>
<td>2.17 (1.00–4.68)</td>
<td>0.049</td>
</tr>
<tr>
<td>Age (continuous variable)</td>
<td>1.00 (0.98–1.03)</td>
<td>0.67</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>MSKCC risk classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favourable</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3.54 (1.55–8.07)</td>
<td>0.0027</td>
<td>3.01 (1.27–7.16)</td>
<td>0.013</td>
</tr>
<tr>
<td>Poor</td>
<td>6.28 (2.39–16.51)</td>
<td>0.0002</td>
<td>3.32 (1.09–10.10)</td>
<td>0.035</td>
</tr>
<tr>
<td>Clear cell histology</td>
<td>0.25 (0.11–0.56)</td>
<td>0.0007</td>
<td>0.22 (0.09–0.51)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>0.41 (0.21–0.81)</td>
<td>0.009</td>
<td>1.02 (0.38–2.72)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

CI, confidence interval; CN, cytoreductive nephrectomy; HR, hazard ratios; MSKCC, Memorial Sloan-Kettering Cancer Center; NLR, neutrophil-to-lymphocyte ratio.
benefit analysis, these authors found that the longer a patient is estimated to live, the greater their OS benefit from CN. These findings suggest that CN may not be universally advantageous and that those with poor prognostic features and rapid progression of disease may not gain OS benefit from this strategy, highlighting the importance of patient selection.\textsuperscript{11}

Our study found a prevalence of CN of 51\%, similar to that found in the study by Heng et al. (59\%) but substantially higher than that seen in the analysis of SEER data.\textsuperscript{8,11} Importantly, we demonstrated a similar magnitude of survival benefit associated with CN to that seen in the aforementioned studies (mOS 23.0 months vs 10.9 months, $P < 0.0001$).\textsuperscript{8,11}

We hypothesised that NLR, as a proposed surrogate marker of inflammation, may have a prognostic role in mRCC outcomes and may assist with patient selection for CN. Consistent with previous published literature, a NLR $\geq$ 5 in our study was associated with inferior OS and maintained its significance in MVA (HR 2.17; 95\% CI 1.00–4.68; $P = 0.049$). Interestingly, CN is associated with survival benefit in both the NLR < 5 and NLR $\geq$ 5 groups. However, the absolute survival difference was greater in patients with baseline NLR < 5, a potentially more favourable prognostic group compared with NLR $\geq$ 5. Therefore, our data may also support the observation made by Heng et al.\textsuperscript{11} that patients with better prognosis may derive greater benefit from CN.\textsuperscript{11}

One of the additional parameters measured by the IMDC risk classification and not by the MSKCC classification is neutrophilia.\textsuperscript{22,23} Thus, by measuring the prognostic impact of NLR, we may have simply created a surrogate of the IMDC prognostic model, and it is not surprising that some of our findings echo those of Heng et al.\textsuperscript{11} A comparison of our results with the prognostic effect of the IMDC model in this cohort would have been informative.

A strength of our study is the use of consecutive, multi-institutional series, capturing practice patterns and outcomes across several centres. It is also the first study investigating CN outcomes and the impact of NLR in an Australian population. Despite the limitations outlined below and while we await prospective clinical trial results, our findings provide reassuring evidence on the benefit of CN and may be particularly relevant to Australian clinical practice. The mOS in our cohort was 11.3 months, substantially lower than the mOS described in pivotal phase III clinical trials (26–29 months), perhaps reflecting potential disparities between clinical trial and ‘real-world’ populations.\textsuperscript{4,5} Additionally, inferior survival in our population may be related to the fact that all patients had metastatic disease from the time of initial diagnosis, and 21\% had MSKCC poor risk disease. In other retrospective series of de novo mRCC patients, mOS varies between 13 and 19 months.\textsuperscript{7,8,10}

Patterns of care and survival outcomes in the full cohort ($n = 212$) of this Australian study were previously reported.\textsuperscript{21} Notably, the mOS in the overall cohort was 29.1 months, consistent with survival data observed in the phase III studies.\textsuperscript{4,3,21}

Our study has several limitations. First, due to its retrospective nature, we were unable to control for selection bias. We found that CN is associated with favourable clinical features, including younger age and clear cell histology, and with the use of systemic therapy. Due to the limited number of reimbursed treatment options during
References


Conclusion

Our retrospective study demonstrates that CN is associated with significantly improved OS in de novo mRCC and should remain an important consideration for all patients. The incremental survival benefit associated with CN was seen irrespective of NLR.

Acknowledgements

We gratefully acknowledge Dr Mahmood Alam and Dr Shams Arifeen from Pfizer Australia for their collaboration.


Heart failure following cancer treatment: characteristics, survival and mortality of a linked health data analysis

R. A. Clark,1 N. M. Berry,1 M. H. Chowdhury,1 A. L. McCarthy,2 S. Ullah,3 V. L. Versace,4 J. J. Atherton,5 B. Koczwara6 and D. Roder7

Flinders Centre 1School of Nursing and Midwifery, 2for Epidemiology and Biostatistics, and 6for Innovation in Cancer, Flinders University, and 7School of Health Sciences, University of South Australia, Adelaide, South Australia, 3School of Nursing, Queensland University of Technology (QUT), and 4Royal Brisbane and Women’s Hospital, Brisbane, Queensland, and 5Greater Green Triangle University Departments of Rural Health, Flinders University and Deakin University, Warrnambool, Victoria, Australia

Key words cardiotoxicity, heart failure, chemotherapy, cardiology, oncology.

Correspondence Robyn A. Clark, School of Nursing and Midwifery, Flinders University, GPO Box 2100, Adelaide, SA 5001, Australia. Email: robyn.clark@flinders.edu.au

Received 16 February 2016; accepted 17 July 2016.
doi:10.1111/imj.13201

Abstract

Background: Cardiotoxicity resulting in heart failure is a devastating complication of cancer therapy. A patient may survive cancer only to develop heart failure (HF), which has a higher mortality rate than some cancers.

Aim: This study aimed to describe the characteristics and outcomes of HF in patients with blood or breast cancer after chemotherapy treatment.

Methods: Queensland Cancer Registry, Death Registry and Hospital Administration records were linked (1996–2009). Patients were categorised as those with an index HF admission (that occurred after cancer diagnosis) and those without an index HF admission (non-HF).

Results: A total of 15 987 patients was included, and 1062 (6.6%) had an index HF admission. Median age of HF patients was 67 years (interquartile range 58–75) versus 54 years (interquartile range 44–64) for non-HF patients. More men than women developed HF (48.6% vs 29.5%), and a greater proportion in the HF group had haematological cancer (83.1%) compared with breast cancer (16.9%). After covariate adjustment, HF patients had increased mortality risk compared with non-HF patients (hazard ratios 1.67 (95% confidence interval, 1.54–1.81)), and 47% of the index HF admission occurred within 1 year from cancer diagnosis and 70% within 3 years.

Conclusion: Cancer treatment may place patients at a greater risk of developing HF. The onset of HF occurred soon after chemotherapy, and those who developed HF had a greater mortality risk.

Funding: This research was supported by the Institute of Health and Biomedical Innovation of Queensland University of Technology under Collaborative Research Development Grant Scheme 2011 and a Flinders University Faculty of Health Sciences Seeding grant.

Conflict of interest: None.
Introduction

Cardiotoxicity resulting in left ventricular failure is a potential outcome of cancer therapy. Patients may survive chemotherapy and radiotherapy only to develop heart failure (HF), which has a higher mortality rate than some cancers. Current guidelines recommend that the development of cardiotoxicity should lead to the reconsideration of further chemotherapy, thus limiting cancer treatment options and potentially affecting cancer outcomes. Treatment-induced cardiotoxicity is well established and may occur in one-third of cancer patients, although current figures are probably underestimated as patients with underlying predisposition to cardiotoxicity are often excluded from cancer trials. Adult survivors of childhood cancers have been shown to have an eightfold risk of cardiac-related mortality. Cardiotoxicity can occur up to 20 years after cancer therapy and may be identified as a lifelong risk as new data emerge, and may become more prevalent as survivorship from childhood cancer improves.

The incidence of cardiotoxicity following chemotherapy varies based on the type of agent, with the cardiotoxicity incidence of anthracyclines between 1% and 26%, high-dose cyclophosphamide between 7% and 28%, trastuzumab between 2% and 28% and tyrosine kinase inhibitors between 0.05% and 11%. These drugs are commonly used to treat breast or haematological cancers; therefore, these cancers are the focus of this study.

Treatment-related risk factors in cancer patients include specific chemotherapy agent(s) (with reversible and irreversible cardiotoxicity), dose exposure and concomitant therapies (including anaesthetic procedures and radiation therapy). In fact, treatment-induced cardiotoxicity should not be considered as the result of a single treatment but rather as the result of additive or supra-additive toxicities, in conjunction with risks, such as stress, history of cardiac disease, genetic profile and body mass index. Cardiotoxicity is likely to become more prevalent as chemotherapy is administered to an ageing population. Vigilant initial monitoring and early intervention during cancer treatment, with continued surveillance after treatment, could prevent or ameliorate cardiotoxicity. A limited number of the possible risk factors associated with this toxicity (such as high cumulative doses of anthracyclines in the context of pre-existing heart disease) is well understood. Before intervention studies are undertaken, the precise nature of the problem needs to be investigated.

This study aimed to gain a greater understanding of the development of HF in patients after exposure to chemotherapy for breast or haematological (leukaemias, lymphomas and related disorders) cancer. The focus of this paper is on the development of HF, acknowledging that other cardiovascular conditions may develop after cancer treatment. The objectives were to describe patient characteristics, duration of onset, mortality and survival between those who developed HF after chemotherapy compared to those who did not. The long-term aim of this research is to understand better the profile of these patients so that appropriate inventions for prevention and potential reversal can be designed.

Methods

Study design

This study was a retrospective audit of linked health administration data from Queensland, Australia. The Queensland Cancer Registry (QCR), the Hospital Admitted Patient Data Collection and Birth, Deaths and Marriages from January 1996 to December 2009 were accessed. Approval was granted by the Metro South Health Service District Human Research Ethics Committee (HREC/11/QPAH/600).

Participants

Primary cancer diagnosis was used to identify the cancer site/morphology using the International Classification of Diseases, Tenth Revision, Australian Modification (ICD-10-AM) and ICD-O (oncology) site codes in the original-linked dataset. Cancer sites were defined as breast (ICD-10-AM: C50) or haematological (leukaemias, lymphomas and related disorders) (ICD-10-AM: C42, C77 and ICD-O: M9590/3-M9989/3), henceforth referred to as ‘haematological cancers’.

Patients who did not undergo chemotherapy were excluded. Participants were categorised as those who had an index HF admission after cancer diagnosis (HF group) compared with those who did not (non-HF group).

Variables

QCR, Death Registry and Hospital Administration records were linked (1996–2009). Index HF must have occurred after the date of cancer registry entry. Demographic information was extracted from the QCR (Table 1). Age was categorised as <20, 20–29, 30–39, 40–49, 50–59, 60–69 and ≥70 for the Cox proportional hazard modelling. Age groupings for the Kaplan–Meier survival curve analysis were based on the median and were categorised as <50, 50–59, 60–69 and ≥70 years.
Chemotherapy-receiving patients were identified from the relevant codes in hospital records, defined by ICD-9-CM (clinical modification) (99.25) and ICD-10-AM (Australian Modification) (96196-00, 96199-00, 96209-00, 96207-00, 96208-00, 96204-00, 13942-00, 13945-00, 13918-00, 13921-00, 13927-00, 13939-0, 13942-0, 13946-0, Z51.1, Z51.2).

An index HF admission was defined as a patient’s first hospitalisation coded for HF. HF diagnosis was based on the ICD-9-CM (428.0, 428.1 and 428.9) and ICD-10-AM (I50.0, I50.1 and I50.9) codes. HF included congestive HF, left ventricular failure and other unspecified cardiomyopathies.

All-cause mortality data were extracted from the Queensland Birth, Deaths and Marriages database – a repository for all registered deaths in Queensland. Patients who died after the end of the study period (31 December 2009) were considered to be alive for the calculation of survival time and mortality.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Heart failure, n = 1062 (6.6%)</th>
<th>Non-heart failure, n = 14 925 (93.4%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (at cancer diagnosis), median (IQR) (years)</td>
<td>67.0 (58–75)</td>
<td>54.0 (44–64)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Age group, n [%] (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>32 (3.0)</td>
<td>820 (5.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>20–29</td>
<td>14 (1.3)</td>
<td>470 (3.1)</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>23 (2.2)</td>
<td>1359 (9.1)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>71 (6.7)</td>
<td>3199 (21.4)</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>166 (15.6)</td>
<td>3926 (26.3)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>322 (30.3)</td>
<td>3054 (20.5)</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>434 (40.9)</td>
<td>2097 (14.1)</td>
<td></td>
</tr>
<tr>
<td>Sex, n [%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>546 (51.4)</td>
<td>10 528 (70.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Male</td>
<td>516 (48.6)</td>
<td>4397 (29.5)</td>
<td></td>
</tr>
<tr>
<td>Marital status, n [%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/De Facto</td>
<td>635 (59.8)</td>
<td>9719 (65.1)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Single/divorced/widowed</td>
<td>427 (40.2)</td>
<td>5206 (34.9)</td>
<td></td>
</tr>
<tr>
<td>Country of birth, n [%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>759 (71.5)</td>
<td>11 221 (75.2)</td>
<td>0.007*</td>
</tr>
<tr>
<td>All other countries</td>
<td>303 (28.5)</td>
<td>3704 (24.8)</td>
<td></td>
</tr>
<tr>
<td>Indigenous status, n [%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indigenous</td>
<td>15 (1.4)</td>
<td>233 (1.6)</td>
<td>0.784</td>
</tr>
<tr>
<td>Non-indigenous</td>
<td>1047 (98.6)</td>
<td>14 692 (98.4)</td>
<td></td>
</tr>
<tr>
<td>Residence (postcode), n [%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>916 (86.3)</td>
<td>12 954 (86.8)</td>
<td>0.609</td>
</tr>
<tr>
<td>Rural/remote</td>
<td>146 (13.7)</td>
<td>1971 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Cancer morphology/site, n [%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>180 (16.9)</td>
<td>7468 (50.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Haematological</td>
<td>882 (83.1)</td>
<td>7457 (50.0)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>728 (68.5)</td>
<td>4166 (27.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SMR</td>
<td>4.19</td>
<td>5.27</td>
<td></td>
</tr>
<tr>
<td>HF-related mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>279 (17.4)</td>
<td>455 (3.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>No. of hospitalisations, median (IQR)</td>
<td>7 (3–15)</td>
<td>8 (4–15)</td>
<td>0.100</td>
</tr>
<tr>
<td>No. of chemotherapy admissions, median (IQR)</td>
<td>5 (2–12)</td>
<td>7 (4–14)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>No. of chemotherapy admissions, quintiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>392 (36.9)</td>
<td>3067 (20.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>4–6</td>
<td>213 (20.1)</td>
<td>4040 (27.1)</td>
<td></td>
</tr>
<tr>
<td>7–9</td>
<td>125 (11.8)</td>
<td>1941 (13.0)</td>
<td></td>
</tr>
<tr>
<td>10–16</td>
<td>179 (16.9)</td>
<td>3050 (20.4)</td>
<td></td>
</tr>
<tr>
<td>≥17</td>
<td>153 (14.4)</td>
<td>2827 (18.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Significantly different at P ≤ 0.05. Haematological cancer = leukaemias, lymphomas and related disorders. Hospitalisations are a combination of admissions for HF and for chemotherapy. HF, heart failure; IQR, interquartile range (25th–75th percentile); SMR, standardised mortality ratio.
Data sources and data linkage

The QCR, which has been collecting data since 1982, was used to identify patients with a primary diagnosis of breast or haematological cancers.\(^{15}\)

The QCR facility and Unit Record numbers were merged with Hospital Admitted Patient Data Collection episodes to identify those who underwent chemotherapy and those with an index HF admission following QCR registration. Details of pre-existing cardiovascular risk factors were not available in this administrative dataset. Death records were obtained from Birth, Deaths and Marriages and were linked to QCR records. Linkage Wiz software (Adelaide, SA, Australia) was used for probabilistic matching.\(^{16}\)

Bias

To reduce false and mismatched linkages,\(^{17}\) a 20-step review process to identify false positives was undertaken within a broader quality control framework. The false positive rate for this methodology has been shown to be 0.3%.\(^{18}\)

Statistical methods

Linked health data were extracted and coded using STATA 13.0 (StataCorp LP, College Station, TX, USA) and analysed using IBM SPSS for Windows version 22.0 (IBM, Armonk, NY, USA). Differences in demographics, cancer treatment history and morphology/site were analysed for between-group differences using Fisher’s exact test and the chi-square test. Where continuous data were non-normally distributed, the data were presented as median (interquartile range (IQR)) and compared using appropriate non-parametric tests. Differences were considered significant at \(P \leq 0.05\).

Standardised mortality ratios (SMR) for all-cause mortality were derived using an indirect standardisation methodology by calculating the age-specific, all-cause death rates of the Australian population for each year within the study period (1996–2009) relative to observed deaths in our study population. Data are presented as the mean of the yearly SMR calculations.

Kaplan–Meier survival curves were derived to compare the time to death from cancer diagnosis between groups and by gender and age using a log-rank test.

Time-varying Cox proportional hazards regression models were used to evaluate factors associated with mortality risk during follow-up in groups adjusted by demographic variables, cancer treatment history and morphology/site (Table 2). Hazard ratios (HR) were used to describe the probability of survival after chemotherapy treatment. The proportional hazard assumptions and goodness of fit of the models were also tested.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HF patients</th>
<th>Non-HF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>Referent</td>
<td>0.078</td>
</tr>
<tr>
<td>20–29</td>
<td>1.98 (0.93–4.25)</td>
<td>0.164</td>
</tr>
<tr>
<td>30–39</td>
<td>1.67 (0.81–3.45)</td>
<td>0.228</td>
</tr>
<tr>
<td>40–49</td>
<td>1.35 (0.75–2.41)</td>
<td>0.062</td>
</tr>
<tr>
<td>50–59</td>
<td>1.39 (0.81–2.37)</td>
<td>0.005*</td>
</tr>
<tr>
<td>60–69</td>
<td>1.64 (0.98–2.75)</td>
<td>2.08 (1.25–3.47)</td>
</tr>
<tr>
<td>≥70</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female versus male</td>
<td>1.32 (1.11–1.55)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/de facto versus all other</td>
<td>1.16 (0.99–1.36)</td>
<td>0.073</td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other versus Australia</td>
<td>0.77 (0.65–0.91)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Cancer site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer versus haematological</td>
<td>1.41 (1.12–1.77)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Number of chemotherapy admissions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>4–6</td>
<td>0.99 (0.94–1.04)</td>
<td>0.711</td>
</tr>
<tr>
<td>7–9</td>
<td>1.00 (0.95–1.06)</td>
<td>0.953</td>
</tr>
<tr>
<td>10–16</td>
<td>0.99 (0.94–1.04)</td>
<td>0.640</td>
</tr>
<tr>
<td>≥17</td>
<td>0.99 (0.93–1.04)</td>
<td>0.604</td>
</tr>
</tbody>
</table>

*Statistically significant at \(P \leq 0.05\). Data were adjusted for age, gender, marital status, country of birth, cancer site and number of chemotherapy admissions. Haematological cancer = leukaemias, lymphomas and related disorders. CI, confidence interval; HF, heart failure; HR, hazard ratio.
Results

Participants

A total of 73,158 breast or haematological cancer records was linked to hospital admissions and death records. Within the QCR, there were 918 patients registered with multiple cancers (one patient with four, seven patients with three and 910 patients with two types of cancers). In order to count each patient once, the primary cancer diagnosis was selected, and all other registrations were excluded \((n = 927)\).

A large proportion \((n = 15,750)\) of the records that fell outside the study time frame was excluded, and 40,494 records of the patients who did not receive chemotherapy were excluded. The final sample included 15,987 patient records, of which 1062 had at least one index HF admission following their cancer diagnosis, and 14,925 had no HF admission. The median follow-up time was 3.34 years (IQR, 1.34–7.25, range: 0–13.9 years) (Fig. 1).

Demographics and clinical characteristics

The median age at cancer diagnosis was 55.0 years (IQR 44–65); 5.3\% \((n = 852)\) were aged ≤20 years, and 34.8\% \((5564)\) were aged over 60 years. As part of this cohort included breast cancer patients, there was a greater proportion of females (69.3\%, 11,074) than males (30.7\%, 4913); 52.2\% (8339) had a primary diagnosis of haematological cancer, and 47.8\% (7648) had a primary diagnosis of breast cancer.

Patients appeared to have given the postcodes for where they lived during cancer treatment, so an urban–rural comparison was not conducted.

Compared to the non-HF group, HF patients were significantly older \((P < 0.001)\), and there was a lower proportion of female patients \((P < 0.001)\) and a greater proportion of patients with haematological cancers \((P < 0.001)\) (Table 1). There were differences in the number of chemotherapy admissions between groups \((P < 0.001)\). Non-HF patients were more likely to be Australian-born and in a Married/De Facto relationship (Table 1).

Clinical outcome data

All-cause mortality was 2.45 times higher in HF than in non-HF patients \((P < 0.001)\), and HF-related mortality was 5.80 times higher in the HF group compared with...
the non-HF group ($P < 0.001$). SMR for all-cause mortality for the non-HF and HF groups were 5.27 and 4.19 times greater than the comparable Australian population, respectively, most likely because of the age differences between these groups.

The onset of HF occurred within 12 months of cancer diagnosis and treatment in 47.1% and within the first 3 years for 69.6% of the HF group (Fig. 2). All-cause mortality (adjusted for age, gender, marital status, country of birth, cancer site and chemotherapy admissions) differed between groups, with the HF group having a greater risk of mortality relative to the non-HF group (HR 1.67 (95% confidence interval (CI), 1.54–1.81), $P < 0.001$) (Fig. 3).

Mean survival times from cancer diagnosis were 9.57 years (95% CI 9.46–9.86, 4166) and 5.30 years (95% CI 4.99–5.62, 728) for the non-HF and HF groups respectively.

The time-varying Cox proportional hazard modelling showed that non-HF patients had an increased risk of mortality with increasing age (Table 2). This was not observed in the HF patients, with no difference in mortality with increasing age, except those aged over 70 years (Table 2). Males had a higher and similar risk of mortality in both the HF and non-HF groups compared with females. Patients who were not Married/De Facto had an increased risk of mortality in the non-HF group, but no difference was evident in the HF group. Patients born in a country other than Australia had a lower risk of mortality among HF patients, and there was a higher risk of mortality in haematological cancers relative to breast cancer in both groups.

In the non-HF group relative to those who had one to three chemotherapy admissions, there was a decrease in mortality risk for each quintile of chemotherapy admissions until ≥17 admissions, where there was a small but significant increase in mortality risk. However, there were no significant differences in mortality risk across quintiles of chemotherapy admissions in the HF group (Table 2).

Kaplan–Meier survival curves of all-cause mortality by age and gender in HF patients indicate similar survival rates between the younger patients (<50 years compared to 50–59 years); however, there was a steeper decline in mortality in older age groups (log-rank $P < 0.001$) (Fig. 4). Survival rates were higher in female patients than in males (log-rank $P < 0.001$).

**Discussion**

In the context of well-established evidence for causality between chemotherapy, radiotherapy and cardiotoxicity, this study aimed to determine differences in characteristics and clinical outcomes of cancer patients who received chemotherapy that has the highest incidence of cardiotoxicity and who subsequently developed HF relative to those who did not. We have shown that 6.6% of breast or haematological cancer patients who received chemotherapy subsequently developed HF. Results from the USA, Australia and Europe have shown HF rates ranging from 1.3% to 4% of the population. Our study suggests that cancer treatment could increase the risk of developing HF by approximately two to three times.

In the HF group, 47.7% of patients had an index HF admission within 12 months following cancer diagnosis and 69.6% within 3 years. This is concerning, especially for patients who develop HF prior to the completion of chemotherapy, which may necessitate treatment termination and influence cancer-specific outcomes.
The median age of HF patients was 67 years compared with 54 years in non-HF patients. In other studies of adults with HF, the median age of HF diagnosis has ranged from 70 to 82.5 years. Our results suggest that cancer treatment might trigger the development of HF at an earlier age than typically observed.

In the HF group, there were a greater proportion of patients with haematological cancers relative to those with breast cancer compared with the non-HF group. This may be due to exposure to different drugs, older age of patients with haematological cancers and additional treatments including radiotherapy.

The difference in trajectory for patients with cardiotoxicity compared with those with cancer or HF alone has been presented schematically in Figure 5.

During the study period, the median number of hospitalisations (HF and chemotherapy admissions combined) and chemotherapy admissions were greater in the non-HF group. This most likely reflects good clinical care by moderating or ceasing treatment at the time of diagnosis of HF. This is supported by our observation that a high proportion of patients developed HF rapidly, thereby resulting in fewer chemotherapy admissions. Furthermore, the number of hospitalisations and chemotherapy admissions may be less in the HF group because of the greater mortality of this population.

Survival time was lower in the HF group compared with the non-HF group, with the combination of cancer and HF responsible for a 67% higher rate of death than cancer alone (Fig. 3). This may be expected as other studies have shown patients with HF having poorer prognosis compared with most solid-organ cancers.

In the HF group, all-cause mortality was 2.45 times greater than the non-HF group. Relative to the Australian population, those in the HF group had a fourfold higher mortality. Those in the non-HF group had a fivefold higher mortality than the overall Australian population. This is likely because of the age differences between groups, with the SMR calculated for the non-HF group relative to a younger population.

In non-HF patients, increases in mortality were observed with increasing age. This was not observed in HF patients, with no differences in mortality between older and younger patients, suggesting that the increased risk of mortality with HF overrides the effect of age alone. Other studies have shown median survival times after HF diagnosis ranging from 3.21 years in women and 5.39 years in men.

The non-HF group also showed a decrease in mortality risk with an increasing number of chemotherapy treatments, until ≥17, but there was no additional effect on mortality risk with an increasing number of chemotherapy admissions in the HF group. This may be due to the moderation of chemotherapy cycles in the HF patients in accordance with the cardiotoxicity treatment guidelines. However, in the context of an observational study, there are numerous confounders that were unable to be considered.

**Strengths and limitations**

The strengths of this study are the large sample size and the inclusion of all cancer patients who underwent chemotherapy over a 14-year period. The ability to link administrative datasets allows for the integration of multiple databases to provide a comprehensive picture of patient outcomes.

However, potential limitations should be considered, many of which are generic to this type of research. This
study was one of the first of a newly established data linkage service, and as such, we could only access datasets that had custodian approval; therefore, we were unable to access information regarding cancer treatment, including chemotherapy drugs, radiotherapy and pre-existing cardiovascular risk factors. Using the available data, we included chemotherapy admissions as a surrogate for drug information and demonstrated differences in treatment regimens in patients who developed HF and those who did not.

The inclusion of breast cancer patients has resulted in an over-representation of female patients. Also, our sample was not representative of the Queensland rural population. Approximately 52% of the residential population lived in rural areas; however, in this study, 13.7% of patients lived in rural Queensland, and it appears that metropolitan contact details were provided while undergoing treatment. Thus, residence was excluded from the Cox proportional hazard models of mortality.

With the inclusion of only HF hospitalisations and not other cardiovascular complications associated with cancer therapy, this study may just be the tip of the iceberg when describing the burden of cardiotoxicity on cancer patients.

Clinical implications

This study showed that 69.9% of patients had an index HF admission within 3 years following cancer diagnosis; therefore, monitoring should continue for a number of years following treatment. The European Society of Medical Oncology recommends that prior to undergoing chemotherapy, patients should be assessed for cardiovascular risk, and vital signs should be monitored during chemotherapy infusion. For children, adolescents and young adults, the American Heart Association recommends monitoring patients to allow for early detection of potential cardiac conditions and timely intervention to

![Figure 4](image-url) Probability of survival after treatment for cancer with chemotherapy in heart failure patients (unadjusted) by ( ), < 50 years; ( ), 50–59 years; ( ), 60–69 years; ( ), ≥ 70 years. (A) Age, (B) gender. ( ), Female; ( ), male.

![Figure 5](image-url) The differential in patient trajectory of physical function declines to mortality for cancer, cardiotoxicity, organ failure and physical and cognitive frailty. Adapted from Murray and Sheik, with permission. ( ), Cancer; ( ), cardiotoxicity; ( ), organ failure; ( ), physical and cognitive frailty.

Clark et al. © 2016 Royal Australasian College of Physicians
prevent, reverse or slow deterioration, and also tailoring cancer therapies to decrease risk of cardiotoxicity.29

Given the emergence of new cancer treatments, we do not know how large the problem of cardiotoxicity associated with cancer treatment is likely to become. There are no accurate data to indicate the most likely stage of the cancer trajectory when HF develops, when intervention should begin and how patients should be best-managed within the health system and in the community. Just as important, little has been published with regards to cancer survivors’ perceived cardiac healthcare needs and concerns or whether they understand the risk of HF.

Conclusion

Compared with HF in the non-cancer population after chemotherapy, this group developed HF more rapidly (47% within 1 year and 69% in 3 years) at a younger age (67 years compared to 70–82.5 years). However, in both our population and the non-cancer population, the prevalence was higher in males. There was a greater mortality risk in those with breast or haematological cancer and HF compared with breast or haematological cancer alone. Further research to understand predictors of cardiac risk in cancer patients is needed to develop strategies for patient management and risk mitigation.

References

6 Wells QS, Lenihan DJ. Reversibility of left ventricular dysfunction resulting from chemotherapy: can this be expected? Prog Cardiovasc Dis 2010; 53: 140–8.
Utility of surgical lung biopsy in critically ill patients with diffuse pulmonary infiltrates: a retrospective review

L. H. Donaldson,1 A. J. Gill2,3 and M. Hibbert4,5

1Malcolm Fisher Department of Intensive Care Medicine, Departments of 2Anatomical Pathology and 3Respiratory Medicine, Royal North Shore Hospital, and 4Department of Surgical Pathology, and 5Northern Clinical School, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

Key words
respiratory insufficiency, pulmonary surgical procedure, biopsy, adult respiratory distress syndrome, intensive care unit.

Abstract
Background: There are conflicting reports regarding the role of surgical lung biopsies in patients who present to the intensive care unit (ICU) with unexplained respiratory failure and diffuse pulmonary infiltrates on imaging.

Aim: To describe the utility of surgical lung biopsies in patients presenting to the ICU with unexplained respiratory failure and diffuse pulmonary infiltrates.

Methods: A retrospective cohort study was performed. All patients admitted to the ICU who underwent a surgical lung biopsy for the investigation of respiratory failure and unexplained pulmonary infiltrates between 1998 and 2012 were included. The primary outcome measures for this descriptive study were the biopsy histopathology, changes in patient management following biopsy and in-hospital mortality.

Results: A total of 30 patients was included in the review. Biopsies in 22 patients (73%) demonstrated diffuse alveolar damage (DAD), with 15 of these biopsies (50%) suggesting a specific underlying aetiology. In 73% of cases (n = 22), the biopsy finding was associated with a change in management, although this generally involved the escalation of prior empiric therapy rather than initiation of a new treatment. Biopsies were performed at a median 10 days after admission (interquartile range 5–17 days), with the majority of patients being treated empirically prior to the biopsy with systemic steroids and broad-spectrum antimicrobials. Mortality was 53%.

Conclusion: In this series, DAD was the most frequent pathology. The biopsy result was associated with a change in management in a majority of the subjects, most frequently an escalation of prior empiric therapy. Mortality was high.

1Present address: Intensive Care Service, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050, Australia.

Funding: None.

Conflict of interest: None.

Disclosure: The authors declare that they have no relationships with any companies that might have an interest in the submitted work in the previous 3 years and have no non-financial interests that may be relevant to the submitted work.
Introduction

Almost one in three patients in intensive care units (ICU) worldwide is treated for respiratory failure.1 Patients with respiratory failure and diffuse pulmonary infiltrates with acute respiratory distress syndrome (ARDS) account for 10.4% of total ICU admissions worldwide.2 While the underlying aetiology of respiratory failure with diffuse pulmonary infiltrates can be determined in many patients, in some, the aetiology remains uncertain. Frequently, these patients respond to empirical therapy with antibiotics, diuretics and careful respiratory support. However, a small number do not. In these circumstances, a surgical lung biopsy (SLB) may be useful.

The role of SLB, however, remains controversial. SLB is an invasive procedure with attendant morbidity and mortality.3,4 There have been few prospective reviews of SLB in acute respiratory failure,5,6 and the reported diagnostic yield from these studies in several retrospective reviews varies widely.3,4,7–9 A recent meta-analysis of these mostly retrospective reviews was supportive of SLB, reporting high rates of specific diagnosis and attendant changes in management in response to the biopsy findings.10

Our clinical impression was that SLB in our institution was frequently performed late, usually demonstrated non-specific changes and rarely contributed to a significant change to management.

The primary aim of this review was to describe our experience with SLB in this group of patients in terms of the biopsy results, the change in management associated with these results and overall inpatient mortality.

Context

Royal North Shore Hospital (RNSH) is a large tertiary hospital in Sydney, Australia. The ICU has an average admission rate of 2963 patients per annum over the past 5 years. Over the same 5-year period, APACHE II (Acute Physiology and Chronic Health Evaluation II) admission data suggest that only 66 patients were admitted to the ICU with ARDS, although this figure does not capture patients who developed ARDS after admission.

Methods

This study comprised a retrospective review of the clinical notes of all patients who met the following inclusion criteria:

1 Admitted to the adult ICU with respiratory failure of unclear aetiology requiring ventilatory support,
2 Diffuse pulmonary infiltrates on chest X-ray and
3 Underwent a diagnostic SLB between 1998 and 2012.

All biopsies were performed in the operating theatre, generally as a video-assisted thoracoscopic surgery procedure.

Patient selection

Patients were identified through a search of the hospital’s surgical pathology database for all SLB specimens examined between the database’s inception in June 1998 and the end of 2012. Cases were initially selected if the biopsy was performed on patients within the ICU or who reported a clinical history consistent with the inclusion criteria.

The initial search identified 46 potential inclusions. After medical record review, 16 patients were excluded; two files could not be retrieved, eight patients were not in the ICU preoperatively, and for six patients the SLB was not performed for the investigation of pulmonary infiltrates.

Data collection

The following data were abstracted from the case notes, ICU flow charts and electronic pathology and radiology resources: age, gender, ICU and hospital mortality, discharge destination, ICU and hospital length of stay (LOS), SLB date, underlying comorbidities, medical therapy before and after biopsy, mode of respiratory support and gas exchange parameters at time of SLB, pre-biopsy working diagnosis, investigations prior to biopsy (particularly positive microbiology, bronchoscopy findings, radiology findings and basic full blood count and biochemistry), biopsy complications, the SLB results and the ultimate diagnosis.

Data were extracted by a single author (LHD) in paper form.

In cases where the histopathological diagnosis was unclear, the original specimens were re-examined and re-reported by a senior pathologist (AJG).

Outcome measures

The primary outcome measures for this descriptive study were the histopathology of the biopsy specimens, any change in medical management following the biopsy and in-hospital mortality. Secondary outcomes included timing of biopsy, biopsy complications and LOS.

We defined a ‘non-specific’ diagnosis as diffuse alveolar damage (DAD) with no clinicopathological features to point to a specific trigger. All other results were considered ‘specific’.
**Statistical analysis**
Continuous variables were expressed as medians (inter-quartile range (IQR)). Given the small sample size and non-normal distribution, associations were tested using non-parametric tests (Mann–Whitney U-test). Categorical data were reported as simple proportions. The association between categorical variables was tested using Pearson’s Chi-square test. Statistical significance was set at \( P < 0.05 \).

**Ethics approval**
Approval for this study at RNSH was granted by the Northern Sydney Local Health District Human Research Ethics Committee.

**Results**
A total of 30 patients who met the inclusion criteria in the 14-year period between 1998 and 2012 was included. As shown in Figure S1, the use of SLB increased over the period, with one biopsy being performed in 1998, while six were performed in 2012. The baseline characteristics are included in Table 1. The median age was 62 years (IQR 57–69). The majority of patients (63%) suffered from at least one significant medical comorbidity listed in Table 1.

**Management prior to biopsy**
Prior to the SLB, 67% of patients were receiving systemic corticosteroids, with 37% on high-dose methylprednisolone (≥500 mg daily); 90% of patients had been treated with an antibacterial agent with or without additional antifungal or antiviral cover (Table 2). Bronchoscopy was performed prior to SLB in 16 cases (53%). In four patients, bronchoalveolar lavage yielded a positive culture. The median time from hospital admission to SLB was 10 days (IQR 5–17 days). At the time of biopsy, 23 patients (77%) were intubated and ventilated, 6 (20%) were on non-invasive ventilation, and 1 patient required ECMO.

**Biopsy Results**
In four cases (13%) where the histopathological diagnosis was unclear, the original specimens were re-examined and re-reported. These are included in Table S1.

In 22 patients (73%), biopsies demonstrated DAD. As described in Table 3, in seven of these biopsies (23%), there were specific histological features, which, in their given clinical context, were consistent with a specific underlying aetiology, most frequently a drug reaction. Interstitial lung disease was seen in four (13%) patients and infection in two (7%) patients. Consequently, SLB yielded a specific result in 15 cases (50%) according to our pre-specified definition.

**SLB and change in management**
In 22 patients (73%), the biopsy findings were associated with a change in management. Most commonly, this was the addition of pulse methylprednisolone (40%). Five patients (17%) were commenced on other

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of included patients (n (%) or median (IQR))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>62 years (57–69)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Median hospital stay</td>
<td>32 days (21–56)</td>
</tr>
<tr>
<td>Median ICU length of stay</td>
<td>16 days (11–29)</td>
</tr>
<tr>
<td>Median time to biopsy</td>
<td>10 days (5–17)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>11 (36%)</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>Connective tissue (CT) disease</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Non-haematological malignancy</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>At least one of the above comorbidities</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>More than one of above</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Malignancy + chronic respiratory disease</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Both haematological and non-haematological malignancies</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Chronic respiratory and CT disease</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Medical management prior to surgical lung biopsy (n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic corticosteroid</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>Methylprednisolone ≥500 mg daily</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>Methylprednisolone 1–499 mg daily</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Hydrocortisone 100 mg QID</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Prednisone 1–50 mg daily</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Antimicrobial cover</td>
<td>27 (90%)</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>27 (90%)</td>
</tr>
<tr>
<td>Trimethoprim and sulfamethoxazole</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Antiviral</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Antifungal</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Other immunosuppressives</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Regular diuretics</td>
<td>14 (47%)</td>
</tr>
<tr>
<td>Regular bronchodilators</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
immunosuppressive agents. In 16 patients (53%), antimicrobial cover was altered (Table 4). Of those that had no treatment change, seven of eight were already on steroid treatment prior to the biopsy, usually at very high doses (63%, 5), and all but one were on broad-spectrum antibiotics.

### Biopsy complications

Clinically important complications of the biopsy occurred in eight patients (26%). Four patients (13%) suffered persistent pneumothorax/bronchopulmonary fistula. Four patients (13%) required increased ventilatory support following their biopsy, most commonly the escalation from non-invasive to invasive ventilation. No other significant complications attributable to the SLB were noted.

### Outcomes

Overall mortality for this group was 53%. There was no difference in mortality associated with a ‘specific’ biopsy result compared to a non-specific result (both 53%, \( P = 1 \)). Patients who were noted to have a change in management following the biopsy result did not appear to have a significantly improved mortality when compared with those whose empirical management was not altered (54 vs 50%, \( P = 0.83 \)).

### Discussion

In this retrospective review of patients undergoing SLB for the investigation of respiratory failure, SLB returned a result of DAD in 73% of cases and a ‘specific’ result (by our predefined terms) in 50% of cases. Management was altered following the SLB results in the majority of cases (73%).

These results differ significantly from those of a recent meta-analysis of SLB in respiratory failure with diffuse pulmonary infiltrates, which found that SLB demonstrated DAD in only 8.5% of the pooled 1705 patients.\(^1\) The most common biopsy results in this pooled analysis were interstitial lung diseases (24.4%) and infectious

---

**Table 3** Biopsy Results % (n)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAD (total)</td>
<td>73% (22)</td>
</tr>
<tr>
<td>DAD with no specific trigger</td>
<td>50% (15)</td>
</tr>
<tr>
<td>DAD with background changes of UIP</td>
<td>7% (2)</td>
</tr>
<tr>
<td>DAD, not otherwise specified</td>
<td>43% (13)</td>
</tr>
<tr>
<td>DAD with features of specific precipitant</td>
<td>23% (7)</td>
</tr>
<tr>
<td>DAD with features consistent with amiodarone drug reaction (characteristic foamy macrophages or lamellar bodies on electron microscopy &amp; consistent clinical history)</td>
<td>13% (4)</td>
</tr>
<tr>
<td>DAD with features consistent of gemcitabine toxicity (patchy intra-alveolar fibrin deposition and hyaline membrane formation with widespread type II pneumocyte hyperplasia (with bizarre and multinucleated forms and squamous metaplasia) and consistent clinical history)</td>
<td>3% (1)</td>
</tr>
<tr>
<td>DAD with features consistent with infective trigger (RSV) (DAD with specific features of bronchiolitis with recent positive RSV immunofluorescence on BAL)</td>
<td>3% (1)</td>
</tr>
<tr>
<td>DAD secondary to APL syndrome (extensive intravascular thromboembolic material and intravascular fibrin)</td>
<td>3% (1)</td>
</tr>
<tr>
<td>Interstitial lung disease (total)</td>
<td>13% (4)</td>
</tr>
<tr>
<td>Organising pneumonia/NSIP</td>
<td>3% (1)</td>
</tr>
<tr>
<td>Organising pneumonia secondary to recent infection</td>
<td>3% (1)</td>
</tr>
<tr>
<td>UIP</td>
<td>7% (2)</td>
</tr>
<tr>
<td>Infection (total)</td>
<td>7% (2)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>3% (1)</td>
</tr>
<tr>
<td>CMV</td>
<td>3% (1)</td>
</tr>
<tr>
<td>Other</td>
<td>7% (2)</td>
</tr>
<tr>
<td>Acute pulmonary oedema</td>
<td>7% (2)</td>
</tr>
</tbody>
</table>

APL, antiphospholipid syndrome; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; DAD, diffuse alveolar damage; NSIP, non-specific interstitial pneumonia; RSV, respiratory syncytial virus; UIP, usual interstitial pneumonia.

**Table 4** Change in management triggered by biopsy, n (%)

<table>
<thead>
<tr>
<th>Change in Management</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of Methylprednisolone (≥500 mg/day)</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>With pre-SLB steroid: hydrocortisone 100 mg QID</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>With pre-SLB steroid: prednisone 25 mg daily</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>With no previous steroid use</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Commencement of other immunosuppressives</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Change to antimicrobials</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Antibacterials recommenced</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Antimicrobials ceased</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Bacterial cover broadened</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Bacterial cover narrowed</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Antiviral added</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Antifungal ceased</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Initiation of plasmapheresis</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Immediate palliation</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>No change to treatment</td>
<td>8 (26%)</td>
</tr>
</tbody>
</table>
diseases (23.6%), both of which were uncommon in the population reported here.

A noticeable difference between this population and that reported elsewhere was the timing of SLB. In our study, this occurred at a median of 10 days from admission, substantially later than in other case series. Given that biopsies tended to be performed at a relatively late stage, extensive empirical treatment, specifically broad-spectrum antimicrobials and high-dose systemic steroids, had been given to the majority of patients, making a change in management that could materially affect patient outcome less likely.

One of the few prospective studies of SLB in respiratory failure published to date has shown that a contributive result from SLB (i.e. one that led to a change in management) significantly improved outcomes in patients with ARDS and negative bronchoalveolar lavage. While biopsies were performed at a similar time to the population reported here (median of 11 days of ventilation), in Papazian et al.’s study, no patients were empirically managed with steroids. Although SLB likely contributed to the study, no patients were empirically managed with steroids. Although SLB likely contributed to change in management in 73% of patients in our series, this usually involved the escalation of immunosuppression or alteration of antibiotic cover; few patients had new therapies commenced.

Overall mortality in this group was high. A specific biopsy result or a change in management following the biopsy result did not appear to significantly impact in-hospital mortality, although a large prospective study would be required to assess adequately any mortality benefit.

This retrospective review is clearly not without significant limitations. Although covering a long period, the included population is relatively small, reflecting the infrequent use of this test at this institution. Nonetheless, this review does suggest the limited use of SLB when used late and after extensive empirical therapy. Management was commonly altered following the biopsy, although this was rarely tailored to a specific pathology, and the study was too small to determine if there was any association with a change in outcome.

**Conclusion**

While this review suggests limited use of late SLB, the question remains whether early biopsy prior to extensive empirical treatment would offer any significant benefit over current management. While randomised trials of such an infrequently performed intervention are unlikely to be performed, further collaboration and consideration of the use of this invasive test is required.

### References


### Supporting Information

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

**Figure S1** Number of surgical lung biopsies performed per year over the period of study.

**Table S1** Results of four re-reported pathology specimens.
Return to sender: the need to re-address patient antibiotic allergy labels in Australia and New Zealand

J. A. Trubiano,1,2,3 L. J. Worth,2,3 K. Urbancic,1,4 T. M. Brown,5 D. L. Paterson,5 on behalf of the Australasian Society for Infectious Diseases Clinical Research Network, M. Lucas,6 on behalf of the Australasian Society of Clinical Immunology and Allergy and E. Phillips7,8

Department of Infectious Diseases and Pharmacy, Austin Health, 2Department of Infectious Diseases, Peter MacCallum Cancer Centre, and 3Department of Medicine, The University of Melbourne, Melbourne, Victoria, 4Centre for Clinical Research, University of Queensland, Brisbane, Queensland, 5Department of Clinical Immunology, Pathwest Laboratory Medicine, Queen Elizabeth II Medical Centre, and 6Institute for Immunology and Infectious Diseases, Murdoch University, Perth, Western Australia, Australia, and 7Department of Medicine, Vanderbilt Medical Center, Nashville, Tennessee, USA

Key words
antibiotic allergy, adverse drug reaction, antibiotic allergy testing, antimicrobial stewardship, skin testing.

Correspondence
Jason Trubiano, Infectious Diseases Physician, Austin Health, PO Box 5555, Heidelberg, Vic. 3084, Australia.
Email: jason.trubiano@austin.org.au

Received 23 May 2016; accepted 8 August 2016.

doi:10.1111/imj.13221

Abstract

Background/Aim: Antibiotic allergies are frequently reported and have significant impacts upon appropriate prescribing and clinical outcomes. We surveyed infectious diseases physicians, allergists, clinical immunologists and hospital pharmacists to evaluate antibiotic allergy knowledge and service delivery in Australia and New Zealand.

Methods: An online multi-choice questionnaire was developed and endorsed by representatives of the Australasian Society of Clinical Immunology and Allergy (ASCIA) and the Australasian Society of Infectious Diseases (ASID). The 37-item survey was distributed in April 2015 to members of ASCIA, ASID, the Society of Hospital Pharmacists of Australia and the Royal Australasian College of Physicians.

Results: Of 277 respondents, 94% currently use or would utilise antibiotic allergy testing (AAT) and reported seeing up to 10 patients/week labelled as antibiotic-allergic. Forty-two per cent were not aware of or did not have AAT available. Most felt that AAT would aid antibiotic selection, antibiotic appropriateness and antimicrobial stewardship (79, 69 and 61% respectively). Patients with the histories of immediate hypersensitivity were more likely to be referred than those with delayed hypersensitivities (76 vs 41%, P = 0.0001). Lack of specialist physicians (20%) and personal experience (17%) were barriers to service delivery. A multidisciplinary approach was a preferred AAT model (53%). Knowledge gaps were identified, with the majority overestimating rates of penicillin/cephalosporin (78%), penicillin/carbapenem (57%) and penicillin/monobactam (39%) cross-reactivity.

Conclusions: A high burden of antibiotic allergy labelling and demand for AAT is complicated by a relative lack availability or awareness of AAT services in Australia and New Zealand. Antibiotic allergy education and deployment of AAT, accessible to community and hospital-based clinicians, may improve clinical decisions and reduce antibiotic allergy impacts. A collaborative approach involving infectious diseases physicians, pharmacists and allergists/immunologists is required.

Introduction

Despite 10% of the population reporting a penicillin ‘allergy’, less than 1% of the population are confirmed as being truly penicillin allergic by formal testing.1–5 In Australia, the prevalence of antimicrobial allergy labels in hospitalised inpatients is 18% and higher in populations with more frequent antibiotic use (e.g. immunocompromised hosts).6–7 Antimicrobial allergy labels are associated with broad spectrum antibiotic usage, antimicrobial resistance, inappropriate prescribing, morbidity and mortality.4,7,8 The majority of antibiotic allergy labels reflect either pharmacologically predictable side effects or mild non-immunologically mediated drug reactions that are amendable to rechallenge or symptomatic management as necessary.9,10 Antibiotic allergy testing (AAT), which combines skin prick testing (SPT), intradermal testing (IDT) and ingestion (usually oral) challenge, has a high negative-
predictive value and can therefore accurately de-label patients previously suspected to have an allergy on clinical criteria alone.\textsuperscript{1,11,12} In an era of increasing antimicrobial resistance, a strategic approach for clinicians to confirm and reliably document antibiotic allergy labels is required.

The aim of this study is to identify the need for and potential barriers to the development of coordinated multidisciplinary AAT programmes in Australia and New Zealand; we surveyed current knowledge and approaches to AAT among allergists, clinical immunologists, infectious diseases physicians, general physicians and hospital pharmacists.

\textbf{Methods}

\textbf{Studied population}

We targeted healthcare providers most closely involved with the diagnosis and management of antibiotic allergies and adverse drug reaction reporting in Australian and New Zealand. These included allergists/clinical immunologists, infectious diseases physicians, general physicians and hospital pharmacists.

\textbf{Survey tool}

A 37-item multiple-choice survey was developed to assess the key antibiotic allergy domains: (i) prevalence; (ii) testing practices; (iii) benefits to antimicrobial stewardship (AMS); (iv) models of care; and (v) clinician knowledge. Stakeholders represented clinical practice, research and supportive care sectors. Consultation and endorsement was sought from the Australasian Society of Clinical Immunology and Allergy (ASCIA) and Australasian Society of Infectious Diseases (ASID). Clarity and presentation of the survey were evaluated and refined by pretesting of the questionnaire by two infectious diseases physicians, two pharmacists and one allergist/clinical immunologist prior to distribution. The survey was delivered electronically through an online portal (Survey Monkey, Palo Alto, CA, USA) by the ASCIA, ASID, the Society of Hospital Pharmacists of Australia (SHPA) and the Royal Australasian College of Physicians (RACP). Local ethics approval by the research ethics committee of the administering institution (Peter MacCallum Cancer Centre, Vic., Australia) was obtained prior to survey distribution (number 15/06L).

\textbf{Survey distribution}

An invitation and link to the survey was distributed through online modalities only, including RACP weekly e-bulletin ($n = 13\,016$), SHPA e-bulletin ($n = 2\,550$), ASCIA e-bulletin ($n = 320$), ASID weekly e-bulletin ($n = 778$) and Ozbug mailing list ($n = 800$). Ozbug is a moderated mailing list for infectious diseases physicians and microbiologists in Australia and New Zealand.\textsuperscript{13} Survey recipients may have been members of multiple listed societies or groups. The online survey was open between 15 March and 2 April 2015, and one electronic reminder was sent to each group midway through the survey period. Anonymity of respondents and associated healthcare facilities was preserved.

\textbf{Analysis}

Responses were included if greater than 10% of survey questions were completed by a single participant. An overall percentage response rate could not be accurately obtained due to the overlapping nature of the surveyed societies and memberships. Survey responses were collated and analysed through Stata v13 (Statacorp, College Station, TX, USA). Categorical variables were summarised using frequency and percentage and compared between groups using a Chi-squared test. Continuous variables were summarised using mean and standard deviation (SD) or median and inter-quartile range as appropriate and compared using a paired $t$-test or Wilcoxon signed-rank test as appropriate. A $P$-value of $<0.05$ was deemed statistically significant.

\textbf{Results}

A total of 277 persons completed the survey. Table 1 summarises the baseline demographics of respondents. Fifty-eight per cent (160/277) were the members of RACP. All Australian states, territories and areas of New Zealand were represented in the survey respondents. There were more respondents with <10 years experience than those with >10 years clinical experience (57\% (157/277) vs 43\% (120/277), $P = 0.002$) (Table 1).

\textbf{Antibiotic allergy label prevalence}

Penicillin allergy label prevalence (8–10\% in published literature)\textsuperscript{5,7} was correctly estimated by 30\% (83/277) of respondents. The majority of respondents (204/277, 74\%) indicated that they reviewed 0–5 patients per week with a penicillin allergy, with a further 21\% (58/277) reviewing 6–10 patients per week.

\textbf{Allergy testing practices}

Whilst 32\% (67/208) indicated they already employed allergy testing, 42\% (118/277) of respondents were
either unaware of or did not have AAT services available to them (Fig. 1). Antibiotic allergy services were available equally to those with <10 years or ≥10 years clinical experience \((P = 0.63)\). Varied skin testing practices were available to respondents (Fig. 1). The allergy phenotypes referred for AAT are demonstrated in Table 2, which shows more respondents refer patients with immediate compared with delayed hypersensitivities \((76\% (110/144) \text{ vs } 41\% (59/144), P = 0.001)\). Gold-standard allergy testing (SPT/IDT plus provocation challenge) was available to 58\% \((91/156)\) of respondents. Sixty-five per cent \((157/240)\) would be comfortable to use penicillin following negative gold-standard allergy testing, whilst 35\% \((83/240)\) remained unsure or would not employ.

### Benefits of AAT to AMS

When asked if AAT would benefit AMS, 74\% \((158/213)\) responded in the affirmative. The removal of an antibiotic allergy label was felt to aid antibiotic selection \((78\%, 165/212)\), antibiotic appropriateness \((69\%, 147/212)\), medication safety \((69\%, 146/212)\), AMS services \((61\%, 129/212)\) and all of the aforementioned \((29\%, 61/212)\). Four per cent \((8/212)\) of respondents felt there would be no measurable benefit for the removal of an antibiotic allergy label. A beside point-of-care antibiotic allergy tool to assist management of patients with ‘labels’ was thought to be of benefit to 71\% \((153/214)\) of respondents.

### Antibiotic allergy models of care

Twenty-six per cent \((55/209)\) felt there were no barriers to AAT, whilst 12\% \((26/209)\) recorded no demand for services. Barriers to AAT are summarised in Figure 2, with an absence of specialist clinicians being the most

![Figure 1](attachment:image.png)
commonly reported. There was a non-significant trend for those with <10 years experience to become new users of AAT services ($P = 0.08$). A referral process involving a combined immunology/infectious diseases stream was preferred (47%, 90/192). Alternative favourable AAT models included referral to or by the following mechanism: (i) automated referral (25%, 47/192), (ii) pharmacist (38%, 72/192), (iii) AMS physician (45%, 86/192), (iv) infectious diseases (37%, 71/192). Preferred delivery of AAT was through clinical immunology/allergy departments (53%, 112/213), a ‘partnership between infectious diseases, pharmacy and immunology’ (39%, 84/213), AMS programmes (5%, 10/213) or infectious diseases physicians (2.3%, 5/213). More infectious diseases physicians (45%; 35/78) and pharmacists (62%; 36/58) preferred and saw the benefits of a partnership model than allergists/immunologists (17%; 9/52) ($P = 0.001$).

### Table 2 Antibiotic allergy phenotypes referred for testing

<table>
<thead>
<tr>
<th>Allergy phenotypes referred for testing, n (%)</th>
<th>Immediate</th>
<th>Delayed</th>
<th>All reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgE</td>
<td>SCAR</td>
<td>MPE</td>
</tr>
<tr>
<td>Infectious diseases physicians (n = 48)</td>
<td>32 (67)</td>
<td>7 (15)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Pharmacists (n = 28)</td>
<td>22 (79)</td>
<td>5 (18)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Allergists/immunologists (n = 53)</td>
<td>47 (89)</td>
<td>1 (2)</td>
<td>17 (32)</td>
</tr>
<tr>
<td>Other (n = 15)†</td>
<td>9 (60)</td>
<td>3 (20)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Total (n = 144)</td>
<td>110 (76)</td>
<td>16 (11)</td>
<td>43 (30)</td>
</tr>
</tbody>
</table>

†Includes general practitioners, general physicians, microbiologists. MPE, maculopapular exanthema; SCAR, severe cutaneous adverse reactions.

#### Discussion

In the current era of increasing antimicrobial resistance, opportunities to improve antibiotic prescribing are understanding of penicillin and beta-lactam cross-reactivity comparing those with <10 and ≥10 years experience (Fig. 3). In patients with a history of immediate penicillin hypersensitivity, only 15% (37/241) would consider ceftriaxone, 41% (101/241) meropenem and 63% (152/241) aztreonam safe to administer in this clinical scenario, despite low rates of cross-reactivity (Table 3). Twenty-four per cent (57/237) of respondents would administer benzylpenicillin in the setting of community-acquired pneumonia, 67% (159/237) preferring ceftriaxone, in a patient with a childhood history of mild delayed hypersensitivity (i.e. maculopapular exanthema (MPE)) to penicillin. Seven per cent (16/237) would employ moxifloxacin in this scenario. In the case of methicillin-sensitive *Staphylococcus aureus* bloodstream infection in a patient with a history of childhood MPE, a first-generation cephalosporin was the treatment of choice (47%, 112/237), followed by fluclaxacillin (26%, 62/237), fluclaxacillin following desensitisation (11%, 26/237), dindamycin (7%, 6/237) and vancomycin (6%, 15/237) therapy.
essential. Attention has turned to antibiotic allergy de-
labelling to enhance AMS programmes.\textsuperscript{17} Before de-
labelling can be incorporated into AMS, assessments of
current Australian and New Zealand antibiotic allergy
service provisions and stakeholder knowledge are
required to identify the barriers to implementing multi-
disciplinary AAT services. We surveyed Australian and
New Zealand clinicians and pharmacists to examine the
current and future requirements of AAT programmes
and attitudes towards antibiotic allergy.

Our survey highlights a demand for AAT among key
stakeholders irrespective of clinical experience, con-
tasted with significant operational barriers. Whilst anti-
biotic allergies encountered by infectious diseases
physicians are being increasingly found to impact on
antibiotic selection, antibiotic appropriateness and anti-
microbial resistance,\textsuperscript{1,8,18} less than half infectious diseases
specialists had AAT available, likely reflective of poor
access. When available, testing to a vast array of β-lac-
tams, including the implicated antibiotic, was offered.
There appears a desire to refer patients with a history of
immediate hypersensitivity over delayed, potentially
reflecting a perception of less robust options for the
management and diagnosis for T-cell mediated reactions. This
is interesting as antibiotics contribute almost 50% of
severe cutaneous adverse reactions,\textsuperscript{19} and both \textit{in vivo}
(skin testing) and \textit{ex vivo} diagnostics are continually
improving.\textsuperscript{20–22} In addition, clinical phenotyping and risk
stratification is even more important for many serious
delayed reactions to avoid future morbidity and mortal-
ity related to re-exposure to a suspect drug or one that is
structurally related. Most respondents were optimistic
that overall AAT could aid AMS and, if more easily
accessible, would employ AAT in their AMS
programmes.

We identified significant knowledge gaps among sur-
veyed clinicians and pharmacists that did not correlate
with years of clinical experience. Compounding either a
true or the perceived absence of AAT is a potential mis-
understanding of antibiotic allergy, previously noted in
the United States.\textsuperscript{23} Whilst historical estimates of IgE-
mediated cephalosporin and penicillin cross-reactivity
were 15–25%, more contemporary studies suggest the
true rate of cross-reactivity to be <2% and potentially

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
\textbf{Statement or question regarding antibiotic allergy} & \textbf{Evidence-based response†} & \textbf{ID} & \textbf{Pharmacists} & \textbf{Allergists/ immunologists} & \textbf{Other‡} \\
\hline
The major cause of cross-reactivity between amoxicillin
and cephalaxin allergy is the beta-lactam ring & False & 48 & 38 & 36 & 48 & 42 \\
What is the rate of immediate third generation
cephalosporin allergy in a patient with penicillin allergy? & <1–2% & 6 & 18 & 48 & 35 & 21 \\
What is the rate of immediate carbapenem allergy in a
patient with penicillin allergy? & <1% & 46 & 31 & 50 & 28 & 40 \\
What is the rate of immediate monobactam allergy in a
patient with penicillin allergy? & <1% & 79 & 46 & 63 & 41 & 61 \\
\hline
\end{tabular}
\caption{Knowledge of antibiotic allergy cross-reactivity}
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{The impact of clinical experience on the utilisation of antibiotic allergy testing and antibiotic allergy knowledge. (■), <10 years clinical experience; (■■), >10 years clinical experience.}
\end{figure}
lower for third and later generation cephalosporins. Recent studies suggest the rate of immediate carbapenem and penicillin allergy cross-reactivity to be also extremely low (<1%). This contrasts with our surveyed stakeholders, 78% of whom suggested a cephalosporin cross-reactivity rate >2 and 58%, a meropenem cross-reactivity of >1%. Furthermore, despite most childhood-onset MPE being secondary to viral exanthema or antibiotic/viral interaction rather than antibiotic exposure, clinicians and pharmacists were reluctant to administer a preferred penicillin therapy in these patients with community-acquired pneumonia and S. aureus bloodstream infection. Despite the high-negative-predictive value of penicillin SPT and oral challenge, 35% of respondents were still unsure or unwilling to prescribe penicillin in the setting of a negative test. Investment in updating undergraduate and continuing medical and pharmacy antibiotic allergy education would enhance clinical knowledge and potentially improve antibiotic utilisation among key stakeholders.

Study limitations include the diversity of the surveyed population, including the fact that some responses were obtained from non-practising clinicians. Notwithstanding this limitation, 85% of respondents were current prescribers of antibiotics and actively engaged in clinical care. An accurate estimate of overall response rates could not be obtained due to overlap across the studied membership bases. As with all studies employing voluntary survey participation, the potential for selection bias is recognised. It is possible respondents represented a biased sample of those with an interest in AAT.

Nonetheless, this survey provides the first attempt at understanding current AAT practices and service provision in Australia and New Zealand.

Although models of antibiotic allergy care have been proposed, a standardised or multidisciplinary approach to AAT testing in Australia and New Zealand does not currently exist. We have demonstrated one of the preferred models to be a partnership between allergists, clinical immunologists, pharmacists and infectious diseases physicians. Similar multidisciplinary models in cancer patient AMS programmes, engaging relevant clinicians, have led to significant improvements in quality of care and mortality benefits. Improved knowledge of antibiotic allergy and the role ATT will help promote allergy services as a safe and effective service.

**Conclusion**

Despite a high antibiotic allergy label prevalence and demand for AAT services, current implementation barriers include lack of access to appropriate specialist healthcare providers to carry out AAT as well as cost of delivery. A collaborative model of infectious diseases physicians, pharmacists and allergists/clinical immunologists would enable targeted AAT delivery to those that require it, improving antibiotic utilisation, choice and drug safety. Current knowledge gaps suggest that education of clinicians and pharmacists and engagement of allergy and infectious diseases networks will be needed to provide the change necessary to fuel such multidisciplinary service models.

**References**


Detection and clinical significance of glomerular M-type phospholipase A₂ receptor in patients with idiopathic membranous nephropathy

H. Liu,1,2,3 W. Luo,1,2,3 S. Gong,1,2,3 and X. Ding1,2,3

1Department of Nephrology, Zhongshan Hospital, Fudan University, 2Shanghai Institute of Kidney and Dialysis, and 3Shanghai Key Laboratory of Kidney and Blood Purification, Shanghai, China

Key words
phospholipase A₂ receptor, idiopathic and secondary membranous nephropathy, proteinuria.

Correspondence
Xiaoqiang Ding, 180 Fenling Road, Xuhui District, Shanghai 200032, China.
Email: ding.xiaoqiang@zs-hospital.sh.cn

Received 18 January 2016; accepted 12 August 2016.
doi:10.1111/imj.13233

Abstract
Background: Glomerular M-type phospholipase A₂ receptor (PLA₂R) is important for diagnosing idiopathic membranous nephropathy (IMN). The relation between glomerular PLA₂R expression and response to treatment remains to be explored.
Aims: We conducted the study to explore the positive rate and clinical significance of glomerular M-type PLA₂R in IMN patients.
Methods: A total of 122 IMN patients receiving neither glucocorticoid nor immunosuppressant therapy prior to renal biopsies was included and followed for more than 1 year. The control group comprised 30 patients with secondary membranous nephropathy and 100 patients with non-membranous forms of nephropathy. PLA₂R level and IgG subclasses in glomeruli were detected. The primary end-point was the reduction of proteinuria to less than 50% of baseline value.
Results: A total of 82.0% of patients with IMN had positive glomerular PLA₂R deposits, compared with 16.7% in the secondary membranous nephropathy group (P < 0.001). Additionally, PLA₂R-positive expression combined with IgG4 ≥ 2+ was found in 94.3% IMN patients, compared with 40.0% in secondary membranous nephropathy patients (P < 0.01). Among IMN patients, the remission rate of proteinuria after either glucocorticoid or glucocorticoid combined immunosuppressant therapy for at least 6 months was 83.9% in the PLA₂R-positive group compared with 54.5% in the negative group (P < 0.05).
Conclusion: The positive rate of glomerular PLA₂R was more prevalent in IMN patients. Both PLA₂R and IgG4 glomerular deposits may help in discriminating between idiopathic and secondary membranous nephropathy. IMN patients with positive PLA₂R expression probably have a more beneficial response to glucocorticoid and/or immunosuppressant therapy.

Introduction
Idiopathic membranous nephropathy (IMN) is the most common pathological type in elderly patients with nephrotic syndrome. With the advancements in pathogenesis research, IMN is currently recognised as an autoimmune disease. In 2002, Debiec et al.1 identified neutral endopeptidase (NEP) in podocytes as the antigen for membranous nephropathy; however, NEP was only observed in a specific subset of IMN patients. In 2009, several American researchers proposed glomerular M-type phospholipase A₂ receptor (PLA₂R) as the pathogenic antigen in IMN; approximately 52–81% of patients with IMN were positive for serum PLA₂R antibodies,2–6 with even higher positive rates in glomeruli.7–9 In addition, IgG deposits in membranous nephropathy were characterised as IgG4 subclass.9,10 We hypothesise that the positive expression of PLA₂R in glomeruli and detection of IgG subclass may help establish a simple and accurate diagnosis of IMN. Furthermore, these factors may correlate with clinical manifestations and treatment response in IMN patients.

Methods
A retrospective study included patients who had renal biopsies in our centre between January 2010 and
January 2014; none of these patients had received glucocorticoid or immunosuppressant therapy prior to renal biopsy. The study group included patients who were both clinically and pathologically established to have IMN and also had been followed-up for more than 1 year. The control group included patients who were clinically and pathologically diagnosed as membranous nephropathy secondary to systemic lupus erythematosus (Class V), hepatitis virus B, hepatitis virus C or tumours, as well as patients whose pathological results were other than membranous nephropathy.

1 Clinical data – Collected information included patients’ gender, age, disease duration, serum albumin, serum creatinine (Scr), estimated glomerular filtration rate (eGFR, calculated by MDRD equation11) and 24-h proteinuria.

2 Renal pathology – Direct immunofluorescence was performed on frozen sections with antibodies for IgG, IgA, IgM, C3, C4, C1q, k and λ light chains (Gene Tech, Shanghai, China) and antibodies for IgG1,IgG4 (Sigma, St Louis, MO, USA). To detect PLA2R, cryosections of renal biopsy specimens were fixed in methanol and acetone and then blocked with 10% bovine serum albumin. The sections were subsequently incubated with 1:100 rabbit polyclonal antibody against human PLA2R1 (Sigma, HPA012657) for 1 h, followed by 1:50 Alexa Fluor 488-labelled goat anti-rabbit IgG antibody F(ab')2 fragments (Molecular Probes, A11070, Eugene, OR, USA). Immunofluorescence intensity was scored semi-quantitatively from 0 to 3+ (0, negative; 1+, weak staining; 2+, moderate staining; 3+, strong staining).

3 Treatment – Patients diagnosed as IMN all received renin angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockades (ARB) for at least 6 months. Glucocorticoids or immunosuppressants were only applied in patients whose proteinuria remained over 3.5 g/day after the 6-month angiotensin blockades. The relative contraindications, such as hyperglycaemia and impaired renal function as well as the economic status, were considered when prescribing immunosuppressive agents.

4 End-points of glucocorticoids or immunosuppressant treatment – The primary end-point is the remission rate of proteinuria, which includes complete remission (24-h urine protein ≤ 0.3 g/day) and partial remission (24-h urinary protein excretion decreased ≥50% from baseline with an absolute value > 0.3 g/day).

Statistical analysis
Quantitative variables were expressed in $\bar{x} \pm s$ and compared by $t$-test. Categorical variables were compared by $\chi^2$ test. A value of $P < 0.05$ was considered statistically significant, and $P < 0.01$ was considered notably statistically significant.

Results
Patients’ renal pathology
A total of 122 IMN patients was included in the study group. In the control group, 30 patients were diagnosed with secondary membranous nephropathy (17 cases of lupus nephritis Class V, 5 cases of hepatitis B-associated glomerulonephritis, 2 cases of tumour-associated glomerulonephritis, 2 cases secondary to syphilis, 1 case related to Sjogren syndrome, 1 case related to Hashimoto thyroiditis, 1 case related to rheumatoid arthritis and 1 case of IgG4-related tubulointerstitial nephritis). In addition, 100 patients diagnosed with non-membranous forms of nephropathy were also randomly selected.

Detection of glomerular PLA2R
All 252 patients underwent glomerular PLA2R detection. In the IMN group, 82.0% (100/122) demonstrated positive PLA2R expression. In the secondary membranous nephropathy group, 16.7% (5/30) of patients were positive for PLA2R, including three cases of HBV-associated membranous nephropathy, one case of IgG4-related membranous nephropathy and one case of lupus nephritis Class V (Table 1).

IgG subclass in IMN and secondary MN patients
IgG1 and IgG4 were detected in 82.0% (100/122) of IMN patients and 96.7% (29/30) of patients with secondary membranous nephropathy. Among these patients, 95.0% (95/100) and 86.2% (25/29) were IgG1-positive in idiopathic and secondary groups respectively ($P > 0.05$). Within the IMN group, 94.0% (94/100) exhibited IgG4-positive deposits in glomeruli, and 85.0% (85/100) had IgG4 scores ≥ 2+, whereas, 31.0% (9/29) cases with secondary membranous nephropathy showed IgG4 expression (vs IMN group, $P < 0.01$); four of these patients (13.8%, 4/29) had IgG4 scores ≥ 2+ (vs IMN group, $P < 0.01$).

Among the 88 IMN patients with positive PLA2R deposits, 94.3% (83/88) demonstrated IgG4 ≥ 2+, whereas 40.0% (2/5) of secondary membranous nephropathy with PLA2R-positive deposits cases demonstrated IgG4 ≥ 2+, both of which were HBV-associated membranous nephropathy (vs IMN group, $P < 0.01$).
Clinical characteristics between PLA2R-positive and PLA2R-negative patients

Within the IMN group, no differences were observed in clinical variables between PLA2R-positive and PLA2R-negative groups, as shown in Table 2. Among 100 cases with PLA2R-positive deposits, 63 cases were followed up over 6 months with an average of 13.8 ± 7.8 months. Seven patients received monotherapy of ACEI or ARB agents, and 56 patients received glucocorticoid and immunosuppressive therapy (46 patients received glucocorticoid combined with a calcineurin inhibitor such as ciclosporine or FK506; 10 patients received glucocorticoid monotherapy or combined Tripterygium wilfordii Hook F). Among the 22 IMN patients with negative-PLA2R deposits, 18 cases were followed up over 6 months, with an average of 11.5 ± 5.7 months. Seven patients received monotherapy of ACEI or ARB agents 10 patients received glucocorticoid combined with calcineurin inhibitor and one received monotherapy of T. wilfordii Hook F. Of the 14 patients receiving monotherapy of ACEI or ARB agents, only one case with positive PLA2R deposits achieved partial remission in proteinuria. In groups receiving either a glucocorticoid or immunosuppressant, the quantitative of 24-h proteinuria and the proportion of nephrotic syndrome decreased, whereas serum albumin increased significantly. Renal function remained stable, as shown in Table 3. Among 56 patients with PLA2R-positive deposits, 47 cases (83.9%) had remission in proteinuria, among which 20 cases (35.7%) experienced complete remission, and 27 (48.2%) showed partial remission. Two patients relapsed after the withdrawal or tapering of immunosuppressants. Among 11 patients with PLA2R-negative deposits, six cases (54.5%) had remission (vs PLA2R-positive IMN group, P < 0.05). Two patients (18.2%) had complete remission, and four patients (36.36%) experienced partial remission.

Discussion

Membranous nephropathy is characterised by the formation of in situ immune complexes in glomeruli. Proteinuria results from complement activation and damage to the glomerular filtration barrier resulting from binding of antibodies to antigens were expressed on podocytes in the epithelial side of the glomerular basement membrane. About 25% of cases are secondary in nature, resulting from lupus nephritis, malignant tumours, medication or post-virus or bacterial infection. IMN is diagnosed only when secondary membranous nephropathy has been excluded. Most IMN patients require glucocorticoid combined with immunosuppressive therapy, whereas secondary membranous nephropathy cases require treatment for the primary disease or cause. Thus, it is critical to differentiate IMN from secondary membranous nephropathy for treatment and prognosis. Unfortunately, it is often difficult to make clinical distinctions as some secondary factors may not be identified until several months or even years after initial manifestation.

After the discovery of PLA2R, researchers confirmed it as the specific antigen for IMN. Serum PLA2R antibodies have been detected in approximately 52–81% IMN patients, making it a unique factor in differentiation. Indeed, some researchers have shown that the positive rate of glomerular PLA2R is higher than in serum; some IMN patients with negative serum PLA2R even have
positive glomerular PLA2R. In the current retrospective study, we confirmed that 82.0% IMN patients had positive glomerular PLA2R expression, whereas only 16.7% patients with secondary membranous nephropathy demonstrated weak positivity of glomerular PLA2R. Therefore, glomerular PLA2R expression is a simple and reliable indicator to distinguish between IMN and secondary membranous nephropathy.

We proposed that the combination of PLA2R and IgG subclass detection might better identify the pathogenesis of membranous nephropathy. In our study, 94.3% IMN patients showed PLA2R-positive expression and moderate IgG4 positivity; the same pattern was only observed in 40% patients with secondary membranous nephropathy. Thus, it is crucial to exclude any secondary factors before making a diagnosis of IMN in patients with positive glomerular PLA2R and negative or weakly positive IgG4. We also found that three patients with hepatitis B-associated membranous nephropathy (defined as patients with a history of hepatitis B, positive hepatitis B surface markers and HbsAg antigen-positive in glomeruli) demonstrated PLA2R-positive expression with moderate IgG4 positivity. IMN cannot be ruled out as reports of patients with hepatitis B-associated membranous nephropathy demonstrating PLA2R-expression and moderate IgG4 positivity indicate the possibility of the coexistence of IMN and secondary membranous nephropathy. As a result, such patients may not improve after antiretroviral therapy compared with patients whose PLA2R and IgG4 staining were negative in glomeruli.6 Our research may not derive such a conclusion because of a limited sample size.

The combination of immunosuppressive agents and glucocorticoid can effectively reduce proteinuria in IMN patients and improve clinical outcomes; however, not all patients respond to the treatment.14-16 We found that PLA2R staining results may predict the response to immunosuppressive therapy in IMN patients. We observed that there were no significant differences in clinical characteristics between IMN patients with different glomerular PLA2R expression; however, the whole remission rate was higher in the PLA2R-positive group, suggesting that patients with positive glomerular PLA2R probably had a better response to immunosuppressive therapy, although there were no differences in partial and complete remission rate. The main restrained factors might be the small amount of samples and the limited follow-up time.

It is speculated that some patients with negative PLA2R should be classified as secondary membranous nephropathy rather than IMN because we failed to trace secondary factors when making the initial diagnosis and during the short time of follow-up. Some patients with malignant tumour-associated membranous nephropathy were not diagnosed until several months or even years after the existence of membranous nephropathy and poorly respond to immunosuppressive therapy. In addition, some IMN cases may be related to antibodies other than PLA2R.14-17,18 Recent research has found that type 1 platelet antigen protein domain response protein 7A (Thrombospondin Type-1 Domain-Containing 7A, THSD7A) is the primary antigen in about 2.5–5% IMN patients and in 8–14% IMN patients negative for PLA2R.19 Response to immunosuppressive agents in IMN patients negative for PLA2R deserves further study.

**Conclusion**

PLA2R staining in glomeruli is a simple and reliable indicator to diagnose IMN. The combination of IgG4...
subclass expression with PLA2R can further improve differentiation between IMN and secondary membranous nephropathy. In addition, positive glomerular PLA2R was associated with a higher remission rate, suggesting that patients in this group may have a more beneficial response to immunosuppressive therapy. This study implies further detailed investigation of larger patient groups with a longer follow-up period.

Acknowledgements

We express our appreciation to all the staff and nurses who devoted their time to this study.

References


Introduction of New South Wales adult subcutaneous insulin-prescribing chart in a tertiary hospital: its impact on inpatient glycaemic control

V. W. Wong,1,2 A. Ho,3 E. Fiakos,4 N. S. Lau1,2 and H. Russell2

1Liverpool Diabetes Collaborative Research Unit, Ingham Institute for Applied Medical Research, SWS Clinical School, 2Diabetes and Endocrine Service, and 4Pharmacy Department, Liverpool Hospital, and 3South Western Sydney Clinical School, University of New South Wales, Sydney, New South Wales, Australia

Key words
insulin therapy, diabetes mellitus, hyperglycaemia, inpatient.

Correspondence
Vincent W. Wong, Diabetes and Endocrine Service, Liverpool Hospital, Locked Bag 7103, Liverpool BC, NSW 1871, Australia. Email: vincent.wong@sswahs.nsw.gov.au

Received 10 April 2016; accepted 13 August 2016.
doi:10.1111/imj.13229

Abstract

Background: Erratic blood glucose levels (BGL) are commonly observed amongst patients with diabetes mellitus during hospital admission. Patients on insulin therapy often do not have their doses titrated adequately by their team doctors during admission, and insulin is well known to be a high-risk medication prone to administration error.

Aim: To assess the impact of a state-wide adult subcutaneous insulin-prescribing chart (ASCIPC) on glycaemic control and insulin-prescribing pattern in a tertiary hospital.

Methods: An audit on the clinical records of inpatients who were on subcutaneous insulin therapy in the first week of July 2014 (prior to ASCIPC, n = 56) and in the first week of July 2015 (10 months after introducing ASCIPC, n = 62) was conducted at Liverpool Hospital.

Results: Following the introduction of ASCIPC, fewer BGL readings were missed (9.1 vs 11.6%, P = 0.032), and medical officers were more likely to adjust insulin dosage (71.0 vs 42.6%, P = 0.002) when compared to baseline. Glycaemic control improved, with lower mean BGL (9.4 ± 2.0 vs 10.4 ± 2.6 mmol/L, P = 0.021) and a greater proportion of BGL within the normal range of 5–10 mmol/L (56.2 vs 47.7%, P = 0.041).

Conclusion: Omission of insulin doses after ASCIPC remained common, with over 40% of patients having at least one dose of insulin omitted during the audit week.

Conclusion: Our study showed that the introduction of ASCIPC had positive impacts on glycaemic management for patients on subcutaneous insulin therapy during admission. More work is required to reduce the rate of insulin omission and to improve further glycaemic control for inpatients.

Introduction

As the prevalence of diabetes mellitus (DM) is on the rise in Australia, optimisation of blood glucose levels (BGL) for inpatients is a common challenge faced by clinicians working in hospital wards. Hyperglycaemia increases the risk of infections and other adverse outcomes for hospital inpatients. For surgical disciplines, early postoperative hyperglycaemia in patients with diabetes was associated with high rates of nosocomial infection.1 On the other hand, patients with elevated BGL following acute myocardial infarction and stroke were found to have an increased risk of death and poor clinical outcomes.2,3 In Australia, between 2009 and 2010, the average length of stay (LOS) in a hospital was higher amongst patients with a principal diagnosis of diabetes (4.3 days) or an additional diagnosis of diabetes (8.0 days) than all other hospitalisations (3.1 days).4

Patients with DM often have erratic BGL during their hospital admission. Their requirement for diabetes medications may fluctuate depending on the metabolic impact of invasive procedures, the presence of pain or infection and the adequacy of their intake of food and fluids. For those who are on insulin therapy, it is important that the dose of insulin be adjusted according to the patient’s glycaemic profile. Until recently, in hospitals in New South Wales (NSW), subcutaneous insulin was prescribed on the regular medication chart section, and this did not allow easy adjustment of insulin dosage. Furthermore, documentation of BGL was highly variable across different hospitals, and BGL were always recorded on a form separate from where the insulin was charted.
The NSW adult subcutaneous insulin-prescribing chart (ASCIPC) was an initiative of the Agency of Clinical Innovation (ACI) Endocrine Network, and different parties involved in the care of patients with diabetes were consulted during its development. On this chart, only subcutaneous insulin is prescribed, but medical officers have to prescribe every single insulin dose for the patient (Supporting information Appendix S1). On the same chart, BGL are documented on the page opposite to the insulin prescription section, so medical officers can easily refer to the patient’s pattern of BGL prior to making their decision regarding insulin dosage. There is also provision to give supplemental insulin (mainly rapid acting insulin) at times when the pre-meal BGL is elevated above certain cut-off levels. The ASCIPC has been endorsed by NSW Health and mandated for use in all of the state’s public hospitals. In 2015, the Australian Commission on Safety and Quality in Health Care also piloted a subcutaneous insulin chart with the aim to assess the safety of insulin prescribing in hospitals.

The aim of this study was to examine the glycaemic control and insulin prescription pattern in a tertiary hospital prior to, and 10 months following, the introduction of the ASCIPC.

Methods
A baseline audit was conducted on the clinical records of patients on subcutaneous insulin therapy and who were inpatients at Liverpool Hospital during the first week of July 2014. All inpatients who were on subcutaneous insulin during that audit week were identified by ward pharmacists, and a list was compiled by the Pharmacy Department. Only patients over the age of 18 years were included in the audit. These patients had either type 1 or type 2 DM and were admitted under the care of medical teams, surgical teams or other disciplines. At that stage, subcutaneous insulin was prescribed on the usual regular medication charts along with all other medications, while BGL were recorded on a separate form in the patients’ clinical records.

The NSW ASCIPC was introduced at Liverpool Hospital in September 2014, following 4 weeks of intensive training for nursing and medical staff. The training was conducted through lectures for junior medical officers (JMO) (referring to both interns as well as resident medical officers) and in-servicing for nursing staff as well as targeted sessions for special units, such as Pharmacy, Emergency Medicine, the Intensive Care Unit and the Anaesthetics Department. The ACI had provided standardised modules and audit forms for helping staff become familiarised with the chart, but we also used these sessions as an opportunity to upskill the staff on inpatient diabetes management. Training for JMO continued in early 2015, with a focus on the new JMO who commenced employment at the hospital in February 2015. In 2015, a training session was organised for each JMO rotation.

The follow-up audit was performed on the clinical records of subjects on subcutaneous insulin therapy and who were inpatients during the first week of July 2015, 10 months after introduction of the ASCIPC at Liverpool Hospital. Again, during the audit week, pharmacists from the same wards collated a list of all inpatients who were on subcutaneous insulin.

From the patients’ clinical records, data, including the subject’s age and gender, diabetes type, glycated haemoglobin (HbA1c) results, diabetes treatment on admission, diabetes treatment at discharge and length of hospital stay, were recorded. At Liverpool Hospital, for patients who are on insulin therapy, BGL should be performed at four time points a day: before breakfast, before lunch, before dinner and before bed. BGL at these time points were documented for each patient during the 7-day audit period. As for insulin prescription, the use of sliding scale insulin (SSI), supplemental insulin, any adjustment of insulin doses and any omission of insulin (either missing insulin prescription by medical staff or failure of administration by nursing staff) were also noted.

The study was approved by the South Western Sydney Human Ethics Research Committee.

Statistical analysis
All continuous variables were presented as mean and standard deviation, but median and interquartile ranges were used if the distribution was nonparametric. For categorical variables, both the percentage and number were shown. In presenting a proportion of BGL readings above 10, 15 and 20 mmol/L or below 4 mmol/L, both pooled data as well as the percentage of readings for each subject were presented. Chi-squared tests and Student’s t-tests were performed to compare variables between patients in the baseline and follow-up audits. The analysis was performed by STATA 7.0 (College Station, TX, USA). A P-value <0.05 was considered statistically significant.

Results
In the first week of July 2014, 56 inpatients on subcutaneous insulin therapy during their admission (pre-chart group) were identified by the Pharmacy Department. In the first week of July 2015, 10 months following the introduction of the ASCIPC, the Pharmacy Department found 62 inpatients on subcutaneous insulin therapy during the audit week (post-chart group). The patients’ characteristics are shown in Table 1. The
mean HbA1c for the two groups were elevated (Table 1), reflecting suboptimal glycaemic control. The majority of patients suffered from type 2 DM, and most were admitted under the care of medical disciplines (including cardiology, respiratory, medical oncology, geriatrics and haematology etc.).

For the pre-chart group, there were 1130 glucose readings recorded during the audit week, compared to 1293 for the post-chart group (Table 2). For the designated four time points of BGL recording, 11.2% of all BGL readings in the pre-chart group that were supposed to be performed were missed, compared to 9.1% in the post-chart group.

In terms of glycaemic control, not only was the mean BGL for each patient better during the audit week in the post-chart group, but the proportions of BGL readings >10, >15 and >20 mmol/L for each patient were all significantly lower in the post-chart group (Table 2). A total of 21 patients (38.9%) in the pre-chart group had at least one reading above 20 mmol/L, compared to 13 patient (21.0%, \( P = 0.035 \)) in the post-chart group. On the other hand, the occurrence of at least one episode of hypoglycaemia (defined as BGL <4.0 mmol/L) between the pre- and post-groups did not differ (22.2 vs 24.2% of patients, respectively, \( P = 0.804 \)). There was a higher proportion of readings within the target BGL range of 5–10 mmol/L for patients in the post-chart group (56.2 vs 47.7% for individual patients, \( P = 0.041 \) (Table 2).

As for the prescription of subcutaneous insulin, 3.2% (2 of 62) patients had SSI as the sole insulin therapy in the post-chart audit week, compared to 16.7% (9 of 54) in the pre-chart group (Table 3). For these 11 patients who were managed with SSI only, their mean BGL was significantly higher than those who were not (11.2 ± 2.4 vs 9.7 ± 2.3 mmol/L, \( P = 0.048 \)).

A total of 44 (71%) patients had their insulin doses adjusted during the post-chart audit week, compared to 23 patients (42.6%) in the pre-chart period (\( P = 0.002 \)). Of greater relevance, amongst patients with higher glucose levels (e.g. mean BGL over 10 mmol/L or those with >10% of their BGL readings above 15 mmol/L), more patients had their insulin doses adjusted in the post-chart group. Supplemental insulin, in addition to their usual insulin doses, was also more commonly used in the post-chart group (54.8 vs 24.1%, \( P < 0.001 \)).

Over 40% of patients had their insulin doses omitted without documented reasons at least once during the

### Table 1 Demographic data for subjects in the audits before and after the introduction of NSW adult subcutaneous insulin-prescribing chart

<table>
<thead>
<tr>
<th></th>
<th>Pre-chart group (n = 54)</th>
<th>Post-chart group (n = 62)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD</td>
<td>65.6 ± 14.9</td>
<td>67.0 ± 13.8</td>
<td>0.613</td>
</tr>
<tr>
<td>Male, % (no.)</td>
<td>48.2 (26)</td>
<td>61.3 (38)</td>
<td>0.156</td>
</tr>
<tr>
<td>Admitted under medicine discipline, % (no.)</td>
<td>75.9 (41)</td>
<td>77.4 (48)</td>
<td>0.557</td>
</tr>
<tr>
<td>Type 2 diabetes, % (no.)</td>
<td>94.4 (51)</td>
<td>93.3 (56)</td>
<td>0.807</td>
</tr>
<tr>
<td>On basal bolus insulin prior to admission, % (no.)</td>
<td>33.3 (18)</td>
<td>37.1 (23)</td>
<td>0.676</td>
</tr>
<tr>
<td>Glycated haemoglobin (IFCC, mmol/mol)</td>
<td>(n = 34)</td>
<td>(n = 43)</td>
<td>0.193</td>
</tr>
<tr>
<td>IFCC, mmol/mol ± SD</td>
<td>68 ± 24</td>
<td>76 ± 33</td>
<td></td>
</tr>
<tr>
<td>NGSP, % ± SD</td>
<td>8.4 ± 2.1</td>
<td>9.2 ± 3.0</td>
<td></td>
</tr>
<tr>
<td>Median length of stay, interquartile range (days)</td>
<td>10, 6–21</td>
<td>11, 6–20</td>
<td>0.886</td>
</tr>
<tr>
<td>Inpatient death, % (no.)</td>
<td>9.3 (5)</td>
<td>6.5 (4)</td>
<td>0.377</td>
</tr>
</tbody>
</table>

IFCC, International Federation of Clinical Chemistry; NGSP, National Glycohemoglobin Standardization Program.

### Table 2 Glucose profile of subjects during audit weeks before and after adult subcutaneous insulin prescribing chart

<table>
<thead>
<tr>
<th></th>
<th>Mean BGL for each subject, mmol/L ± SD</th>
<th>Pooled data, BGL readings &gt;10 mmol/L, % (no)</th>
<th>For each subject, % of BGL &gt;10 mmol/L, mean ± SD</th>
<th>Pooled data, BGL readings &gt;15 mmol/L, % (no)</th>
<th>For each subject, % of BGL &gt;15 mmol/L, mean ± SD</th>
<th>Pooled data, BGL readings &gt;20 mmol/L, % (no)</th>
<th>For each subject, % of BGL &gt;20 mmol/L, mean ± SD</th>
<th>Pooled data, BGL readings &gt;4.0 mmol/L, % (no)</th>
<th>For each subject, % of BGL &gt;4.0 mmol/L, mean ± SD</th>
<th>Pooled data, BGL readings 5–10 mmol/L, % (no)</th>
<th>For each subject, % of BGL 5–10 mmol/L, mean ± SD</th>
<th>Pooled data, BGL readings missed, % (no)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-chart (1130 BGL)</td>
<td>10.4 ± 2.6</td>
<td>44.7 (505)</td>
<td>46.0 ± 26.6</td>
<td>15.0 (170)</td>
<td>15.3 ± 15.6</td>
<td>3.6 (41)</td>
<td>3.8 ± 6.5</td>
<td>2.4 (28)</td>
<td>2.4 ± 5.5</td>
<td>48.1 (544)</td>
<td>47.7 ± 23.6</td>
<td>11.6 (148)</td>
<td>0.021</td>
</tr>
<tr>
<td>Post-chart (1293 BGL)</td>
<td>9.4 ± 2.0</td>
<td>34.9 (451)</td>
<td>35.9 ± 23.5</td>
<td>9.7 (126)</td>
<td>10.1 ± 10.9</td>
<td>1.3 (17)</td>
<td>1.8 ± 4.1</td>
<td>1.9 (24)</td>
<td>1.7 ± 3.4</td>
<td>55.2 (714)</td>
<td>56.2 ± 20.6</td>
<td>9.1 (129)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Pooled data, BGL readings >15 mmol/L, % (no) | 15.0 (170) | 9.7 (126) | <0.001 |
| Pooled data, BGL readings >20 mmol/L, % (no) | 3.6 (41) | 1.3 (17) | <0.001 |
| Pooled data, BGL readings >4.0 mmol/L, % (no) | 2.4 (28) | 1.9 (24) | 0.292 |
| Pooled data, BGL readings 5–10 mmol/L, % (no) | 2.4 ± 5.5 | 1.7 ± 3.4 | 0.453 |
| Pooled data, BGL readings missed, % (no) | 48.1 (544) | 55.2 (714) | <0.001 |

BGL, blood glucose level.
audit week, but there was no difference between the two groups (Table 3). However, using pooled data, in the pre-chart period, 90 out of a total of 1076 insulin doses (8.3%) were missed, which was higher than that of the post-chart period (56 out of a total of 1014 doses, 5.5%, P = 0.012). None of the subjects (both pre- and post-chart) developed diabetic ketoacidosis or had BGL >25 mmol/L following the omission of insulin doses.

**Discussion**

In this study, we demonstrated that following the introduction of the NSW ASCIPC in a tertiary hospital, inpatients who were on subcutaneous insulin therapy had lower mean BGL and a lower proportion of BGL exceeding 10, 15 or 20 mmol/L but did not have a greater risk of hypoglycaemia. Furthermore, we observed that with this new chart, JMO were more likely to make adjustments to insulin doses in response to recorded BGL, and there were fewer patients who were managed solely by the SSI regimen, when compared to the period prior to ASCIPC. Supplemental insulin was also used more frequently. However, we noted that over 43% of patients missed at least one insulin dose in the post-chart audit during the audit week, and the reasons were not documented in the clinical notes.

Glycaemic instability, especially hyperglycaemia, is commonly observed amongst inpatients with DM, and therefore, they should have their diabetes therapy adjusted according to their glucose levels. In the past, when insulin was prescribed on the normal medication chart, once the insulin was charted, the doses may not be reviewed by JMO for the entire week. If doses of insulin were to be altered, the insulin prescription order had to be cancelled and re-written in its entirety. Furthermore, BGL were often documented on a form separate from the medication chart together with other observations, such as blood pressure and heart rates, which reduced the visibility of abnormal BGL readings. It is well documented that patients with DM have longer LOS in hospital, and this could be related to the increased risk of infection or other adverse outcomes consequent to inpatient hyperglycaemia. To date, only a few studies had shown that better inpatient glycaemic control resulted in shorter LOS and lower rates of adverse outcomes.5,6 Our study did not show any differences between the two groups in terms of LOS and inpatient mortality despite better glycaemic control in the post-chart period, but this was probably not unexpected as the study was not designed to look at clinical outcomes.

Insulin therapy is a common source of medication errors in hospitals, and insulin has always been in the top 10 of the high-alert medicines worldwide.7 Poor documentation of insulin dose by JMO can result in administration errors, while constant re-writing of insulin prescription because of dosage changes on the regular medication chart is messy and confusing for nursing staff. Furthermore, the frequent use of SSI and lack of review of insulin dosages despite persistent hyperglycaemia often propagates poor inpatient glycaemic control.8,9 On the other hand, the use of supplemental insulin (where extra rapid-acting insulin is given in addition to the usual prandial dose if pre-meal BGL is elevated) is underutilised and is poorly understood.

One of the anticipated advantages of the ASCIPC is that BGL are documented on the same chart where subcutaneous insulin is prescribed, and this would allow JMO to review more readily their patient’s glycaemic profile and adjust insulin dosage. Additionally, as the word ‘unit’ is already printed on the ASCIPC, the prescribed dose is clearer for nursing staff and hence negates one important source of administration error (e.g. confusion over ‘u’ and ‘0’; hence, 20u can be interpreted as 200).

However, the introduction of an alternative medication chart specific for subcutaneous insulin is costly, requires ongoing education for staff and may cause confusion for users (at least initially). It had been difficult to predict whether ASCIPC will improve glycaemic control and ensure safe insulin prescription for patients with DM. Indeed, in the first few months following the introduction of ASCIPC, a common issue was the failure of
team doctors to chart the daily insulin doses for their patients, leaving this task for the after-hours JMO. There was also a knowledge gap amongst JMO regarding titration of insulin doses and misunderstanding over the concept of pre-meal supplemental insulin as distinct from SSI. In the first 2 months after the introduction of ASCIPC, there was an increase in the number of incident reports relating to insulin therapy. Furthermore, the post-chart audit showed that the omission of insulin was still common, although the percentage of missed doses (from the total number of insulin doses) in pooled data was actually lower when compared to baseline. It is possible that insulin was omitted for valid reasons, but the documentation of these reasons was often poor. In trying to address this problem, we need to explore the common reasons for insulin omission and encourage proper documentation in the clinical notes. An alert system that reminds medical and nursing staff that the patient is on subcutaneous insulin therapy may have merits. In any case, the ongoing education of both medical and nursing staff will be required.

Other studies had assessed the effectiveness of an insulin-prescribing chart. In Queensland, an intravenous as well as subcutaneous insulin chart had been developed, and although glycaemic control was not significantly different following the introduction of the subcutaneous insulin chart, there was improvement in the clarity of insulin prescription and the frequency of usage of supplemental insulin. Cheung et al. performed an audit on their locally developed subcutaneous insulin chart, which was similar to the NSW ASCIPC. Following the introduction of their insulin chart, Cheung et al. reported an increase in the number of BGL performed daily and a higher proportion of BGL between 4.0 and 9.9 mmol/L (54.1 vs 51.8%, $P = 0.01$). Interestingly, they showed a reduction in the incidence of hypoglycaemia, but there was no difference in the proportion of BGL above normal range.

There are some limitations in our study. We chose July as the audit week 12 months apart to ensure that JMOs‘ workload was comparable across the two audit periods and the JMO could have varying levels of clinical skills in prescribing subcutaneous insulin during the two periods. In late 2014 and early 2015, the education sessions for JMO and nursing staff with regards to using ASCIPC may have improved their knowledge of diabetes management and thus contributed to the greater competency in diabetes management. In 2015, education sessions for diabetes management were scheduled four times a year. Prior to that, the JMO would only receive a 30-min session during orientation week regarding diabetes management and two education sessions a year from the endocrine team that covered not just diabetes management but also other endocrine diseases. We believe that the ‘package’ of both the ASCIPC as well as regular education of medical and nursing staff has been critical in improving glycaemic management for hospital inpatients.

**Conclusion**

Our study suggested that the whole process involved in the introduction of ASCIPC made a positive impact on the glycaemic management of inpatients with DM who were on subcutaneous insulin therapy in a tertiary hospital. BGL were monitored more readily by nursing staff, and JMO were more likely to make adjustments to insulin doses in response to the glucose levels. This resulted in greater proportion of BGL between 5 and 10 mmol/L, which was the normal range recommended by the Australian Diabetes Society guidelines for inpatient diabetes management. The ASCIPC is a highly useful tool that facilitates glucose management in hospital, but it is likely that increased education of JMO and nursing staff may play an important role in improving inpatient glycaemic control. Finally, the fact that only 56% of all glucose levels were within the target glucose range after adopting ASCIPC means that more work needs to be performed to improve glycaemic control for patients with DM during hospital admission. Further audits of insulin charts should be performed, and we eagerly await the results of the National Subcutaneous Insulin Chart Pilot.

**References**

5 Wong VW, Manoharan M, Mak M. Managing hyperglycaemia in patients with diabetes on enteral nutrition: the role of a specialized diabetes

7 Institute of Safe Medication Practice (USA). List of high alert medicine; 2008.


**Supporting Information**

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

**Appendix S1** Adult subcutaneous insulin-prescribing chart.

**BRIEF COMMUNICATIONS**

**Rates of neutropenia in adults with influenza A or B: a retrospective analysis of hospitalised patients in South East Queensland during 2015**

P. Higgins,¹ N. Runnegar,² R. J. Bird¹,³ and K. A. Markey¹,⁴,⁵

¹Haematology Department, and ²Infection Management Services, Princess Alexandra Hospital, ³Department of Immunology, QIMR Berghofer Medical Research Institute, and ⁴School of Medicine, University of Queensland, Brisbane, and ⁵School of Medicine, Griffith University, Gold Coast, Queensland, Australia

**Key words**

neutropenia, influenza, adult.

**Correspondence**

Kate Markey, Department of Immunology, QIMR Berghofer Medical Research Institute, 300 Herston Road, Brisbane, Qld 4006, Australia.

Email: kate.markey@qimr.edu.au

Received 9 March 2016; accepted 17 May 2016.

doi:10.1111/imj.13239

**Abstract**

Neutropenia in adult patients is often attributed to intercurrent viral infections; however, there are limited data describing the frequency or natural history of this phenomenon. We examined all patients presenting to three large hospitals in the Metro South region of South East Queensland with laboratory-confirmed influenza A or B throughout the 2015 influenza season (January–October). Four hundred and thirty-six patients were studied and 15.3% of this cohort were neutropenic (absolute neutrophil count <2.0 × 10⁹/L) with no identifiable cause other than the influenza. Importantly, the majority of cases were mild, with absolute neutrophil count remaining >1.0 × 10⁹/L. The incidence of neutropenia was significantly higher in association with influenza B than influenza A (18.3% vs 10.3%). We conclude that mild, transient neutropenia is common among patients with influenza infection and advise that it should not cause alarm or invite specific investigation unless severe or prolonged.

Influenza and influenza-like illness account for a significant number of presentations to Australian hospitals each year, with rates for 2015 reaching 80 per 1000...
Presentations in the peak months of influenza season.\textsuperscript{1} During the period from 1 January to 9 October 2015, there were 89,519 laboratory-confirmed cases of influenza in Australia,\textsuperscript{1} with 26,271 of these occurring in Queensland.

Neutropenia is a common finding in paediatrics with 1.5–9% of children (without malignancy) presenting to hospital found incidentally to be neutropenic.\textsuperscript{2,3} The majority of these paediatric patients with transient neutropenia present with infectious symptoms\textsuperscript{4} with an infectious agent proven in approximately 50% of cases, most commonly viral in nature.\textsuperscript{2,5} This benign, transient neutropenia occurs predominantly in the 3-month to 2-year age group,\textsuperscript{3,4,6,7} but is still observed in older children. Influenza A was confirmed as the infectious agent in 6–13% of neutropenic children in two studies\textsuperscript{8,9} and a 2009 study which specifically assessed H1N1 influenza reported that 19% of children with flu-like symptoms who tested positive for H1N1 were neutropenic compared with only 1.7% of those who tested negative.\textsuperscript{6} Whilst neutropenia in previously well adults is also commonly ascribed to intercurrent viral infection\textsuperscript{5,10} clinical data are lacking in the literature.

In Australia in 2015, influenza B accounted for 62% of all influenza notifications (predominantly B/Yamagata). Of the influenza A viruses, those that were subtyped A(H3N2) were found most commonly, outnumbering A(H1N1) by 3:1. This pattern was also seen in Queensland with 63% of notifications being for influenza B. For influenza A cases that were typed, H3N2 was identified most commonly.\textsuperscript{1} During the 2015 influenza season, a large number of consultation requests was directed to the adult haematology service at our hospital regarding neutropenia in patients with clinical influenza-like illness or proven influenza infection. Given the paucity of literature on the subject, we sought to quantify the rates of this phenomenon in our patient population.

All patients over the age of 18 who were positive for influenza A or B by nucleic acid testing on nasopharyngeal aspirates/swabs performed at three major hospitals in the Metro South area of Brisbane from January to October 2015 were included in our retrospective cohort analysis. Neutropenia was defined as absolute neutrophil count (ANC) <2.0 x 10\(^9\)/L (reference range in Pathology Queensland Laboratories, 2.0–7.0 x 10\(^9\)/L).\textsuperscript{11} and common terminology criteria for adverse events (CTCAE) guidelines define grade 1 neutropenia as less than lower limit of normal and >1.5 x 10\(^9\)/L.\textsuperscript{12} Only data from Pathology Queensland Laboratories were available. Clinical data were obtained from the review of patient discharge summaries and those with another obvious cause for their neutropenia were excluded. Data were compiled using Microsoft Excel and statistical testing performed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, CA, USA). Permission to access Auslab (Pathology Queensland database) and patient discharge summaries was granted by the Metro South Human Research Ethics Committee (HREC/15/QPAH/717).

In the period January–October 2015, there were 436 individual presentations (among 435 patients, as one patient presented twice in the study period) with laboratory-proven influenza presenting in the Metro South area. Influenza B was most common (59.3%), with influenza A alone and A + B co-infection contributing the remaining 41% of cases (Table 1). There was no difference in the proportion of neutropenic patients as a function of age. Data are summarised in Figure 1.

Of these 436 cases, there were full blood count (FBC) records available in 395 patients (90.6%). Seventy-nine patients (20%) had documented neutropenia, however, another cause was probable in 22 patients (12 patients receiving chemotherapy, 8 patients with sepsis or other documented systemic infections, 1 patient with liver cirrhosis and hypersplenism and 1 patient on sodium valproate). Thus, 57 of the 373 assessable patients were neutropenic during the period of their influenza illness with no other likely cause, representing 15.3% of all influenza-positive patients. Interestingly, the incidence of neutropenia was higher in the influenza B infected

\begin{table}[h]
\centering
\caption{Influenza-associated neutropenia}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Characteristic & N (% of total) & Age ± SD years & Female (%) & FBC in course of illness & ANC < 2.0, other cause identified & Flu-associated neutropenia (days 1–6) \\
\hline
Total & 436 & 54.3 ± 21.9 & 230 (52.7) & 395 (90.5) & 22 (5.6) & 57 (13.5) \\
Influenza A & 166 (38) & 58.2 ± 19.6 & 85 (51.2) & 153 (92.1) & 8 (5.2) & 15 (10.3) \\
Influenza B & 259 (59.3) & 51.8 ± 23.0 & 139 (53.6) & 231 (89.1) & 13 (5.6) & 40 (18.3) \\
Influenza A + B & 11 (2.5) & 55.6 ± 20.8 & 6 (54.5) & 11 (100) & 1 (9.1) & 2 (20) \\
Any influenza + any other & 43 (9.8) & 54.9 ± 23.5 & 28 (65.1) & 40 (93.0) & 3 (7.5) & 5 (13.5) \\
Influenza A + other resp virus & 10 (2.3) & 52.9 ± 16.1 & 7 (70) & 8 (80) & 1 (13) & 1 (13) \\
Influenza B + other resp virus & 32 (7.3) & 55.6 ± 25.9 & 21 (66) & 31 (97) & 1 (3) & 4 (13) \\
Influenza A + B + other resp virus & 1 (0.23) & 53 & 0 (0) & 1 (100) & 1 (100) & 0 (0) \\
\hline
\end{tabular}
\end{table}

\textsuperscript{1}Neutropenia attributed to influenza because no other cause was identifiable from the clinical records. \textsuperscript{2}Rate of neutropenia in influenza B versus influenza A reached statistical significance, \(P = 0.0378\). ANC, absolute neutrophil count; FBC, full blood count; SD, standard deviation.
Brief Communications

**Figure 1** Study schematic. Influenza-associated neutropenia rates calculated after considering number of patients where full blood count was performed and excluding those patients who had an alternative explanation for their neutropenia. NAT, nucleic acid testing.

Group compared with the influenza A group (18.3% vs 10.3%; \( P = 0.0378 \)).

Of our influenza-positive cohort, 43 had a concomitant respiratory virus (19 respiratory syncytial virus, 10 parainfluenza 3, 10 adenovirus, 2 parainfluenza 1 and 2 human metapneumovirus) and in 40 of these a FBC was performed. Eight patients were found to be neutropenic, but in three cases, another cause was identified. Overall 5/37 (13.5%) patients with a concomitant virus (in addition to influenza) were neutropenic. This was not statistically different to the influenza-only cohort rate of neutropenia (\( P = 1.00 \)), suggesting that within the limits of this small sample, no additional risk of neutropenia is conferred by multiple viral infections.

Other cytopenias are described in Table 2. Lymphopenia (<1 \( \times 10^9/L \)) was very common and seen in 43% of patients at diagnosis. Counts ranged from 0.16 to 0.99 \( \times 10^9/L \) with a mean of 0.65 \( \times 10^9/L \). Of the non-neutropenic group, 25% were mildly lymphopenic at diagnosis with an average count of 0.66 \( \times 10^9/L \).

C-reactive protein was performed in 102 (32%) non-neutropenic patients and 13 (16%) of neutropenic patients. Mean CRP was lower in the neutropenic group (15 mg/L) than the non-neutropenic group (84 mg/L), though given the inconsistent testing, no further conclusions can be drawn.

We next analysed the severity and kinetics of neutropenia in this patient group. Figure 2A demonstrates the day 0 ANC in all patients, and Figure 2B demonstrates the distribution of ANC where total count was below the normal limits. FBC was not repeated after diagnosis in the majority of patients with influenza A, but was performed for a reasonable proportion of the influenza B cohort, thus ANC as a function of time post-diagnosis is shown for the influenza B cohort in Figure 2C.

Resolution of neutropenia was confirmed by available laboratory testing in only 21 cases with the number of days until documented normal ANC (>2.0 \( \times 10^9/L \)) varying from 1 to 98 days after laboratory confirmation of influenza infection (though no interim counts were available, making evaluation of the true duration of neutropenia impossible). Although there is a paucity of follow-up data, no patient who underwent follow-up FBC after day 10 had a persistent neutropenia. There were two patients with neutropenia with no other known cause who received granulocyte-colony stimulating factor (G-CSF). In the first case, the neutrophil count normalised on day 3, and in the second on day 5. Overall nine patients received G-CSF, and seven were receiving chemotherapy and are excluded from this analysis.

We also assessed the treatments offered to this patient cohort during their admission to hospital. Forty-five percent of neutropenic patients were treated with antibiotics. Predominantly therapy aimed to treat a potential bacterial cause of their influenza symptoms, but in one case it was to treat a concurrent urinary tract infection. Of those who received antibiotics, 12 recorded ANC <2.0 \( \times 10^9/L \) on the day of, or day before, the diagnostic test confirming influenza. Of the remainder, the neutrophil count decreased between days 1 and 4 with an average of 2 days from diagnosis. Following the assumption that in most cases investigations for influenza and the start of antibiotic therapy occurred at day zero then we acknowledge that antibiotic therapy may potentially have contributed to the decrease in counts in 14 cases. If we were to consider this a confounder, and exclude these patients from the analysis, 43 of 397 or 11% of patients in this study would still be confirmed as cases of influenza-associated neutropenia.

Given that oseltamivir (Tamiflu) is also known to cause neutropenia, we next examined whether its use...

<table>
<thead>
<tr>
<th>Characteristic (day 0)</th>
<th>FBC available at day 0</th>
<th>Neutropenia (ANC &lt; 2.0 ( \times 10^9/L ))</th>
<th>Leucopenia (WBC &lt; 4.0 ( \times 10^9/L ))</th>
<th>Lymphopenia (&lt;1.0 ( \times 10^9/L ))</th>
<th>Thrombocytopenia (&lt;140 ( \times 10^9/L ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>366</td>
<td>45 (12.2)</td>
<td>56 (15.3)</td>
<td>158 (43.2)</td>
<td>59 (16.1)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>143</td>
<td>13 (9.1)</td>
<td>17 (11.8)</td>
<td>59 (41.2)</td>
<td>19 (13.2)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>216</td>
<td>30 (13.8)</td>
<td>37 (17.1)</td>
<td>96 (44.4)</td>
<td>39 (18.1)</td>
</tr>
<tr>
<td>Influenza A + B</td>
<td>7</td>
<td>2 (28.5)</td>
<td>2 (28.5)</td>
<td>3 (42.8)</td>
<td>1 (14.2)</td>
</tr>
</tbody>
</table>

No subgroup had statistically different results to the influenza cohort as a whole. Contingency analysis was performed using Fisher’s exact test.

ANC, absolute neutrophil count; FBC, full blood count; WBC, white blood cells.
could be a confounding factor in our study. Only nine patients with neutropenia were treated with oseltamivir. Of these six patients had neutropenia with no other cause and three had a pre-existing known cause of their neutropenia. All of the patients who received oseltamivir also received antibiotics. Given these low numbers, it is unlikely that this is a confounder in this case.

**Discussion**

Our research demonstrates that there is a significant rate of neutropenia in adult patients presenting to hospital with confirmed cases of influenza and that for the 2015 season this was more common in the influenza B subgroup. Importantly, neutropenia was mild, and appeared transient.

There is little literature on neutropenia in association with viruses in the adult population. A recent prospective study has examined 850 adult patients with laboratory-confirmed influenza. They demonstrated that leucopenia (defined as a white blood cells <4 cells/mm³) occurred in 8.3% of patients with confirmed influenza A and in 26.8% of patients with confirmed influenza B. Specific rates of neutropenia were not reported. Another study, specifically focusing on the H1N1 strain of influenza A has demonstrated similar rates of leucopenia, and a 45.8% rate of lymphopenia, but again, did not report specific rates of neutropenia.

From our data, it is important to note that no patients who were tested beyond day 10 following laboratory confirmation of influenza were found to be neutropenic, suggesting that the duration is likely short (though we could not confirm this as insufficient patients were followed until resolution, a key limitation of this work). There is unlikely to be late-onset neutropenia (beyond day 10) as a result of influenza virus infection, and thus caution should be exercised in attributing late-onset neutropenia to influenza infection. In the majority of cases, the neutropenia was not severe and therefore severe neutropenia (<0.5 x 10⁹/L) should prompt consideration of another cause for the neutropenia. Prolonged neutropenia in these patients should also prompt investigation for other causes.

To our knowledge, this is the first report focusing on the incidence and character of neutropenia occurring in association with influenza infection. As only patients who presented to hospital with influenza are included, we may have selected for a more unwell cohort of patients than is seen in the community with influenza, and thus our reported incidence may overestimate the true incidence in all patients. Further, the findings may not be generalisable to other influenza epidemics given the higher incidence of neutropenia seen in patients with influenza B and the variability of dominant influenza strains between seasons. A larger, prospective study confirming our reported incidence and following all patients until resolution of neutropenia would be a useful follow up to extend these findings.

**Acknowledgements**

K. A. Markey is a Queensland Health Junior Research Fellow. The authors thank Dr Siok Tey and Dr Andrea Henden (QIMR Berghofer Medical Research Institute and Department of Haematology, Royal Brisbane and Women’s Hospital) for their critical reading of the manuscript.
Use of computed tomography abdomen and pelvis for investigation of febrile neutropenia in adult haematology patients

H. Y. Lim, M. Ashby, B. Williams and A. Grigg
Department of Clinical Haematology, Austin Health, Melbourne, Victoria, Australia

Key words
computed tomography, febrile neutropenia, autologous stem cell transplant, acute myeloid leukaemia.

Abstract
We retrospectively evaluated the use of computed tomography abdomen and pelvis (CTAP) in febrile neutropenic autologous stem cell transplant (ASCT) and acute myeloid leukaemia (AML) patients. CTAP was more common in ASCT patients (59%) compared with AML (31%; P < 0.001). Although abnormal findings were reported in 51%, only 10% resulted in therapy change (addition of anaerobic antibiotic/bowel rest), which would have otherwise been instituted based on clinical grounds. CTAP in these patients rarely provide useful information unsuspected clinically.
Computed tomography (CT) scanning is commonly used to aid in the early diagnosis and treatment of febrile neutropenia (FN) in severely myelosuppressed patients with haematological malignancies.¹ Most published studies evaluating the utility of CT scanning in this context have been in the paediatric setting; in few adult studies, the focus has been mainly on the role of CT chest imaging.² However, CT scans of the abdomen and pelvis (CT abdomen/pelvis (CTAP)) are also frequently performed, either alone or concurrently with chest imaging, to investigate FN in patients despite the paucity of evidence supporting their use.²,³

In this retrospective study, we documented the nature of CT scans performed in two groups of profoundly myelosuppressed adult haematological patients in our centre and specifically evaluated the diagnostic utility and therapeutic impact of CTAP performed during episodes of FN in this setting.

All haematology patients undergoing autologous stem cell transplant (ASCT) or receiving chemotherapy (induction, reinduction or consolidation) for acute myeloid leukaemia (AML) with curative intent at Austin Health, a major tertiary healthcare provider in Victoria, Australia, from 1 January 2010 to 28 February 2015, were identified retrospectively through the unit database. These two patient groups were selected for the purpose of this study due to their high risk of FN. Only patients who experienced FN and had CT performed as a consequence were included in this analysis. Patients treated with palliative intent or those who did not have CT performed in the context of FN were excluded. For the purpose of this study, FN was defined as a temperature ≥38°C and an absolute neutrophil count (ANC) of <0.5 × 10⁹/L.¹

Clinical inpatient and outpatient records, pathology and radiology results were obtained from computerised medical records. Clinical data collected included age, haematological condition, chemotherapy regimen, time to FN, investigations performed, symptoms, antibiotic regimen and subsequent change to management following imaging, if applicable. Approval for this review was obtained from the Austin Human Research Ethics Committee (LNR/14/Austin/661).

The vast majority of the AML patients in our institution were managed in a ward with high-efficiency particulate air (HEPA) filtration from the time of diagnosis until count recovery post induction therapy or during periods of neutropenia following consolidation therapy. The same haematology consultants looked after both groups of patients. AML patients routinely received antifungal prophylaxis with oral posaconazole suspension (200 mg thrice a day) from chemotherapy commencement until recovery of ANC to >0.2 × 10⁹/L.

Intravenous AmBisome (100 mg thrice weekly) was used in patients intolerant of posaconazole. In the ASCT population, prophylactic fluconazole (200 mg daily) was used in all patients receiving busulfan-melphalan (bemu; mel) conditioning and selected patients receiving BEAM (carmustine, etoposide, cytarabine and melphalan).

The unit protocol specified that patients without a penicillin allergy received piperacillin/tazobactam as the first-line empiric antibiotic for FN unless there was evidence of haemodynamic compromise, in which case the combination of meropenem, gentamicin and vancomycin was instituted. The antibiotic regimen was then tailored accordingly to the culture results and clinical scenario.

The protocol also recommended repeat blood cultures and a high-resolution CT chest in patients with persistent or recurrent unexplained fevers after more than 72 h of antibiotics. While not protocolised, CTAP was generally performed in persistently febrile patients, with significant abdominal symptoms such as tenderness, distension, profuse diarrhoea or ileus.

Comparisons between the two groups (ASCT and AML) were analysed by Fisher’s exact test for categorical data and the findings were considered significant if the two-tailed probability of type I error was ≤0.05. Two-sided 95% confidence interval (CI) for the relative risk (RR) was calculated based on the assumption of a Poisson distribution of the observed cases.

Table 1 summarises the details of the study patients, ASCT and AML, and the nature and frequency of any CT scans performed. Table 2 summarises the patient symptoms, scan findings and impact on therapy of the CTAP in the two groups.

A higher proportion of AML patients compared with ASCT patients underwent CT imaging of any type as part of FN management (81% of all AML patients (52% of all inpatient chemotherapy cycles) vs 27% of all ASCT patients, respectively). Of the scans performed in ASCT patients as part of investigations for FN, 59% of total scans (33/56) were CTAP in comparison with 31% (56/179) of the scans in the AML patients. Within the ASCT cohort, CTAP scans were more frequently performed in recipients of BEAM or bu-mel conditioning (18/61: 30%) than in recipients of melphalan conditioning only (11/82: 13%; P = 0.02; RR: 2.2; 95% CI: 1.12–4.31). One patient in the ASCT cohort underwent two CTAP during the same admission.

The incidence of CTAP abnormalities was 45% (25/56) in the AML cohort and 64% (21/33) in the ASCT group. Of those scans with an abnormal finding, the most common abnormality in each group was enterocolitis (17/25 in the AML cohort and 16/21 in the ASCT group, comprising 37% of all CTAP performed). Diverticulitis was noted in 4% of all CTAP. Other findings were...
uncommon. Overall, abnormalities were more common in patients with symptoms compared with those without (67% (33/64) vs 12% (3/25), \( P = 0.002 \)).

CTAP rarely led to substantial changes in subsequent management of the patients. Combining the two groups, only nine patients (10% of those undergoing a CTAP) had changes in therapy potentially attributable to the results, although the retrospective nature of the study and limitations of documentation make it unclear whether the CT findings were the sole determinant of these changes in all cases. Therapeutic changes consisted almost exclusively of either bowel rest or addition of metronidazole to antibiotics regimens, despite these already containing anaerobic coverage with piperacillin/tazobactam or meropenem. No surgical intervention was required in either group.

During this period, one (7%) and nine (8%) patients died of sepsis in the ASCT and AML groups respectively.

**Discussion**

Our review documented that CT imaging is commonly done in our institution as part of the investigative workup for FN, but the type of imaging differed between the study cohorts. CTAP was the most common imaging performed in ASCT recipients, likely reflecting the more intense gastrointestinal mucositic effects of myeloablative conditioning. In contrast, CT chest was the most common CT investigation in AML patients, reflecting concerns of pulmonary fungal infection in the context of prolonged severe neutropenia.

Overall CTAP was performed in 32% of the patients. Abnormalities were seen in just over half of these scans, the most common of which was enterocolitis. These observations contrast with those from the paediatric literature, in which the frequency of abnormal findings has been reported as 12–19% for CT abdomen and 0% for CT pelvis, although these studies evaluated patients with a variety of malignancies receiving treatment regimens of variable myelosuppressive intensity in comparison with our adult patients who were uniformly treated intensively.  

A key finding of our study was that the CTAP findings were generally consistent with the clinical findings and had minimal impact on management, particularly with respect to antibiotic therapy or surgical intervention. The current guidelines recommend bowel rest, intravenous fluids, parenteral nutrition, broad-spectrum antibiotics (active against *Pseudomonas aeruginosa, Escherichia coli*, other gram-negative bacilli and anaerobes) and normalisation of neutrophil counts for the management of neutropenic enterocolitis, although it is noted that there is a lack of high-quality prospective studies to support this.  

Most patients, however, would fall within the scope of guideline recommendations for empirical antimicrobial therapy of FN. Of note, our study population routinely received antibiotics with anaerobic coverage and the value of adding metronidazole to broad-spectrum therapy is questionable. The potential benefit of anaerobic coverage is mitigated by the fact that FN patients are prone to nosocomial infection, which is usually caused by aerobic bacteria.  

**Table 1** Characteristics of autologous stem cell transplant (ASCT) and acute myeloid leukaemia (AML) patients and details of computed tomography (CT) scans

<table>
<thead>
<tr>
<th></th>
<th>ASCT</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of all patients undergoing ASCT or AML treatment</td>
<td>146</td>
<td>110 (total of 175 inpatient chemotherapy cycles)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>58 (18–73)</td>
<td>61 (18–81)</td>
</tr>
<tr>
<td>Male</td>
<td>92 (63%)</td>
<td>62 (56%)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma cell dyscrasia</td>
<td>84 (58%)</td>
<td>AML</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>43 (29%)</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>12 (8%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (5%)</td>
<td></td>
</tr>
<tr>
<td>Number of patients who received CT</td>
<td>40 (27%)</td>
<td>89 (81%) (in 91 admissions, 52% of all inpatient chemotherapy cycles)</td>
</tr>
<tr>
<td>Chemotherapy received by patients who received CT</td>
<td>High-dose melphalan 82 (56%)</td>
<td>Induction 59 (65%)</td>
</tr>
<tr>
<td>BEAM</td>
<td>31 (21%)</td>
<td>Consolidation 25 (27%)</td>
</tr>
<tr>
<td>Bu-mel</td>
<td>29 (20%)</td>
<td>Re-induction 7 (8%)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>Median (range) number of days from first FN to first CT</td>
<td>3 (0–22)</td>
<td>7 (0–25)</td>
</tr>
<tr>
<td>Total number of CT</td>
<td>56</td>
<td>179</td>
</tr>
<tr>
<td>Types of CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT abdomen/pelvis</td>
<td>33</td>
<td>56</td>
</tr>
<tr>
<td>CT chest</td>
<td>17</td>
<td>73</td>
</tr>
<tr>
<td>CT sinus</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>16</td>
</tr>
</tbody>
</table>

BEAM, carmustine, etoposide, cytarabine and melphalan; Bu-mel, busulfan-melphalan; FN, febrile neutropenia.
not receiving antifungal prophylaxis. The decision to implement bowel rest in a small group of patients could arguably be implemented in most patients on clinical grounds alone. In no case did findings necessitate surgical intervention.

The retrospective nature of this study with a relatively small cohort of patients receiving aggressive antibiotic therapy and antifungal prophylaxis obviously limits evaluation of the true yield and clinical impact of the utility of CTAP in FN; as for many studies of this ilk, larger prospective studies are needed to confirm or refute our preliminary observations. Nevertheless our observations suggest that CTAP in adult haematology patients with FN receiving aggressive antimicrobial prophylaxis and broad-spectrum antimicrobial therapy rarely provides useful information unsuspected clinically or result in therapeutic changes, which would not have otherwise been made on clinical grounds. Unnecessary CT scans are expensive, and potentially harmful because of an increase in cumulative radiation exposure above acceptable thresholds, particularly in ASCT recipients, many of whom have already had multiple imaging episodes. Moreover, scans often necessitated substantial time outside our HEPA-filtered facility, which may expose patients to the risk of fungal infection.

Although we believe the use of empiric CTAP in the routine diagnostic algorithm of FN is not justified, particularly in patients with no abdominal symptoms or with the typical right iliac fossa tenderness characteristic of typhilitis, we acknowledge that larger studies are needed to confirm these findings. We specifically cannot exclude the utility of this imaging in patients with severe peritonism and/or haemodynamic compromise in whom gastrointestinal perforation is strongly suspected; of note subsequent to our analysis, a CTAP in an AML patient with severe lower left quadrant pain and peritonism revealed local perforation of a diverticulum, which nevertheless was managed conservatively.

**Table 2** Details of computed tomography (CT) abdomen/pelvis findings and outcome

<table>
<thead>
<tr>
<th></th>
<th>ASCT</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CT abdomen/pelvis</td>
<td>33</td>
<td>56</td>
</tr>
<tr>
<td>With intravenous and oral contrast</td>
<td>27</td>
<td>51</td>
</tr>
<tr>
<td>With intravenous contrast only</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>With oral contrast only</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Non-contrast</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Number of patients</td>
<td>32</td>
<td>51</td>
</tr>
<tr>
<td>Concurrent chest imaging</td>
<td>12 (36%)</td>
<td>31 (55%)</td>
</tr>
<tr>
<td>Abdominal symptoms:</td>
<td>24 (73%)</td>
<td>40 (71%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Both</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Generalised peritonism</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Persistent FN without abdomi-</td>
<td>9 (27%)</td>
<td>19 (34%)</td>
</tr>
<tr>
<td>nal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension (defined as systolic blood pressure &lt;90 mmHg)</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Inotropic support required</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Positive findings (% of scan)</td>
<td>21 (64%)</td>
<td>25 (45%)</td>
</tr>
<tr>
<td>Enterocolitis</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Positive findings according to symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>19/24 (79%)</td>
<td>24/40 (60%)</td>
</tr>
<tr>
<td>Absent</td>
<td>2/9 (22%)</td>
<td>1/16 (6%)</td>
</tr>
<tr>
<td>Therapy change</td>
<td>3 (1/4%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Bowel rest</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Addition of anaerobic cover</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukaemia; ASCT, autologous stem cell transplant; FN, febrile neutropenia.

antibiotics with anaerobic coverage is likely to be limited. High-risk patients also received antifungal prophylaxis, consistent with the recently published local consensus guidelines.\(^{10,11}\) It is conceivable that there may be a higher yield of CTAP findings impacting on management in patients with FN not receiving routine anaerobic coverage as part of their FN protocol or in high-risk patients

**References**

9. Andreyev HJ, Davidson SE, Gillespie C, Allum WH, Swarbick E. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of...
Beta-blockers are under-prescribed in patients with chronic obstructive pulmonary disease and co-morbid cardiac disease

P. A. Neef,1 C. F. McDonald,2,3 L. M. Burrell,4 L. B. Irving,3,5 D. F. Johnson1,3 and D. P. Steinfort3,5

1General Medicine and 2Department of Respiratory and Sleep Medicine, Austin Health, 3Department of Medicine, The University of Melbourne, 4Department of Medicine and Cardiology, The University of Melbourne, Austin Health, and 5Department of Respiratory and Sleep Medicine, Melbourne Health, Melbourne, Victoria, Australia

Key words
beta-blocker, chronic obstructive pulmonary disease, COPD, cardiovascular disease, prescription.

Abstract
The use of beta-blockers in patients with chronic obstructive pulmonary disease and co-morbid cardiovascular disease is controversial, despite increasing evidence to support their use as safe and efficacious. This study retrospectively assessed the rates of beta-blocker prescription in patients admitted to two Australian tertiary hospitals for acute exacerbation of chronic obstructive pulmonary disease. This revealed that less than half of patients (45%) with known cardiac indications were receiving beta-blocker therapy, evident across all degrees of airways disease severity. Further work is needed to ensure that medical management of this patient group is optimised.

The use of beta-blockers in patients with chronic obstructive pulmonary disease (COPD) and co-morbid cardiovascular disease remains contentious. Based on robust data demonstrating mortality benefits, Australian and international guidelines recommend long-term beta-blocker therapy in patients with chronic heart failure (HF) with reduced ejection fraction (HFrEF) and in patients following acute myocardial infarction (AMI).1–6 The use of cardioselective beta-blockers in patients with mild to moderate COPD has been proven to be safe in regards to long-term respiratory function and symptoms.7 COPD is no longer recognised as a definite contraindication and most patients are considered good candidates for the use of cardioselective beta-blockers in co-morbid cardiac disease.1,2,8

The mortality and morbidity benefits attributable to beta-blockers in patients with cardiovascular disease are also seen in those with co-morbid COPD. Initiation of beta-blocker therapy in patients with COPD reduced mortality rates in cohorts with co-morbid cardiovascular disease.9–12 This is particularly important considering that a significant proportion of mortality in patients with COPD is attributable to cardiovascular disease.13,14 Despite this encouraging evidence supporting the use of beta-blockers in COPD, international studies identify under-prescription of beta-blockers in this cohort at both specialist and generalist levels.15,16 We conducted a retrospective cohort study to determine if beta-blocker under-prescribing occurs in the Australian setting, as if this was the case it would present a significant opportunity for quality improvement.

A retrospective cohort study was conducted across two tertiary metropolitan hospitals (Melbourne Health and Austin Health). This study was approved by the Melbourne Health Human Research Ethics Committee.

We assessed the prescription rates of long-term beta-blockers in COPD patients with co-morbid cardiovascular disease. The study cohort included patients admitted to hospital for acute exacerbation of COPD (AE-COPD) between July 2013 and June 2014. Patients were identified using the International Classification of Diseases, Tenth Edition coding system, including primary diagnosis of AE-COPD-unspecified (J44.9), or primary diagnosis of pneumonia (J10-16) and/or primary diagnosis of acute respiratory failure (J96) with secondary diagnosis of AE-COPD.

Patient demographics were recorded, including age, gender, length-of-stay, smoking status and treating...
specialty team. Cardiac and respiratory function tests were recorded if completed within 1 year of admission. Respiratory function test results were recorded and classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging, with significant bronchodilator reversibility defined as increase in forced expiratory volume in 1 s (FEV₁) >200 mL and/or by at least 12% with salbutamol. Co-morbidities were recorded, including hypertension, ischaemic heart disease, previous AMI, chronic HF and atrial fibrillation. Transthoracic echocardiography results were recorded; patients were categorised with HFrEF if left ventricular EF was ≤40%, and HF with preserved EF if left ventricular EF was >40%.

An indication for beta-blocker therapy was defined as a history of prior AMI and/or HFrEF. Beta-blocker and other medication use were recorded by review of electronic medical records and medication charts. Patients were determined to have long-term beta-blocker use if they were admitted with a current prescription of beta-blocker medication.

Data and statistical analysis was performed using STATA (Version 14.1, Statacorp, College Station, TX, USA). Categorical variables were compared using χ² test and Fisher’s exact test using two-tailed P-values. Statistical significance was defined as P-value <0.05.

One thousand and seventy-one patients were admitted to hospital and met the inclusion criteria during the study period. Fifty-seven percent of these patients had HFrEF, 176 (39%) had HF with preserved EF and 64 (14%) had echocardiography results that had not been undertaken or results could not be retrieved. Of the 214 patients with HFrEF, 109 (51%) were receiving beta-blockers at the time of admission. When examining HFrEF without a history of prior AMI, only 25 (31%) of the 80 patients were on beta-blocker therapy.

Three hundred and seventy-three (35%) patients had a previous history of an AMI with 178 (48%) of this group on beta-blocker therapy. One hundred and fourteen patients had a history of both AMI and HFrEF, with 82 (72%) receiving beta-blockers. Thirty-two (22%) patients had unknown left ventricular function and past AMI, with 22 (49%) of these patients receiving beta-blockers.

The majority of patients with COPD and a known beta-blocker indication had spirometric GOLD stage II disease (50–79% predicted FEV₁, and FEV₁/vital capacity <0.7) (29%). GOLD stage IV (very severe airway obstruction, FEV₁ <30% predicted) was significantly associated with decreased rates of prescription in both prior AMI and HFrEF, compared to lesser degrees of severity (P < 0.01). Only 25 (4%) patients with an indication for a beta-blocker had significant bronchodilator reversibility on spirometry. This group was not statistically significant and less likely to be prescribed beta-blockers than those without bronchodilator reversibility (P = 0.9). In 107 (18%) patients, spirometry had not been undertaken or results could not be retrieved.

Cardioselective beta-blockers accounted for 86.1% of beta-blocker prescriptions. The most commonly prescribed beta-blocker was bisoprolol (31%), with metoprolol (28%), nebivolol (17%) and carvedilol (13%) accounting for the majority.

**Discussion**

Our results demonstrate that a significant proportion of patients admitted to tertiary centres with COPD have cardiovascular co-morbidities for which beta-blockers

---

**Table 1** Proportion of patients who were receiving long-term beta-blocker prescription at the time of admission for whom a known indication of beta-blockers exists.

<table>
<thead>
<tr>
<th>Prior AMI</th>
<th>HFrEF</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>178/373 (47.7%)</td>
<td>109/214 (50.9%)</td>
</tr>
<tr>
<td>GOLD stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>28/54 (51.9%)</td>
<td>10/25 (40%)</td>
</tr>
<tr>
<td>II</td>
<td>63/116 (54.3%)</td>
<td>26/52 (50%)</td>
</tr>
<tr>
<td>III</td>
<td>41/98 (41.8%)</td>
<td>29/52 (55.8%)</td>
</tr>
<tr>
<td>IV</td>
<td>5/33 (15.2%)</td>
<td>1/13 (7.7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>41/72 (56.9%)</td>
<td>24/35 (68.6%)</td>
</tr>
<tr>
<td>BD reversibility†</td>
<td>5/17 (29.4%)</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>Without BD reversibility†</td>
<td>173/356 (48.6%)</td>
<td>88/206 (42.7%)</td>
</tr>
</tbody>
</table>

†Significant bronchodilator reversibility defined as increase in FEV₁ > 200 mL and/or by at least 12% with salbutamol. AMI, acute myocardial infarction; BD, bronchodilator; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HFrEF, heart failure with reduced ejection fraction.
are unequivocally indicated yet are under-prescribed. Our findings are consistent with other international studies identifying significant under-treatment of cardiac disease in patients with COPD.\textsuperscript{8,17}

Approximately half the patients with COPD and a history of prior AMI and/or HFrEF were receiving beta-blocker therapy on admission. Under-prescription was evident in patients with all GOLD spirometric stages of severity in whom long-term safety has been clearly demonstrated.\textsuperscript{7}

It is encouraging that patients with COPD who had both prior AMI and HFrEF had beta-blocker prescription rates of up to 72\%. According to international cardiac society guidelines, beta-blocker therapy is particularly recommended in this group of patients in order to prevent the progression of ventricular dysfunction and cardiac-related deaths.\textsuperscript{2,8,9} However, even in this high-risk group we identified significant potential for quality improvement in the 28\% of these patients not receiving beta-blocker therapy.

Prior studies demonstrated under-prescription of beta-blockers in other COPD cohorts with long-term prescription rates varying between 36\% and 79\%.\textsuperscript{9,17} Swennen et al. demonstrated that less than half of general practitioners surveyed would continue beta-blocker therapy in COPD patients with co-morbid HF,\textsuperscript{16} suggesting that clinician education may be a requirement of any quality improvement intervention to improve beta-blocker prescribing. Encouragingly, a recent study of COPD patients post-AMI demonstrated that prescription rates of beta-blockers over 90\% are achievable.\textsuperscript{15}

The cause for under-prescribing in our cohort remains unclear. International studies indicate consistent under-treatment of COPD patients, including with revascularisation interventions.\textsuperscript{16} This suggests either a therapeutic nihilism for COPD patients, or that clinicians are unaware of the established benefits of cardiovascular disease management in COPD. Jones et al. compared the perspectives of cardiologists and respiratory physicians with regard to beta-blocker prescribing in airways disease.\textsuperscript{16} They reported that cardiologists and respiratory physicians were equally willing to prescribe beta-blockers in most patients; however, the former were more likely to prescribe in subgroups with high risk of bronchoconstriction, potentially due to a better understanding of the benefits of beta-blockers. It is clear that patients with COPD and AMI have a higher 1-year mortality and a higher risk of subsequent new-onset HF after MI compared with patients without COPD.\textsuperscript{19} Cardiac-related mortality is highly prevalent in long-term COPD patients and is the most common cause of death in patients with mild-moderate severity COPD.\textsuperscript{20,21} Additionally, a significant proportion of the increased mortality rate following hospital discharge after AE-COPD is from cardiac disease.\textsuperscript{15}

Level I evidence indicates the use of cardioselective beta-blockers in COPD patients with co-morbid cardiovascular disease does not adversely affect respiratory symptoms, FEV1, beta-agonist response or quality-of-life.\textsuperscript{7,11} Additionally, a 6-year prospective Australian study observed no adverse effects on lung function, respiratory symptoms or mortality in COPD patients commenced on beta-blockers, but noted an increase in COPD exacerbation rates.\textsuperscript{22} Mortality benefits have been demonstrated in COPD patients with the use of beta-blockers following AMI, coronary artery bypass grafts and co-morbid chronic HF.\textsuperscript{9,12,21} Evidence suggests that beta-blockers may even exert mortality benefits in COPD independent of those with overt cardiovascular disease.\textsuperscript{9,11,24-28} Whilst the evidence is conflicting, recent studies suggest they may actually decrease rates of acute exacerbations of COPD, adding further weight to their inclusion in management of COPD patients with co-morbid cardiovascular disease.\textsuperscript{22,24,29-31} Hospital admission with acute COPD exacerbation may be a particularly pertinent time to consider introduction of beta-blocker therapy in this cohort.

This is a retrospective observational study with the known limitations inherent in this study methodology. Cardiac function was unable to be recorded in 64 patients. Of these, 32 had a prior history of AMI, and therefore in only 32 (7\%) of all the patients included in this study was the indication status for beta-blockers unknown. We believe that this small percentage does not affect our conclusion regarding this significant under-utilisation of beta-blocker therapy. The reasons for patients not receiving a beta-blocker are multifactorial. A limitation of the study is that potential unknown contraindications to beta-blocker use such as bradycardia, hypotension or adverse drug reaction may be underestimated given the retrospective nature of the study.

We recognise that the exact role of beta-blockers in COPD patients with co-morbid cardiac disease remains uncertain. While extensive level III evidence uniformly suggests mortality benefit in this group,\textsuperscript{8,12,23,31} and level I evidence confirms safety of beta-blockers in patients with COPD,\textsuperscript{7} no prospective studies have established efficacy, nor identified any sub-groups potentially at risk of harm (e.g. patients with reactive airways disease). We believe that current evidence supports use of beta-blockers in selected patients with COPD and co-morbid cardiac disease, and American College of Cardiology Foundation/American Heart Association guidelines specifically recommend beta-blockers in COPD patients, observing ‘most patients with chronic obstructive pulmonary disease remain reasonable candidates for beta-blockade’.\textsuperscript{3} We do acknowledge that careful selection of patients is also recommended so as to exclude those with reactive airways disease, particularly considering the
increasing understanding of the asthma-COPD overlap syndrome.²²²³

Our paper identified potential under-prescription of beta-blockers in COPD patients, suggesting a significant potential for quality improvement. Our paper does not provide evidence of clinical efficacy of beta-blockers in COPD and such studies are keenly required. We would echo the comments of Cochrane et al., who suggested cautious use of beta-blockers guided by clinical judgement, until further evidence is available in the form of prospective interventional trials of beta-blocker.²²

This is the first Australian study to examine specifically beta-blocker prescribing rates in patients admitted with AE-COPD and co-morbid cardiovascular disease. We identify significant under-prescribing in COPD patients with clinical indications where a mortality benefit of beta-blockers is established, and suggest this represents a significant opportunity for quality improvement. We encourage clinicians to ensure that these patients’ medical management is optimised and appropriate beta-blocker therapy is not overlooked.

References
Pharyngoesophageal dysphagia: an under recognised, potentially fatal, but very treatable feature of systemic sclerosis

C. Rajapakse
Wellington Regional Rheumatology Unit, Hutt Valley DHB, Lower Hutt, New Zealand

Key words
scleroderma, pharyngoesophageal dysphagia, aspiration pneumonia.

Correspondence
Chula Rajapakse, Wellington Regional Rheumatology Unit, Hutt Valley DHB, Lower Hutt 5010, New Zealand.
Email: rajapaks@ihug.co.nz

Received 7 February 2016, accepted 20 August 2016.
doi:10.1111/imj.13243

Abstract
Dysfunction of upper pharyngoesophageal region in systemic sclerosis (SSc) is infrequent, poorly recognised and poorly documented in the literature. Yet, it can have very distressing and even fatal consequences that may yet be very responsive to appropriate management. This paper documents the findings and outcome of management of a series of five patients with SSc who had pharyngoesophageal dysphagia to demonstrate the above. Following the documentation of a patient with SSc that had severe pharyngoesophageal dysphagia in 1981, this paper reports the findings in five patients with SSc presenting thereafter, having the same manifestations. Patients 1–4 who had barium swallow and fluoroscopy, demonstrated pharyngoesophageal dysfunction as basis of their symptoms. Patient 1 had fatal outcome from pulmonary haemorrhage following repeated bouts of aspiration pneumonia. Patients 2 and 3 had a long history of SSc and were on appropriate medical treatment. They developed a short history of dysphagia that resolved with additional improvements in swallowing techniques. Patient 4 had a short history of scleroderma, but severe and very distressing dysphagia that failed to respond to improved swallowing techniques alone, but responded well to the addition of medical treatment for SSc, over a 14–24 months period. Patient 5 had a short history of SSc and dysphagia that responded well to medical treatment over 6–12months. We conclude that pharyngoesophageal dysphagia in SSc, is a rare, very distressing and potentially fatal manifestation that can have a very favourable outcome with appropriate management.

Funding: None.
Conflict of interest: None.

© 2016 Royal Australasian College of Physicians
Abnormalities in mid and lower oesophageal motility in systemic sclerosis (SSc) are well recognised and occur frequently. However, upper pharyngoesophageal abnormalities in SSc are both much less frequent and much less frequently recognised.

The first report of pharyngoesophageal dysphagia from the same author appeared in 1981. In this report, the patient had gross narrowing of cervical, pharyngoesophageal lumen with lack of relaxation of upper oesophageal sphincter in response to pharyngeal contractions with spill over into the trachea. The upper oesophageal muscles were thickened due to infiltration of an oedematous collagenous matrix between muscle fibres that were atrophic. The patient eventually died of aspiration pneumonia.

In the only other report on pharyngoesophageal involvement in SSc, the relative frequency of this, especially in relation to lower oesophageal involvement is documented.

We report here a series of five patients with SSc with pharyngoesophageal dysphagia. We describe their varying clinical presentations and features, their management and outcome and draw attention to the importance of early diagnosis and appropriate management that could change a potentially disabling and fatal disease into a rewarding and successful one.

Following the experience with the patient documented in 1981, note was made of all SSc patients presenting subsequently, who clinically had dysphagia localised to the pharyngoesophageal region, either on presentation or during the course of their management. These patients were investigated for pharyngoesophageal dysfunction with fluoroscopic studies along with other standard management interventions. The findings and outcome of management in these patients were carefully and prospectively documented.

These findings are now presented.

**Patient 1:** a 70-year-old woman who presented in 1992 with long standing SSc and a history of progressively worsening dysphagia of a few months duration. She complained of choking, regurgitation of food and of excessive saliva around mouth possibly due to inability to swallow it. She also gave a history of recurrent chest infections, presumed aspiration pneumonia.

On examination, her hands demonstrated typical sclerodactyly and there was saliva dribbling round her mouth, with which she was constantly wiping with a tissue.

Barium (Ba) swallow and fluoroscopy revealed a slight delay in swallow reflex with retention in the valleculae following swallow, penetration of material above and below vocal chords both during and after swallow and a sense of residual material in the pharynx. Cough was partly effective in clearing this material.

She was commenced on omeprazole and D-penicillamine as was conventional at that time for SSc. In view of ongoing nasogastric feeding, a gastrostomy was performed in September 1994. Repeat Ba fluoroscopy showed no improvement. Despite gastrostomy, she continued to have chest infections though for the main part she maintained a reasonable quality of life at home. She eventually died of a severe pulmonary haemorrhage in July 1996.

Post-mortem revealed a proximal web a short distance below the epiglottis, though this caused no significant obstruction. The distal oesophagus was normal. Both lungs had marked haemorrhagic congestion most prominent in the lower lobes with no obvious pneumonia.

**Patient 2:** a 76-year-old woman who presented in January 2001 with a long history of calcinosis, Raynauds, esophagitis, sclerodactyly, taelengiectasia (CREST) syndrome, with Raynaud phenomenon, sclerodactylty, reflux symptoms and lower oesophageal dysphagia. Upper gastrointestinal endoscopy revealed a sliding hiatus hernia and a lower oesophageal ulcer benign on biopsy. Ba swallow confirmed the sliding hiatus hernia with gastrooesophageal reflux.

In January 2008 she developed an episode of coughing during and after meals. Pharyngoesophageal dysphagia was suspected. Ba swallow and fluoroscopy revealed mid and lower oesophageal dilatation, a small sliding H/H and free flow gastric contents into the oesophagus. There was no narrowing of gastrooesophageal junction with the oesophagus emptying well under gravity on erect position.

In the pharyngoesophageal region, there was reduced posterior pharyngeal wall approximation resulting in post-swallow vallecular residue, inconsistent epiglotic deflection in presence of anterior hyoid excursion, consistent penetration and occasional aspiration of thin fluids, probably consequent to both of the above. Secondary swallow facilitated partial clearance.

She was recommended to continue her current diet, but to alternate fluid and solids to facilitate pharyngeal clearing and to have two swallows per bolus. She was given a trial period of swallowing rehabilitation to target improved base of tongue to post-wall approximation. All this led to a successful reversal of her swallowing problems.

**Patient 3:** a female born in 1968 who had SSc diagnosed in 1985 and had been under the care of our unit since. During the course of these years, she has had significant peripheral vascular disease, interstitial lung disease and mild bronchiectasis. For her interstitial lung disease she had been treated with courses of intravenous cyclophosphamide.

In 2012, she complained of dysphagia localised to pharyngoesophageal region. Ba swallow and fluoroscopy...
demonstrated premature spillage from oropharyngeal phase to pyriform sinuses with impaired bolus transfer through pharynx leading to pharyngeal residue, requiring multiple swallows and cyclic ingestion to clear out bolus of all consistencies.

She was advised to remain upright for 60 mts post-solids or fluid and alternate solids with fluid to facilitate clearance of pharyngeal residue. Symptoms soon resolved with use of these techniques.

Patient 4: a 70-year-old woman who was presented in December 2011 to A & E on multiple occasions with ‘food getting stuck’ in pharyngoesophageal region, requiring instrumentation to remove. Following initial ear nose throat and later gastroenterology evaluation she had a Ba swallow and fluoroscopy (Fig. 1). This demonstrated cricopharyngeal incoordination with delayed relaxation of post-wall leaving persistent impression and delayed emptying. She also had a dilated oesophagus tapering to the gastroesophageal junction with poor emptying, suggestive of achalasia cardia making the gastroenterologist to feel that this was the basis of her swallowing problems. However, manometric studies excluded it.

At this stage, the gastroenterologist felt that the only therapeutic option was improving her swallowing techniques, but held out a poor prognosis. As predicted, the response was poor which left a very disappointed and dejected patient. However, in view of ‘scleroderma looking hands’, she was referred to rheumatology for management of these.

At rheumatology in October 2012, she was confirmed as having SSc clinically, with sclerodactyly among other features. On investigation she had an antinuclear antibody 1280, creatinine phospho kinase 1117 troponins 345 (Fig. 2).

Following her first consultation she was commenced on treatment with weekly methotrexate, prednisone 10 mg and nifedipine (Adalat).

By August 2013 she conceded some improvement in stiffness of hands and swallowing. By February 2014 she was feeling much better in all her manifestations. By August 2014 she felt that her swallowing was near normal as were her other features of scleroderma. The elevated muscle enzymes normalised by July 2013 while the cardiac enzymes normalised fully slightly later.

She has since had a chest infection in September 2014, left-sided pneumonia in June 2015, a left middle cerebral artery thrombotic stroke also in June 2015 from all of which she has fully recovered. Her swallowing however was unaffected during all of these events.

Patient 5: a 57-year-old man who presented in May 2014 with a 2–4 months history of diffuse stiffness especially in the hands, Raynaud syndrome and dysphagia localised to pharyngoesophageal region. On examination, his hands were puffy and stiff consistent with SSc. He had dilated nail fold blood vessels supporting the diagnosis.

He was treated as for a patient with SSc with weekly methotrexate, prednisone 10 mg and sildenafil for his Raynaud syndrome. Over 6–12 months, his symptoms improved with resolution of limb stiffness and dysphagia. On gradual discontinuation of prednisone his symptoms returned and has required a minimum of 5 mg of prednisone a day to remain symptom free.

In summary, the important findings in our five patients with pharyngoesophageal dysphagia are as follows:

- Patients 1–4 who had Ba swallow and fluoroscopy, demonstrated pharyngoesophageal dysfunction as basis of their symptoms.
- Patient 1 had a fatal outcome from pulmonary haemorrhage following repeated bouts of aspiration pneumonia. She came before the era of use of aggressive immuno-modulatory and vasodilator treatment in scleroderma and hence did not receive them.
- Patients 2 and 3 had a long history of SSc and while on appropriate medical treatment developed a short history of dysphagia that resolved with the addition of improvements in swallowing techniques.
- Patient 4 had a short history of SSc and severe dysphagia that failed to respond to improved swallowing techniques alone, but responded well to addition of medical treatment for SSc, over a 14–24 months period.
- Patient 5 had a short history of SSc and dysphagia that responded well to medical treatment over 6–12 months period.

Discussion

Since the first report of pharyngoesophageal dysphagia in SSc in 1981, there have been few if any reports on the subject. In 1991, Montesi et al. in a study of 51 patients with SSc did video fluoroscopy during Ba swallow to evaluate for oropharyngeal deglutination abnormalities. They found that 13 (26%) had swallowing dysfunction that included oral leakage, retention, penetration, mild to moderate aspiration and upper oesophageal sphincter incoordination, possibly similar to what our patients had while 80% had abnormalities in the oesophageal phase of swallowing. This emphasises what is well known, which is that lower oesophageal dysfunction rather than
Pharyngoesophageal dysfunction is what is common in SSc. It also gives an indication of the frequency with which one could expect pharyngoesophageal dysfunction, like our patients had, in SSc.

However, our report is the first that details the clinical characteristics of a series of such patients as we have done. These had a wide spectrum of severity, from mild and easily reversible to severe with a fatal outcome. Our experience also demonstrates that with appropriate management, what could appear to be a very disabling and hopeless situation, could have a very pleasing and successful outcome when the condition is recognised and appropriate management is instituted as in the case of patient 4. This potential for improvement was not apparently known to the managing gastroenterologists of this patient, demonstrating a good reason for making this knowledge, widespread.

Dribbling of saliva around the mouth requiring constant mopping as is seen in pseudo-bulbar palsy, due to the severity of swallowing impairment, was a striking feature of the patient 1 in this series and the patient reported in 1981. The oral leakage described by Montesi et al., may well be similar to what these two patients had.

However, all our patients were neurologically intact making it difficult to argue for a neurological basis for the dysphagia in these patients. Arguing that this could be a lone neurological manifestation is also not tenable when an alternative, that is SSc pathogenesis-related dysphagia (see below) is forthcoming.

The elevated muscle enzyme in patient 4 whose resolution roughly paralleled the clinical improvement suggests a significant contribution from myositis to her symptoms. Delayed cricopharyngeal relaxation as seen in this patient has been described before in oropharyngeal dysphagia associated with inflammatory myopathy, further supporting a myopathic basis for this patient’s dysphagia.

Such delays in cricopharyngeal relaxation and elevations of muscle enzymes were not seen in any of the other patients in this series, which would arguably make even a localised myositis less likely to be the basis of dysphagia in these others in this series, especially when an alternative explanation, that is based on the pathogenesis of SSc, is available.

Ba studies in patients 1–4 excluded acid reflux, secondary stricture or oesophageal narrowing from any other cause as the basis of dysphagia in this series. In patient 1, the post-mortem finding of a web was confirmed as not causing an obstruction and was not seen on Ba studies in life. In patient 5, the findings were so typical of earlier patients and the response to combination of vasodilator and immune modulator treatment in the absence of proton pump inhibitor was so convincing that Ba studies were not performed.

This would leave pharyngoesophageal dysfunction linked to the pathogenesis of SSc as a significant contributor to the dysphagia in this series of patients. This would be similar to the pathogenesis of dysmotility seen elsewhere in the gastrointestinal tract, including in the lower oesophagus and small bowel where functional blind loops occur.

The beneficial response to vasodilator (nitroprusside and sildenafil) and immune modulator treatment (methotrexate and cyclophosphamide), demonstrated particularly by patients 4 and 5 would also support such a pathogenesis as these treatments target two important cornerstones of this pathogenesis, viz. the immune-inflammatory abnormalities and vasculopathy.

Fibrosis with secondary muscle atrophy as seen in the case report of 1981 would be a late sequel to these earlier changes be it in the pharyngoesophageal region or...
more distally in the gastrointestinal tract and would be less likely to respond to these treatments.

On the other hand, the improvements observed in the pharyngoesophageal dysphagia of patients 2 and 3 to relatively minimal physical interventions does raise the possibility that this may be a more frequent occurrence than is realised and that it may be reversing with standard treatment without being appreciated by clinicians.

Improved swallowing techniques would complement medical treatment as happened in our patients. The demonstration of aspiration in Ba fluoroscopic studies of patients 1 and 2, the occurrence of pneumonia, probably aspiration in patients 1 and 4 and occurrence of both in the patient reported in 1981 would suggest that fluoroscopic studies to look for pharyngoesophageal dysfunction should be done when confronted with pneumonia in patients with SSc and if present be treated appropriately as we have done. Clinicians managing SSc patients should be alert to the possibility of pharyngoesophageal dysfunction being the basis of dysphagia, to make an early diagnosis and for early institution of aggressive medical treatment and improved swallowing techniques, as a way of improving what could be a very distressing situation with a potentially fatal outcome to a rewarding resolution of symptoms. Also, SSc patients presenting with pneumonia should have fluoroscopic studies to see if pharyngoesophageal dysfunction with aspiration is present.

References

Concomitant plasmapheresis and cladribine infusion for the treatment of life-threatening systemic lupus erythematosus

A 43-year-old man with complicated systemic lupus erythematosus (SLE) was referred to our institution for aplastic anaemia and evaluation for haemopoietic stem cell transplant. He was diagnosed 4 years prior to presentation and was treated with multiple lines of standard SLE regimens. He developed aplastic anaemia treated with rabbit anti-thymocyte globulin and cyclosporine. Upon relapse, a higher dose of cyclosporine was administered, but was complicated by intrahepatic obstructive jaundice. A third line of mycophenolate mofetil, another course of anti-thymocyte globulin and cyclosporine, also failed. He was started on rituximab resulting in resolution of anaemia for 4 months. Three months later, after prednisone was tapered, he developed thrombocytopenia. The patient’s condition progressively worsened with anasarca, chylous ascites and chylous pleural effusion. His condition further declined. Haematology–oncology was consulted for more aggressive therapies.

He was started on plasma exchange for eight treatments (95% total plasma volume to 5% albumin replacement) and cladribine (0.05 mg/kg/day) continuous intravenous infusion for 7 days. Over several weeks, his condition improved. There was marked improvement in C3 and C4 complement levels after treatment (Fig. 1). His overall course required 99 days in the hospital, including three intensive care unit transfers. His steroid dose was tapered, and the patient was maintained on prednisone 5 mg daily and plaquenil 200 mg twice daily. To date, 3 years since his treatment with cladribine and plasmapheresis, his disease remains stable.

This case demonstrates the challenges in SLE patients who fail standard treatments. This patient developed multi-organ failure, including rare complications, such as chylous ascites and chylothorax.1,2 Cladribine, a lymphotoxic drug used as an anti-leukaemic agent, was used as a salvage treatment to curtail the underlying autoimmune process and reset the immune system. Experience with use of cladribine in SLE is limited. Cladribine was studied in patients (n = 12) with SLE-associated glomerulonephritis resulting in a normalisation of renal function in 43% of cases.3 A case was reported on a patient with severe lupus nephritis refractory to standard therapy who was treated successfully with cladribine.4

A unique aspect of our approach was the concomitant use of plasmapheresis to reduce SLE autoantibodies. Plasmapheresis was employed as a bridge until the onset of lymphocytic depletion by cladribine. Plasma exchange is not a standard treatment in SLE.

The most common adverse effect of cladribine is infection due to depletion of T and B cells. Our patient developed cytomegalovirus reactivation without evidence of active cytomegalovirus disease and was successfully treated preemptively with foscarnet.

This case along with other reports illustrate that cladribine can be used as alternative in inducing remission in life-threatening SLE cases that are refractory to multiple

---

Figure 1 Levels of complement proteins C3 and C4 pre- and post-plasmapheresis and cladribine infusion. (—), C3; (—–), C4.
standard treatments. This case underscores the importance of a multi-disciplinary approach, particularly the role of haematology and medical oncology, in treating patients with cytotoxic drugs who have failed standard therapies, which are outside standard rheumatology practice.

References


Large volume subcutaneous lymphoedema drainage

Lymphoedema in advanced cancer can arise as a complication of previous pelvic surgery or radiation, metastatic lymphadenopathy or hypoalbuminaemia.1 It can prove intractable to usual pharmacological and mechanical treatments1 and can cause intolerable symptoms at the end of life.2

Options for the management of lower extremity lymphoedema include elevation of the affected limbs, use of compression bandaging/hose, exercise, diuretics, aqua lymphatic therapy and rarely, lower extremity subcutaneous lymphoedema drainage.3

Subcutaneous drainage was used as a ‘last resort’ in a 70-year-old man with metastatic colorectal cancer. The patient had severe lower limb oedema extending up to the groin with scrotal swelling resulting in poor quality of life for approximately 4 months. He had previously trialled combinations of diuretics with little effect.

After application of topical anaesthetic cream, four 16G black eye subcutaneous needles were inserted at an angle of about 45° in the medial aspect of both upper calves and dorsum of both feet. These were connected to standard urinary catheter bags. The patient was asked to sit out in a chair for gravitational assistance with drainage. Three hours post-insertion, a total of 6 L had drained. While the patient was in bed overnight, the bags were left on the bed with connecting tubes unclamped. A total of 17 L was drained over the next 3 days with a resultant reduction in weight from 88.5 kg on admission to 71 kg on removal of the drains. The patient’s scrotal and upper leg swelling was significantly reduced resulting in considerably improved comfort and mobility.

The patient was haemodynamically stable throughout the procedure. His renal function worsened from a baseline creatinine of 146–208 mmol/L, precipitating removal of the drains on day 3. The serum creatinine improved spontaneously to within normal limits in 1 week with oral fluids only. There was transient leakage of fluid post-removal of needles, but this resolved spontaneously over a few hours. There were no issues with infection.

The same patient was readmitted 3 weeks later with recurrent lower limb oedema. Four subcutaneous needles were inserted medially in the lower limbs and 16.3 L drained over the following 2 days.

Several case series in patients with advanced malignancy and lower limb oedema, refractory to conventional therapy have reported benefit from subcutaneous lymphoedema drainage.1,4,5 Most authors have documented fluid drainage ranging from 250 mL to 8 L. No other cases report the large volumes removed in our case.1,4,5

We have attempted this procedure on a number of occasions with variable results. In some cases, no or minimal fluid drained despite re-positioning of needles. We do not recommend the use of this technique in any patient in whom all other options have not been trialled, but if successful, it can improve the quality of life in patients with end-stage disease. Characteristics that might select for successful drainage include spontaneous weeping of subcutaneous fluid and pitting non-fibrotic lymphoedema, but more experience is necessary to confirm this.
Acknowledgements

We acknowledge the patient for his contribution and consent to this case study.

Received 15 February 2016; accepted 29 February 2016.

doi:10.1111/imj.13241

References


Visceral leishmaniasis triggering (mimicking) macrophage activation syndrome in a patient with adult onset Still disease

A 28-year-old man was diagnosed with adult onset Still disease (AOSD) after the exclusion of other causes of prolonged fever. According to Yamaguchi, he fulfilled three of four major (fever, arthralgias, leukocytosis) and four of five minor criteria (sore throat, lymphadenopathy, hepatosplenomegaly, negative rheumatoid factor/antinuclear antibodies). Treatment with prednisone (0.5 mg/kg) produced a good clinical and laboratory improvement and azathioprine (2 mg/kg) was added to ameliorate symptoms of iatrogenic Cushing syndrome. Six months later, the patient reported bouts of high fever, elevation of C-reactive protein (CRP) and leucopenia. Azathioprine was stopped, an empiric antibiotic therapy was given, and prednisone dose raised (1 mg/kg). Blood and other cultures came back negative for bacteria and viruses. Despite a higher dose of prednisone, the patient was still febrile, with elevated CRP, and leucopenia, hepatosplenomegaly, thrombocytopenia, moderate elevation of transaminases, hypofibrinogenaemia and marked hypertriglyceridaemia and hyperferritinaemia. Histology of the bone marrow showed 60% cellularity with a large number of histiocytes. Additional antibiotics were given together with antifungal drugs, granulocyte colony-stimulating factor...

Figure 1 Bone marrow aspirate (May-Grünwald-Giemsa staining, x1000): (A) numerous amastigotes may be seen outside of mononuclear phagocytic system; and (B) amastigotes within cytoplasm of a histiocyte.
and intravenous immunoglobulins. According to Ravelli et al., the patient fulfilled all four laboratory criteria and two of three clinical criteria for the diagnosis of macrophage activation syndrome (MAS). A decision to treat the underlying active AOSD as a potential trigger for MAS was reached. Prednisone was continued and cyclosporine A and anakinra (100 mg/day) were started. The patient had a partial laboratory response but relapsed after 33 days. Anakinra was discontinued and tocilizumab (8 mg/kg) was given with only a partial response. Cytology of the bone marrow was repeated only to discover a large number of cytoplasm free and histiocyte bound Leishmania amastigotes (Fig. 1) and the diagnosis of visceral leishmaniasis was made. There was no evidence of haemophagocytosis in the bone marrow. Amphotericin-B treatment led to normalisation of all the laboratory findings. In a follow-up period of 9 months, he has remained stable on low dose prednisone (0.05 mg/kg) and cyclosporine A (1 mg/kg).

AOSD is characterised by systemic inflammation; the diagnosis should be reached by exclusion.\(^1\) MAS is a life-threatening illness often triggered by an infectious agent, underlying disease or medication, sometimes the cause remains unknown. It is thought to be a secondary/ acquired form of haemophagocytic lymphohistiocytosis.\(^2,3\) MAS is often a complication of systemic juvenile idiopathic arthritis.\(^4\) Treatment regimens include different immunosuppressives (like HLH-2004 protocol).\(^3\)

Symptoms and presentation of AOSD are comparable to systemic juvenile idiopathic arthritis, including MAS as a potential complication.\(^6\) After our patient developed symptoms of MAS, further analyses were made to find the cause/trigger. Active AOSD was thought to be the trigger, but the initial therapy of cyclosporine A and anakinra (IL-1 inhibitor) was partially successful. Switching from anakinra to the IL-6 inhibitor tocilizumab also had a temporary effect. Repeated evaluation of the bone marrow provided the diagnosis of visceral leishmaniasis. The patient did not inhabit and did not travel to endemic regions so it was unknown where and when the infestation with leishmaniasis occurred.

Clinical and laboratory presentation of leishmaniasis and MAS can overlap.\(^7\) A higher incidence of leishmaniasis was reported from leishmaniasis-endemic regions in patients with rheumatic diseases treated with TNF-α inhibitors. It remains unclear whether leishmaniasis was a primary infestation or a reactivation of latent disease and whether tumor necrosis factor-alpha inhibitors or prolonged immunosuppression rendered the patients more susceptible to leishmaniasis.\(^8\)

Although rare in non-endemic areas, leishmaniasis should be included in the differential diagnosis of patients with AOSD who develop signs of MAS.

Received 21 January 2016; accepted 18 July 2016.

doi:10.1111/imj.13234

M. Barešić,\(^1\) G. E. Janka,\(^2\) K. Gjadoř-Kujećdić,\(^3\) Š. Zekan\(^4\) and B. Anić\(^1\)

1Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, and 2Department of Pathology and Cytology, University of Zagreb, School of Medicine, University Hospital Center Zagreb, 3University Hospital for Infectious Diseases ‘Dr. Fran Milatjević’, Zagreb, Croatia and 4Pediatric Hematology and Oncology, University Medical Center Eppendorf, Hamburg, Germany

References


General Correspondence

Family escalation of care: well meaning, but where’s the evidence

The National Safety and Quality Health Service Standards (NSQHS) defines quality standards around healthcare processes and largely uses auditing of process rather than outcomes as their marker of quality. Whilst this is reasonable if there is a clear link between practice and outcomes (e.g. thromboprophylaxis prescription and thromboembolism prevention), it is of dubious value if the link is based on supposition and anecdote. In Standard 9 ‘Responding to Deterioration’, family escalation of care (FEC), whereby patients or family escalate care independently of their treating team, is a developmental target with some Australian hospitals already implementing FEC systems. It is likely to become mandatory in the Version 2 of the standards; however, the evidence underlying FEC is largely descriptive without clear evidence of patient benefit.

We ran a pilot FEC programme called ‘HELP Call’ on a busy medical ward in a Melbourne inner-city referral hospital for 6 months. The hospital has a well-established medical emergency team (MET)/Code Blue system and had recently introduced bedside nursing handover to improve patient care and communication. There were 764 admissions over the 6-month period, 598 (78.3%) of which were general medical admissions. There were 764 admissions over the 6-month period, 598 (78.3%) of which were general medical admissions. There were no HELP calls for the 6-month period. There were 35 MET and nine Code Blues calls, including three cardiac arrests. Four hundred and forty-one (58%) of the patients were born overseas and 245 (32.1%) documented a language other than English as their preferred language.

FEC in an inner-city medical ward with an ethnically diverse population was not utilised. Reasons for this may include insufficient education of staff and patients, existing staff and ward processes that adequately address patients’ needs, the presence of effective alternative escalation services or an inability of patients to engage with the process due to literacy, cognitive or language barriers.

Others have also found that FEC may be inefficient for addressing deterioration. In a UK audit of Call for Concern where calls for the year numbered 202, only three (1%) required critical care intervention. Australian data presented at the ISQua 2013 conference on a number of NSW hospitals reported that most had few or no calls.

Although family escalation may be superficially attractive, medicine is littered with well-intentioned ideas that have subsequently proved to be ineffective or harmful. To demand that hospitals adopt an unproven intervention over alternative locally developed systems for engaging with patients and addressing deterioration suggests ideology rather than good practice.

Widespread adoption of interventions based on good intentions is not a substitute for trials and careful evaluation of the evidence. At a time when ‘choosing wisely’ campaigns are being instituted to reduce low value, non-evidence based therapies, it is concerning that the NSQHS may mandate the introduction of an unproven intervention across an entire hospital system. In doing this, they would create a self-perpetuating cycle where rather than patient outcomes, compliance with dogma defined practice and its regimented auditing are the goals.

The hospital community should await the evidence before implementing family escalation as should the NSQHS prior to mandating it.

Received 12 April 2016; accepted 28 April 2016.

doi:10.1111/imj.13238

A. Tobin

Department of Intensive Care, St Vincent’s Hospital Melbourne, Melbourne, Victoria, Australia

References


2 Odell M. Family escalation of care: a patient and relative initiated Call for Concern (C4C) service. In: 8th International Conference on Rapid Response Systems and Medical Emergency Teams; 2013 May 13–14; London, UK.


A hybrid of conventional medical terminology and patient-friendly terminology

I applaud the efforts of Wernick and co-workers to simplify medical terminology in clinic letters and hospital reports. Their work demonstrated that patients appreciated the simplified language free of medical jargon. The authors did not however analyse the utility of Internet searches using conventional medical terminology compared to translated terms (e.g. paroxysmal nocturnal dyspnoea vs walking at night breathless). Translated terms may be less efficient when patients search the Internet when they receive only the user friendly translated version. When physicians use conventional medical terminology, they simplify Internet searches for patients and improve education after clinic visits.

I suggest a hybrid option between conventional reports with terms such as ‘echocardiogram’ and populist reports using the term ‘heart ultrasound’. This is the same golden mean as listing generic drug name followed by the trade name used by the patient (thyroxine (Oroxine) 100 mcg daily). Here are several examples:

1 I have requested a fluorodeoxyglucose positron emitted tomography brain scan (metabolic imaging with positron emitted tomography) looking for…
2 The electroencephalogram or brain electrical mapping showed slow waves without sharp waves or features of epilepsy.
3 This man could not perform a valid spirometry (lung function test) because respiratory effort would be inconsistent.
4 Magnetic resonance imaging brain scan showed mild cerebral atrophy (shrinkage) and white matter hyperintensity (damage to white matter often related to high blood pressure, diabetes or heart disease).

Received 24 May 2016; accepted 27 June 2016.
doi:10.1111/imj.13236
P. Regal
Department of Geriatric Medicine, Regal Elderly Medicine, Wyong, New South Wales, Australia

Reference

Wiley offers an optional open access model: OnlineOpen, in over 1250 journals. OnlineOpen is available to authors who wish to make their article available to non-subscribers on publication, or whose funding agency requires grantees to archive the final version of their article.

- Open access: freely available on Wiley Online Library and PubMed Central
- Fully compliant with open access mandates – meeting the requirements of funding organizations and institutions where these apply
- Option available for over 1250 Wiley journals
- An icon clearly signals that your article is OnlineOpen
- Authors can publish OnlineOpen retroactively
- For research articles, short communications and review articles

For more information on OnlineOpen including details of fees visit: wileyonlinelibrary.com/onlineopen
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
12 hours apart without food. No food should be consumed for at least two hours before and one hour after the dose. For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and should be taken immediately. Not more than one teaspoon of applesauce and no food other than applesauce must be used.

Hypersensitivity to nilotinib or excipients.

Precautions:

Thrombocytopenia, neutropenia and anaemia managed by temporary withdrawal or dose reduction; complete blood counts every two weeks for the first two months, monthly thereafter or as clinically indicated; patients at risk of QTc prolongation (e.g. patients with hypokalaemia, hypomagnesaemia, congenital long QT syndrome, with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia; patients taking anti-arrhythmic drugs or other drugs that may lead to QT prolongation); ECG is recommended prior to treatment, repeat after 7 days and as clinically indicated; correct hypokalaemia or hypomagnesaemia prior to treatment; uncommon cases of cardiovascular events included peripheral arterial events were reported in 48 month extended follow-up trial in newly diagnosed CML patients and observed in the post-marketing reports. Grade 3/4 cases of cardiovascular events included peripheral arterial thrombosis, stroke, non-fatal myocardial infarction, non-fatal heart failure, other coronary events, sudden death.

Monitoring of response to therapy in Ph+ CML should guide appropriate CML management.

Indications:

Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) in chronic phase. Treatment of chronic or accelerated phase Ph+ CML in adult patients resistant or intolerant of at least one prior therapy including imatinib. Design: Patients with newly diagnosed Ph+ CML: 300 mg twice daily; patients with Ph+ and AP CML, adjusted to or tolerated at all doses in prior therapy including imatinib: 400 mg twice daily. Monitoring of response to therapy in Ph+ CML after good prior cell therapy. Dosage: Should be taken about 12 hours apart without food. No food should be consumed for at least two hours before and one hour after the dose. For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and should be taken immediately. Not more than one teaspoon of applesauce and no food other than applesauce must be used.

Internal Medicine Journal

www.blackwellpublishing.com/IMJ

Journal of Paediatrics and Child Health

www.blackwellpublishing.com/JPC

WILEY-Blackwell Publishing

PBS Information: Authority Required. Refer to PBS Schedule for full Authority Information.

Please review approved Product Information before prescribing. Approved Product Information can be accessed at http://www.novartis.com/au_products_healthcare.html. Please note changes(s) in Product Information.

Indications: Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) in chronic phase. Treatment of chronic or accelerated phase Ph+ CML in adult patients resistant or intolerant of at least one prior therapy including imatinib. Design: Patients with newly diagnosed Ph+ CML: 300 mg twice daily; patients with Ph+ and AP CML, adjusted to or tolerated at all doses in prior therapy including imatinib: 400 mg twice daily. Monitoring of response to therapy in Ph+ CML after good prior cell therapy. Dosage: Should be taken about 12 hours apart without food. No food should be consumed for at least two hours before and one hour after the dose. For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and should be taken immediately. Not more than one teaspoon of applesauce and no food other than applesauce must be used.

Hypersensitivity to nilotinib or excipients.

Precautions:

Thrombocytopenia, neutropenia and anaemia managed by temporary withdrawal or dose reduction; complete blood counts every two weeks for the first two months, monthly thereafter or as clinically indicated; patients at risk of QTc prolongation (e.g. patients with hypokalaemia, hypomagnesaemia, congenital long QT syndrome, with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia; patients taking anti-arrhythmic drugs or other drugs that may lead to QT prolongation); ECG is recommended prior to treatment, repeat after 7 days and as clinically indicated; correct hypokalaemia or hypomagnesaemia prior to treatment; uncommon cases of cardiovascular events included peripheral arterial events were reported in 48 month extended follow-up trial in newly diagnosed CML patients and observed in the post-marketing reports. Grade 3/4 cases of cardiovascular events included peripheral arterial thrombosis, stroke, non-fatal myocardial infarction, non-fatal heart failure, other coronary events, sudden death.

Monitoring of response to therapy in Ph+ CML should guide appropriate CML management.

Indications:

Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) in chronic phase. Treatment of chronic or accelerated phase Ph+ CML in adult patients resistant or intolerant of at least one prior therapy including imatinib. Design: Patients with newly diagnosed Ph+ CML: 300 mg twice daily; patients with Ph+ and AP CML, adjusted to or tolerated at all doses in prior therapy including imatinib: 400 mg twice daily. Monitoring of response to therapy in Ph+ CML after good prior cell therapy. Dosage: Should be taken about 12 hours apart without food. No food should be consumed for at least two hours before and one hour after the dose. For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and should be taken immediately. Not more than one teaspoon of applesauce and no food other than applesauce must be used.

Hypersensitivity to nilotinib or excipients.

Precautions:

Thrombocytopenia, neutropenia and anaemia managed by temporary withdrawal or dose reduction; complete blood counts every two weeks for the first two months, monthly thereafter or as clinically indicated; patients at risk of QTc prolongation (e.g. patients with hypokalaemia, hypomagnesaemia, congenital long QT syndrome, with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia; patients taking anti-arrhythmic drugs or other drugs that may lead to QT prolongation); ECG is recommended prior to treatment, repeat after 7 days and as clinically indicated; correct hypokalaemia or hypomagnesaemia prior to treatment; uncommon cases of cardiovascular events included peripheral arterial events were reported in 48 month extended follow-up trial in newly diagnosed CML patients and observed in the post-marketing reports. Grade 3/4 cases of cardiovascular events included peripheral arterial thrombosis, stroke, non-fatal myocardial infarction, non-fatal heart failure, other coronary events, sudden death.

Monitoring of response to therapy in Ph+ CML should guide appropriate CML management.
Editorial

1249 Pill testing at music festivals: can we do more harm?
J. Schneider, P. Galettis, M. Williams, C. Lucas and J. H. Martin

Review

1252 Management of diabetes in Indigenous communities: lessons from the Australian Aboriginal population
M. D. Ngam, S. Chutter and L. J. Maple-Brown

Clinical Perspectives

1259 Alcohol use disorders in Australia
C. H. Freyer, K. C. Morley and P. S. Haber

Original Articles

1269 Clinical trials of medicinal cannabis for appetite-related symptoms from advanced cancer: a survey of preferences, attitudes and beliefs among patients willing to consider participation

1276 The revolving door: antibiotic allergy labelling in a tertiary care centre

1284 Determining the efficacy of the chronic disease self-management programme and readability of “living a healthy life with chronic conditions” in a New Zealand setting
J. F. Cheng, F. Areenhold and A. J. Broadhurst

1291 Benefit from cytoreductive nephrectomy and the prognostic role of neutrophil-to-lymphocyte ratio in patients with metastatic renal cell carcinoma
D. Day, V. Karpasapan, E. Ikram, Y. Yip, N. Lawrentschuk, J. D. Dunn, A. A. Azad, S. Wong, M. Rosenfeld, G. Gibbs and B. Yone

1297 Heart failure following cancer treatment: characteristics, survival and mortality of a linked health data analysis
R. A. Clark, N. M. Berry, M. H. Chowdhury, A. L. McCarthy, S. Ullah, V. L. Versace, J. J. Atherton, B. Koczwara and D. Roder

1306 Utility of surgical lung biopsy in critically ill patients with diffuse pulmonary infiltrates: a retrospective review
L. H. Donaldson, A. J. Gill and M. Hibbert

1318 Detection and clinical significance of glomerular M-type phospholipase A₂ receptor in patients with idiopathic membranous nephropathy
H. Lu, W. Lao, S. Gong and X. Ding

1323 Introduction of New South Wales adult subcutaneous insulin-prescribing chart in a tertiary hospital: its impact on inpatient glycemic control
V. Y. Weng, A. He, E. Foden, N. S. Luna and H. Rassell

Brief Communications

1328 Rates of neutropenia in adults with influenza A or B: a retrospective analysis of hospitalised patients in South East Queensland during 2015
P. Higgins, N. Banagan, R. J. Bird and K. A. Martin

1332 Use of computed tomography abdomen and pelvis for investigation of febrile neutropenia in adult haematology patients
H. Y. Lim, M. Ashley, B. Williams and A. Gigg

1336 Beta-blockers are under-prescribed in patients with chronic obstructive pulmonary disease and co-morbid cardiac disease
P. A. Niel, C. F. McInnes, L. M. Barrall, L. B. Irving, D. F. Johnson and D. P. St.review

1340 Pharyngoesophageal dysphagia: an under recognised, potentially fatal, but very treatable feature of systemic sclerosis
C. Rajapakse

Letters to the Editor

1345 Concomitant plasmapheresis and cladribine infusion for the treatment of life-threatening systemic lupus erythematosus
W. P. Delacruz, A. Cap and N. Shumway

1346 Large volume subcutaneous lymphoedema drainage
S. Hrypa and J. B. Hardy

1347 Visceral leishmaniasis triggering (mimicking) macrophage activation syndrome in a patient with adult onset Still disease
M. Barešic, G. E. Janka, K. Gjadrov-Kuveždic, Š. Zekan and B. Anić

General correspondence

1349 Family escalation of care: well meaning, but where’s the evidence
A. Stills

1350 A hybrid of conventional medical terminology and patient-friendly terminology
P. Rege

Diabetes in Indigenous Australians
Alcohol use disorders
Medicinal cannabis and advanced cancer: clinical trials
Antibiotic allergy labelling
Heart failure after cancer treatment
Pharyngoesophageal dysphagia and systemic sclerosis