Editorial

123 Chronic kidney disease in disadvantaged populations
G. García-García and V. Ion on behalf of the World Kidney Day Steering Committee

Clinical Perspectives

134 Deep brain stimulation for Parkinson disease in Australia: current scientific and clinical status
P. C. Poortvliet, P. A. Silburn, T. J. Coyne and H. J. Chernay

Original Articles

140 Early and late changes in markers of aortic stiffness with breast cancer therapy

148 Enteric fever in the Pacific: a regional retrospective study from Auckland, New Zealand

155 Characteristics favouring a delayed disposition decision in the emergency department
L. Perimal-Lewis, P. H. Hakendorf and C. H. Thompson

160 Epidemiology, disease burden and outcomes of cirrhosis in a large secondary care hospital in South Auckland, New Zealand
J. C. Huang, W. W. Bai, K. Ruan, W. Stubbieke, A. Upton, S. Selvaratnam, E. J. Gane and S. J. Gerred

170 Dose tailoring of anti-tumour necrosis factor-alpha therapy delivers useful clinical efficacy in Crohn disease patients experiencing loss of response

177 Management and outcomes of axial isolated distal deep vein thrombosis at North Shore Hospital, New Zealand: a retrospective audit
A. Y. Li, T. Woold, V. Babu-Vyom, V. Rosland, D. Simon and E. Merriman

183 Prevalence of prediabetes in patients with acute coronary syndrome: impact on in-hospital outcomes
M. M. AbuShady, Y. Mahamad, B. Enway and W. Namas

189 Comprehensive dietary education in treated gout patients does not further improve serum urate
B. Holland and N. W. McGill

203 Clinical outcome of drug-eluting versus bare-metal stents in patients with calcified coronary lesions: a meta-analysis
B.-C. Zhang, C. Wang, W.-H. Li and D.-Y. Li

Brief Communications

211 Haemostatic hyponatraemia: a case series at a single Victorian tertiary centre during January 2014
S. A. Yang, D. A. Reid and A. E. Tiber

214 Treatment of refractory sternal varicose haemorrhage with embolisation and sclerosis
V. Valaydon and P. Devnon

218 Delayed onset of benign pleural effusion following concurrent chemoradiotherapy for inoperable non-small-cell lung cancer

Personal Viewpoint

221 No payments, copayments and faux payments: are medical practitioners adequately equipped to manage Medicare claiming and compliance?
M. A. Farn, J. L. Nettle and J. Adams

Letters to the Editor

Clinical-scientific notes

228 Non-enhancing subcortical white matter lesions in central nervous system Listeriosis
A. Salonga-Beyes, M. S. Babu, S. Bhuta, S. Bradley and A. Jones

230 Effective treatment of Kaposi sarcoma with everolimus in a patient with membranous glomerulonephritis

231 Drug safety in Aboriginal Australians: three cases of angiotensin-converting enzyme inhibitor angioedema
H. Maltajan, T. Thynne, G. M. Galb and E. W. Poh

General correspondence

233 Vancomycin vintage: my favourite DRESS
T. M. Korman, J. D. Turnidge and M. L. Grayson

234 Author reply

235 Access to ‘investigational’ cancer drugs: perspective of a trainee
J. C. Koo

Corrigendum

236

INTERNAL MEDICINE JOURNAL

Volume 45 Issue 2 February 2015

Advances in ankylosing spondylitis and axial spondyloarthritis

Deep brain stimulation for Parkinson disease

Breast cancer therapy: markers of aortic stiffness

Enteric fever in the Pacific

Axial isolated distal deep venous thrombosis

Dose tailoring of anti TNF-α therapy
Editor-in-Chief
Jeff Szer, Melbourne

Continuing Education

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
Paul Middleton, Sydney
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 McLintock, 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
Damienn 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
Louise Young-Wilson, 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)
Soliris® (eculizumab, rmc) is now PBS (Section 100) listed for the treatment of aHUS*1

IN PATIENTS WITH aHUS, SOLIRIS:
• Inhibits complement-mediated TMA2
• Protects vital organs against the risk of TMA3
• Soliris therapy resulted in rapid and sustained reduction of complement-mediated haemolytic activity3
• Ongoing Soliris treatment resulted in significant and continued improvement in renal function1

Early intervention with Soliris in aHUS is vital in maximising clinical benefit3

Soliris in aHUS · Targets the cause · Protects vital organs · Transforms lives2

*SOLIRIS IS THE ONLY TGA APPROVED TREATMENT FOR aHUS2

*For details of the PBS Section 100 eligibility criteria for aHUS, contact Medical Information at Alexion. Telephone 02 9091 0500 or email alexion.australia@alxn.com

aHUS = atypical Haemolytic Uraemic Syndrome. TMA = Thrombomicroangiopathy.
**WARNING: SERIOUS MENINGOCOCCAL INFECTION**

SOLIRIS increases the risk of meningococcal infections

- Vaccinate patients with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of SOLIRIS; revaccinate according to current medical guidelines for vaccine use.
- Patients less than 2 years of age and those who are treated with SOLIRIS less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary.

**SOLIRIS** (eculizumab, rmc) Minimum Product Information. **INDICATION:** Treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) to reduce haemolysis and patients with atypical haemolytic uraemic syndrome (aHUS). **CONTRAINDICATIONS:** Hypersensitivity to eculizumab, murine proteins or excipients. Do not initiate in PNH patients with unresolved Neisseria meningitidis infection or who are not currently vaccinated against Neisseria meningitidis. Do not initiate in aHUS patients with unresolved Neisseria meningitidis infection, who are not currently vaccinated against Neisseria meningitidis or who do not receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. **PRECAUTIONS:** Meningococcal Infection – see Boxed Warning – Provide patients with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of SOLIRIS; revaccinate according to current medical guidelines for vaccine use. Other Systemic Infections – Patients may have increased susceptibility to infections, especially with encapsulated bacteria. Administer with caution to patients with active systemic infections. Provide patients with information from the CMI to increase their awareness of potential serious infections and the signs and symptoms of them. **Discontinuation** – Closely monitor any PNH patient who discontinues treatment for at least 8 weeks to detect serious intravascular haemolysis and other reactions. Closely monitor any aHUS patient who discontinues treatment for at least 12 weeks to detect serious thrombotic microangiopathy complications. **Anticoagulation Therapy** – SOLIRIS® should not alter anticoagulant management. **PNH Laboratory Monitoring** – Measure serum LDH levels, monitor for signs and symptoms of intravascular haemolysis. **Monitoring of Potential Serious Infections** – Consider thrombocytopenia to be a sign of serious infection. **Haemophilia A and B** – Administer with caution to patients with haemophilia A or B. **Other** – Patients with a history of severe allergic reaction to eculizumab should not receive SOLIRIS. **DOSAGE AND ADMINISTRATION:** See Section 3.5. **ADVERSE EFFECTS:** Common: Headache, dizziness, nausea, pyrexia, infection, leucopenia. Most serious adverse reaction in clinical trials was meningococcal infection. In aHUS patients aged < 12 years of age: diarrhoea, vomiting, pyrexia, upper respiratory tract infection and headache. **DOSE AND ADMINISTRATION:** Patients must be administered a meningococcal vaccine at least 2 weeks prior to initiation of therapy or receive prophylactic antibiotic treatment for at least 2 weeks after vaccination. Patients must be revaccinated according to current medical guidelines for vaccine use. **DOSAGE in PNH** – 600 mg every 7 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 days later, then 900 mg every 14 days thereafter. Administer at the recommended regimen time points or within two days of these time points. **DOSAGE in aHUS** – Adults (≥ 18 years of age): 900 mg every 7 days for the first 4 weeks, followed by 1200 mg for the fifth dose 7 days later, then 1200 mg every 14 days thereafter. Administer at the recommended time points or within two days of these time points. **Administration:** Dilute to a final concentration of 5 mg/mL according to recommendations in the full PI. Do not administer as an intravenous push or bolus injection. Administer by intravenous infusion over 25 to 45 minutes via gravity feed, a syringe-type pump, or infusion pump. If an adverse reaction occurs, the infusion may be slowed or stopped at the discretion of the physician. Total infusion time should not exceed two hours following completion of the infusion for signs of an infusion reaction. To reduce the microbiological hazard, use as soon as practicable after preparation. If necessary, hold at 2° to 8°C for not more than 24 hours. **Applications and Consent Forms:** Application and consent forms for SOLIRIS treatment are available from the LSDP website: http://www.health.gov.au/lspd#/Eculizumab

Please refer to the Australian Product Information for Soliris (eculizumab, rmc) before prescribing Soliris, including Boxed WARNING regarding serious meningococcal infection. Please contact Alexion Pharmaceuticals Australasia Pty Ltd on 1800 788 189 to request the Full Product Information.

PBS Information: This product is listed on the PBS as a Section 100 item for the treatment of aHUS. Refer to PBS Schedule for full authority information.

Soliris (eculizumab) is funded on the Life Saving Drug Program for the treatment of PNH. Application and consent forms for Soliris treatment are available from the LSDP website: http://www.health.gov.au/lspd#Eculizumab

BREAKING BOUNDARIES CREATING CONNECTIONS

RACP CONGRESS CAIRNS 24–27 MAY 2015

INTERACT, DEBATE, CONNECT.
JOIN US IN TROPICAL NORTH QUEENSLAND.

FIND OUT MORE
WWW.RACPCONGRESS2015.COM
OR USE THE QR CODE
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-0000-2014).
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.

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)
VFEND® (voriconazole) 50/200mg tablets. 200mg powder for injection, 40mg/mL powder for oral suspension. Indications: Invasive aspergillosis; serious Candida, Scedosporium spp, Fusarium spp infections; other serious fungal infections in patients intolerant/refractory to other therapy. Prophylaxis in patients at high risk of developing invasive fungal infections. Contraindications: Hypersensitivity to drug/excipients, concomitant pimozide, quinidine, *rifabutin, rifampicin, carbamazepine, long-acting barbiturates, ≥400mg once daily efavirenz, high dose (≥400mg bd) ritonavir, ergot alkaloids, sirolimus, St John’s Wort. Precautions: Hypersensitivity to azoles proarrhythmic conditions; anaphylactoid type reactions during infusion (cease if severe); electrolyte disturbances (correct before treatment); monitor for hepatic/renal/pancreatic function; photosensitivity; skin reactions; other risk factors for malignant skin lesions; periodic visual disturbances, prolonged visual adverse events; safety/effectiveness not established in children <2 years; concomitant short acting opiates, long acting opiates, everolimus, fluconazole, phenytoin or low dose (100mg bd) ritonavir (do risk/benefit); NSAIDs; other concomitant medications; Lapp lactase deficiency, fructose intolerance, sucrase-isomaltase deficiency or glucose-galactose malabsorption; patients on low sodium diet; pregnancy Category B3; ensure contraception in women of child-bearing potential; lactation; driving; operating machinery. See full PI for details.

Adverse Effects: Common: visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, abdominal pain. See full PI for details.

Dosage and Administration: Adults/adolescents: IV 6mg/kg q 12h (first 24 hours) then 3–4mg/kg q 12h, or orally 200–400mg q 12h (first 24 hrs) then 100-200mg bd depending on indication & body weight. *Prophylaxis: IV 6mg/kg q 12h (first 24 hrs), then 4mg/kg q 12h or orally 100–200mg bd depending on indication & body weight. Children 2-12 yrs; initiate therapy with 6mg/kg IV bd. Refer to PI for full dosing schedule. V010113.

Editorial

123 Chronic kidney disease in disadvantaged populations
G. Garcia-Garcia and V. Jha on behalf of the World Kidney Day Steering Committee

Review

127 Advances in classification, basic mechanisms and clinical science in ankylosing spondylitis and axial spondyloarthritis
P. C. Robinson and H. Benham

Clinical Perspectives

134 Deep brain stimulation for Parkinson disease in Australia: current scientific and clinical status
P. C. Poortvliet, P. A. Silburn, T. J. Coyne and H. J. Chenery

Original Articles

140 Early and late changes in markers of aortic stiffness with breast cancer therapy

148 Enteric fever in the Pacific: a regional retrospective study from Auckland, New Zealand

155 Characteristics favouring a delayed disposition decision in the emergency department
L. Perimal-Lewis, P. H. Hakendorf and C. H. Thompson

160 Epidemiology, disease burden and outcomes of cirrhosis in a large secondary care hospital in South Auckland, New Zealand
J. C. Hsiang, W. W. Bai, Z. Raos, W. Stableforth, A. Upton, S. Selvaratnam, E. J. Gane and S. J. Gerred

170 Dose tailoring of anti-tumour necrosis factor-alpha therapy delivers useful clinical efficacy in Crohn disease patients experiencing loss of response

177 Management and outcomes of axial isolated distal deep vein thrombosis at North Shore Hospital, New Zealand: a retrospective audit
A. Y. Li, T. Woulfe, V. Rolfe-Vyson, V. Rowland, D. Simpson and E. Merriman

183 Prevalence of prediabetes in patients with acute coronary syndrome: impact on in-hospital outcomes
M. M. AbuShady, Y. Mohamady, B. Enany and W. Nammas

189 Comprehensive dietary education in treated gout patients does not further improve serum urate
R. Holland and N. W. McGill
Share your wealth of knowledge
Submit your manuscript today

Internal Medicine Journal
The Official Journal of the Adult Medicine Division of The Royal Australasian College of Physicians (RACP)

Internal Medicine Journal actively recruits influential and topical material in all areas of medical practice and science for their upcoming publications. You are invited to submit your original medical research, whether it be laboratory and clinical, for consideration today.

To view author guidelines visit the Journal homepage at www.wileyonlinelibrary.com/journal/imj

Edited by: Jeff Szer
Print ISSN: 1444-0903
Online ISSN: 1445-5994
Frequency: Monthly
Impact Factor (2009): 1.786

Submit your manuscript online at:
http://mc.manuscriptcentral.com/imj
195 Hyponatraemia at hospital admission is a predictor of overall mortality
L. Balling, F. Gustafsson, J. P. Goetze, M. Dalsgaard, H. Nielsen, S. Boesgaard, M. Bay, V. Kirk, O. W. Nielsen, L. Køber and K. Iversen

203 Clinical outcome of drug-eluting versus bare-metal stents in patients with calcified coronary lesions: a meta-analysis
B.-C. Zhang, C. Wang, W.-H. Li and D.-Y. Li

Brief Communications

211 Heatwave hyponatraemia: a case series at a single Victorian tertiary centre during January 2014
S. A. Yong, D. A. Reid and A. E. Tobin

214 Treatment of refractory stomal variceal haemorrhage with embolisation and sclerosis
Z. Valaydon and P. Desmond

218 Delayed onset of benign pleural effusion following concurrent chemoradiotherapy for inoperable non-small-cell lung cancer

Personal Viewpoint

221 No payments, copayments and faux payments: are medical practitioners adequately equipped to manage Medicare claiming and compliance?
M. A. Faux, J. L. Wardle and J. Adams

Letters to the Editor

Clinical-scientific notes

228 Non-enhancing subcortical white matter lesions in central nervous system Listeriosis
A. Salonga-Reyes, M. S Badve, S. Bhuta, S. Broadley and A. Jones

230 Effective treatment of Kaposi sarcoma with everolimus in a patient with membranous glomerulonephritis

231 Drug safety in Aboriginal Australians: three cases of angiotensin-converting enzyme inhibitor angioedema
H. Mahajan, T. Thynne, G. M. Gabb and E. W. Poh

General correspondence

233 Vancomycin vintage: my favourite DRESS
T. M. Korman, J. D. Turnidge and M. L. Grayson

234 Author reply

235 Access to ‘investigational’ cancer drugs: perspective of a trainee
J. C. Kuo

236 Corrigendum
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
EDITORIAL

Chronic kidney disease in disadvantaged populations

Of all of the forms of inequality, injustice in health is the most shocking and inhumane.

Dr Martin Luther King, Jr

The 12 March 2015 will mark the 10th anniversary of World Kidney Day (WKD), an initiative of the International Society of Nephrology and the International Federation of Kidney Foundations. Since its inception in 2006, WKD has become the most successful effort ever mounted to raise awareness among decision makers and the general public about the importance of kidney disease. Each year WKD reminds us that kidney disease is common, harmful and treatable. The focus of WKD 2015 is on chronic kidney disease (CKD) in disadvantaged populations. This article reviews the key links between poverty and CKD and the consequent implications for the prevention of kidney disease and the care of kidney patients in these populations.

CKD is increasingly recognised as a global public health problem and a key determinant of the poor health outcomes. There is compelling evidence that disadvantaged communities, that is, those from low resource, racial and minority ethnic communities, and/or indigenous and socially disadvantaged backgrounds, suffer from marked increases in the burden of unrecognised and untreated CKD. Although the entire populations of some low- and middle-income countries could be considered disadvantaged, further discrimination on the basis of local factors creates a position of extreme disadvantage for certain population groups (subsistence farmers, those living in some rural areas, women, the elderly, religious minorities, etc). The fact that even in developed countries, racial and ethnic minorities bear a disproportionate burden of CKD and have worse outcomes suggests that there is much to learn beyond the traditional risk factors contributing to CKD-associated complications.

About 1.2 billion people live in extreme poverty worldwide. Poverty negatively influences healthy behaviours, healthcare access and environmental exposure, all of which contribute to healthcare disparities (Table 1). The poor are more susceptible to disease because of lack of access to goods and services, in particular clean water and sanitation, information about preventive behaviours, adequate nutrition and reduced access to healthcare.

CKD in developed countries

In the USA, ethnic minorities have a higher incidence of end-stage renal disease (ESRD). Despite similar prevalence rates for early stages of CKD, poor outcomes such as ESRD are 1.5–4 times higher among minorities (i.e. African-American, Hispanic and Native Americans). Poverty further increases the disparity in ESRD rates, with African-Americans being at greater risk. In the UK, rates of treated ESRD are higher in ethnic minority groups and with increasing social deprivation. Similarly in Singapore, the CKD prevalence is higher among Malays and Indians compared with the Chinese, with socioeconomic and behavioural factors accounting for 70–80% of the excess risk.

ESRD incidence is also higher among the less advantaged indigenous populations in developed countries. Canadian First Nations people experience ESRD at rates 2.5–4 times higher than the general population. In Australia, the increase in the number of indigenous people starting renal replacement therapy (RRT) over the past 25 years exceeded that of the non-indigenous population by 3.5-fold, largely because of a disproportionate (>10-fold) difference in ESRD due to type II diabetic nephropathy, a disease largely attributable to lifestyle issues, such as poor nutrition and lack of exercise. Indigenous populations also have a higher incidence of ESRD because of glomerulonephritis and hypertension. Compared with the US general population, the ESRD incidence rate is higher in Guam and Hawaii, where the proportion of indigenous people is high, again driven primarily by diabetic ESRD. Native Americans have a greater prevalence of albuminuria and higher ESRD incidence rate. Nearly three quarters of all incident ESRD cases among this population have been attributable to type II diabetes.

CKD in developing countries

Poverty-related factors such as infectious diseases secondary to poor sanitation, inadequate supply of safe water, environmental pollutants and high concentrations of disease-transmitting vectors continue to play an important role in the development of CKD in low-income
countries. Although rates of diabetic nephropathy are rising, chronic glomerulonephritis and interstitial nephritis are among the principal causes of CKD in many countries. Of note is the emergence of HIV-associated nephropathy as the major cause of CKD in sub-Saharan Africa. A high prevalence of CKD of unknown aetiology has been reported in rural agricultural communities from Central America, Egypt, India and Sri Lanka. Male farm workers are affected disproportionately, and the clinical presentation is suggestive of interstitial nephritis, confirmed on renal biopsies. The strong association with farm work has led to suggestions that exposure to agrochemicals, dehydration and consumption of contaminated water might be responsible. Additionally, the use of traditional herbal medications is common and frequently associated with CKD among the poor. In Mexico, CKD prevalence among the poor is twofold to threefold higher than the general population, and the aetiology is unknown in 30% of ESRD patients.

**Low birth weight and risk of CKD in the disadvantaged populations**

An association between low birth weight (LBW) due primarily to nutritional factors and kidney disease has been described in disadvantaged populations. The frequency of LBW is more than double in the Aboriginal population than in the non-Aboriginal population of Australia. The high prevalence of albuminuria in this population has been linked to low nephron number related to LBW. Morphometric studies of kidney biopsies in the Aboriginals show glomerulomegaly, perhaps secondary to nephron deficiency, which might predispose to glomerulosclerosis. A correlation between LBW and CKD has also been described in poor African-Americans and Caucasians living in the Southeastern USA. Similarly, in an Indian cohort, LBW and early malnutrition were associated with later development of metabolic syndrome, diabetes and diabetic nephropathy. The finding of a high prevalence of proteinuria, elevated blood pressure and CKD of unknown aetiology in South Asian children may also be explained by this mechanism.

**Disparities in access to RRT**

A recent analysis shows that globally, there were 2.6 million people on dialysis in 2010, 93% in high- or upper-middle-income countries. By contrast, the number of people requiring RRT was estimated at 4.9–9 million, suggesting that at least 2.3 million died prematurely because of lack of access to RRT. Even though diabetes and hypertension increase the burden of CKD, the current provision of RRT is linked largely to two factors: per capita GNP and age. suggesting that poverty is a major disadvantage for receiving RRT. By 2030, the number of people receiving RRT around the world is projected to increase to 5.4 million. Most of this increase will be in developing countries of Asia and Africa (T. Liyanage et al.; unpubl. data, 2014).

Access to RRT in the emerging world is dependent mostly on the healthcare expenditures and economic strength of individual countries, with the relationship between income and access to RRT being almost linear in low- and middle-income countries. In Latin America, RRT prevalence and kidney transplantation rates correlate significantly with gross national income and health expenditure, while in India and Pakistan, less than 10% of all ESRD patients have access to RRT. Additionally, developing countries have low transplant rates because of a combination of low levels of infrastructure; geographical remoteness; lack of legislation governing brain death; religious, cultural and social constraints; and commercial incentives that favour dialysis.

There are also differences in utilisation of renal replacement modalities between indigenous and non-indigenous groups in the developed countries. In Australia and New Zealand, the proportion of people receiving home dialysis is considerably lower among indigenous people. At the end of 2007 in Australia, 33% of non-indigenous people requiring RRT were receiving home-based dialysis therapies, in contrast to 18% of Aboriginal people. In New Zealand, home-based dialysis was utilised by 62% of non-indigenous RRT population but only by 42% of Maori/Pacific Islanders. The rate of kidney transplantation is also lower among disadvantaged communities. Maori and Pacific people are only

---

**Table 1** Possible mechanisms by which poverty increases the burden of disease

<table>
<thead>
<tr>
<th>Health behaviour</th>
<th>Access to healthcare</th>
<th>Biological factors</th>
<th>Environmental factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lack of information on preventive behaviours</td>
<td>• Lack of access to healthcare providers</td>
<td>• Low birth weight</td>
<td>• Increased exposure to pollutants</td>
</tr>
<tr>
<td>• Lack of knowledge on how best to respond to an episode of illness</td>
<td>• Greater distance from healthcare providers</td>
<td>• Genetic predisposition</td>
<td>• Increased exposure to communicable diseases</td>
</tr>
<tr>
<td>• Health beliefs and unhealthy behaviours</td>
<td>• Lack of out-of-pocket resources</td>
<td>• Cumulative biological risk profiles</td>
<td>• Lack of clean water and sanitation</td>
</tr>
<tr>
<td>• Lack of access to preventive health services</td>
<td>• Inadequate nutrition</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2015 Royal Australasian College of Physicians
25% as likely to get a transplant as European New Zealanders, and the proportion of indigenous people who underwent transplantation and had a functioning kidney transplant is lower among Aboriginal Australians (12%) compared with non-indigenous Australians (45%). In the UK, white individuals from socially deprived areas, South Asians and blacks were all less likely to receive a pre-emptive renal transplant or living donor transplants than their more affluent white counterparts. A multinational study found that when compared with white patients, the likelihood of receiving a transplant for Aboriginal patients was 77% lower in Australia and New Zealand, and 66% lower in Canadian First Nations individuals. Disparities in renal care are more evident in developing nations. Data from India show that there are fewer nephrologists and nephrology services in the poorer states. As a result, people living in these states are likely to receive less care. In Mexico, the fragmentation of the healthcare system has resulted in unequal access to RRT. In the state of Jalisco, the acceptance and prevalence rates in the more economically advantaged insured population were higher (327 pmp and 939 pmp, respectively) than for patients without medical insurance (99 pmp and 166 pmp, respectively). The transplant rate also was dramatically different, at 72 pmp for those with health insurance and 7.5 pmp for those without it.

The bidirectional relationship between poverty and CKD

In addition to having a higher disease burden, the poor have limited access to resources for meeting the treatment costs. A large proportion of patients who are forced to meet the expensive ESRD treatment costs by incurring out-of-pocket expenditure get pushed into extreme poverty. In one Indian study, over 70% patients undergoing kidney transplantation experienced catastrophic healthcare expenditures. Entire families felt the impact of this, including job losses and interruptions in education of children.

Outcomes

Overall, mortality rates among those who do receive RRT are higher in the indigenous, minorities and the uninsured populations, even after adjustment for comorbidities. The hazard ratios for death on dialysis relative to the non-indigenous group are 1.4 for Aboriginal Australians and New Zealand Maori. The Canadian First Nations patients achieve target levels for blood pressure and mineral metabolism less frequently. In the USA, living in predominantly black neighbourhoods was associated with higher than expected mortality rates on dialysis and increased time to transplantation. Similarly, black patients on peritoneal dialysis had a higher risk of death or technique failure compared with whites.

In Mexico, the mortality on peritoneal dialysis is threefold higher among the uninsured population compared with Mexican patients receiving treatment in the USA, and the survival rate is significantly lower than the insured Mexican population, while in India almost two thirds of the patients are unable to continue dialysis beyond the first 3 months because of financial reasons.

Summary

The increased burden of CKD in disadvantaged populations is due to both global factors and population-specific issues. Low socioeconomic status and poor access to care contribute to healthcare disparities and exacerbate the negative effects of genetic or biologic predisposition. Provision of appropriate renal care to these populations requires a two-pronged approach: expanding the reach of dialysis through development of low-cost alternatives that can be practised in remote locations, and implementation and evaluation of cost-effective prevention strategies. Kidney transplantation should be promoted by expanding deceased donor transplant programmes and use of inexpensive, generic immunosuppressive drugs. The message of WKD 2015 is that a concerted attack against the diseases that lead to ESRD, by increasing community outreach, better education, improved economic opportunity and access to preventive medicine for those at highest risk, could end the unacceptable relationship between CKD and disadvantage in these communities.
Editorial

References


Advances in classification, basic mechanisms and clinical science in ankylosing spondylitis and axial spondyloarthritis

P. C. Robinson1,2 and H. Benham1,2,3

1University of Queensland Diamantina Institute, Translational Research Institute, 2Department of Rheumatology, Princess Alexandra Hospital and 3Department of Medicine, University of Queensland School of Medicine, Brisbane, Queensland, Australia

Key words
spondyloarthritis, axial spondyloarthritis, ankylosing spondylitis, anti-TNF, magnetic resonance imaging, classification criteria.

Abstract
The field of spondyloarthritis (SpA) has seen huge advances over the past 5 years. The classification of axial disease has been redefined by the axial SpA criteria that incorporate disease captured before radiographic damage is evident as well as established erosive sacroiliac joint disease. Our knowledge of genetics and basic immunological pathways has progressed significantly. In addition, revolutionary progress has been achieved with the availability of tumour necrosis factor inhibitors for treating patients with moderate to severe disease. In parallel, several of novel biomarkers have been identified that show significant promise for the future. Advances in magnetic resonance imaging have helped define positive disease. We have identified that T1 and short tau inversion recovery sequences are best for the diagnosis of axial SpA, and gadolinium contrast is not additive for diagnosis. Progress has been made in identifying potential agents and strategies that reduce radiographic progression. Several referral strategies aimed at appropriate identification of patients have been trialled and found to be effective. There is still substantial work ahead, but the advances of the last 5 years have made a huge and tangible difference at the clinical coalface, and we suggest that this trend will continue.

© 2014 Royal Australasian College of Physicians
Introduction

In the past 5 years, the field of spondyloarthritis (SpA) has seen significant progress. New classification criteria have been proposed and there have been significant advances in basic science and therapeutics. This progress is welcome as for decades little progress was made in treating this disease. This review aims to cover the significant advances in ankylosing spondylitis (AS) and axial SpA (axSpA), a term now being used to encompass AS and other forms of axSpA.

Classification

The classification of SpA has been, and continues to be, an area of significant interest and controversy.\(^1,2\) We currently lack a thorough understanding of the basic mechanisms of disease pathogenesis. Therefore, diagnosis and classification remain, at this present time, based primarily on signs and symptoms.

Initial classification criteria for SpA as a whole included the Amor criteria\(^1\) and European Spondyloarthiritis Study Group (ESSG) criteria.\(^4\) These criteria were designed to capture the entire spectrum of SpA, not purely axial disease. When measured against physician diagnosis as gold standard, the Amor and ESSG criteria have sensitivity and specificity of 87–90% each.\(^3\) These criteria have some scope to capture SpA earlier in its disease course, but their more general nature means that they are unable to identify specifically early axSpA.

There were always clearly patients who did not meet the mNY criteria but had active debilitating axSpA, and a proportion of these patients progress to mNY AS.\(^7\) With the stimulus of the introduction of tumour necrosis factor (TNF) inhibitors as effective treatments, a new classification system was proposed by Assessment of Spondylo-Arthritis International Society (ASAS) that aimed to capture both early and established disease.\(^6\) This introduced the concept of axSpA that includes two groups. The first is patients with mNY AS, and the second is patients who do not meet the mNY criteria but have classifiable disease called non-radiographic axSpA (nr-axSpA).

Patients can meet criteria for axSpA in two ways (Table 1): (i) by virtue of having plain film evidence of erosion (the same as for the mNY criteria) or magnetic resonance imaging (MRI) evidence of sacroiliac joint inflammation and one feature of SpA from a list of 11, such as psoriasis or anterior uveitis (‘imaging arm’); or (ii) by being human leucocyte antigen (HLA)-B27 positive and having two features of SpA, from a list of 10 (‘HLA-B27 arm’).

The ASAS axSpA criteria (both arms combined) against a physician gold standard have a sensitivity and specificity of 83% and 84% respectively. The imaging arm alone has a sensitivity of 66% and a specificity of 97%. This clearly demonstrates that positive imaging, be that with plain film or MRI, has high specificity but lacks sensitivity when assessed against physician gold standard. An interesting longitudinal study that performed MRI and sacroiliac joint biopsies in patients with early SpA and followed them up demonstrated that the sensitivity for MRI may not be as high as thought; the study suggested 31%. The SpA community has no experience with correlating histological sacroiliac joint inflammation and clinical symptoms so the actual clinical relevance of this finding is unclear.\(^9\)

The introduction of the axSpA criteria has demonstrated that there is a set of patients with disease that will not progress to mNY AS, as these cohorts have lower HLA-B27 carriage rates and more females compared with cohorts of established AS.\(^1,10\) It has enabled the identification of early disease that previously was not well captured and precipitated trials of effective agents such as anti-TNF in early disease, demonstrating...
excellent efficacy. Therefore, it seems that the field is moving towards the use of the term ‘axial spondyloarthritis’ instead of ‘ankylosing spondylitis’ to describe the wider axial disease group. However, AS will continue to be used to describe the more advanced form and provide homogenous groups for biological research.

**Basic science: genetics**

The genetics of AS has come a long way since the discovery of HLA-B27 in 1973. The advent of large-scale array-based genotyping, the genome wide association study (GWAS) and significant international collaboration now means that there are 41 independent genetic associations for AS. The salient features of these associations are the clustering in immunological pathways such as the interleukin-23 (IL-23), antigen processing and presentation, and lymphocyte development and activation. In addition, a genetic interaction has been identified between HLA-B27 and a gene that encodes an enzyme called endoplasmic reticulum aminopeptidase (ERAP1); this enzyme processes peptides prior to presentation on the cell surface on MHC class I molecules. Variants of ERAP1 only increase the risk of AS when HLA-B27 is present. In addition the same interaction is observed with HLA-B40, another AS associated HLA-B allele. These interactions strongly suggest that the mechanism by which HLA-B27 contributes to AS development is through its antigen presentation function. Whether it is presenting the wrong antigen, not presenting an antigen or changing the mix of presented antigens is wholly unclear. In fact, a newer theory suggests that HLA-B27 may contribute to disease pathogenesis in the setting of an ‘immunodeficient’ state. A summary of the current theories of how HLA-B27 might contribute to SpA pathogenesis is shown in Table 2.

The other interesting and important finding from the significant body of recent genetic research is the significant sharing of risk variants between immune-mediated diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus. This sharing is both concordant and discordant in that variants can at times be protective for one disease but increase risk for another disease. An excellent example is the TNFRSF1A variants that reduce risk in AS but increases risk for multiple sclerosis.

**Basic science: immunology**

Advances in genetic research have allowed for concurrent evolution in understanding the basic immunology underpinning the pathogenesis of SpA. GWAS studies have identified susceptibility genes common to SpA and associated conditions including psoriasis and IBD. Polymorphisms in these commonly shared genes impact innate immunity, antigen presentation and IL-23 modulated pathways in SpA disease development. IL-23 signalling appears pivotal in the pathogenesis of SpA. Human data demonstrate increased production and sensitivity to IL-23 and expansion of both adaptive and innate IL-23-responsive cells, within joints and the periphery of patients with various forms of SpA. However, the initial inflammatory and/or microbial stimulus resulting in IL-23 production, where anatomically this might occur, and how IL-23 drives SpA in genetically prone individuals has been puzzling.

Understanding the mechanisms of IL-23 signalling and subsequently the pathogenesis of SpA has been hindered by the lack of appropriate SpA animal models. However, a recent publication by Sherlock et al. utilising minicircle DNA technology to overexpress systemically IL-23 in B10.RIII mice resulted in the subsequent identification of a previously undescribed lineage of IL-23 responsive, resident entheseal T cells. This has been widely acknowledged as a significant advance. The entheseal cells identified are CD3 + CD4-CD8 + IL-23R + RORγt+ and show upregulated expression of both IL-17 and IL-22 (IL-23-dependent cytokines). This model provides an elegant link between enthesitis and systemic expression of IL-23, allowing further postulation that disease initiation in SpA may be linked to IL-23 produced at a distant site. Intriguingly, the mice were also shown to develop a psoriasis-like phenotype in the setting of the IL-23 overexpression, further linking Ps with IL-23 and SpA. In addition the CD3 + CD4-CD8 + IL-23R + RORγt- cells were shown to produce

---

**Table 2: Theories of how HLA-B27 could cause disease in axial spondyloarthritis**

<table>
<thead>
<tr>
<th>Theory</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritogenic peptide hypothesis</td>
<td>HLA-B27 presents a peptide to CD8 T cells through its classical presentation function contributing to the induction of disease</td>
</tr>
<tr>
<td>Endoplasmic reticulum stress theory</td>
<td>Properties of HLA-B27 results in protein misfolding in the endoplasmic reticulum and causes stress, subsequently inducing disease through IL-23 production and subsequent modulation of downstream pathways</td>
</tr>
<tr>
<td>Cell surface homodimer hypothesis</td>
<td>HLA-B27 forms homodimers on the cell surface that interact with innate immune cells to induce disease</td>
</tr>
<tr>
<td>Immunodeficiency hypothesis</td>
<td>HLA-B27 presents an altered type or number of peptides resulting in the immune system inadequately or inappropriately dealing with gut microbes</td>
</tr>
</tbody>
</table>

HLA, human leucocyte antigen; IL, interleukin.
IL-22 and subsequently activate STAT-3 dependent osteoblast-mediated bone remodelling at the enthesis. This IL-22 and STAT-3-dependent osteoproliferative effect at the enthesis recapitulates the characteristic disease phenotype seen in human SpA.

Leading on from this work, IL-23 signalling involving gut, joints and skin in SpA has been investigated in a further new animal model of SpA. Ruutu et al. demonstrated that BALB/c ZAP-70\(^{\text{T}}\) mice systemically exposed to \(\beta-1,3\)-glucan (curdlan) develop a disease closely resembling human SpA. After curdlan administration, SKG mice develop both axSpA and peripheral SpA, 50–60% develop small intestine inflammation reminiscent of human Crohn disease, 25% develop unilateral uveitis and all the mice develop psoriasis-like skin inflammation. Inhibition of IL-23 in the curdlan-treated SKG mice suppresses the development of SpA (both axial and peripheral arthritis) and the ileitis. Interestingly, IL-23 is secreted by the gut in response to curdlan and promotes endoplasmic reticulum stress and proinflammatory cytokine production locally while altering intestinal mucosal barrier integrity.

These recent data highlight that the development of SpA may be driven by microbial stimuli and likely involve multiple IL-23-mediated downstream pathways at various tissue sites in genetically predisposed individuals. The field remains enthusiastic towards the development of therapeutics targeting IL-23-responsive cells or their generation to improve clinical outcomes for patients with SpA.

**Clinical science**

The introduction of anti-TNF agents into clinical practice was a landmark in the treatment of axSpA. Since that time, there have been several compounds trialled that have shown promise and several that have not. Originating from the discovery of the involvement of IL-17 and IL-23 in SpA monoclonal antibodies to these agents have been trialled in axSpA patients. Both of these agents have shown promise in phase 2 trials. However, one caveat with the use of anti-IL-17 in axSpA is the observation that it worsens IBD. Around 60–70% of axSpA patients have either overt or subclinical IBD, and therefore this may substantially curtail the use of this agent for axSpA treatment unless a biomarker or other means to stratify patients is found. Unfortunately, trials of anti-CD20 therapy (rituximab) only showed efficacy in those who had not failed anti-TNF therapy in a small trial. This suggests that failure of anti-TNF agents marks a slightly different biological subtype of disease. A trial of the co-stimulatory blocking agent CTLA-Ig (abatacept) in 30 patients failed to show a major response. Two agents targeting IL-6 agents (tocilizumab and sarilumab) and an anti-IL-1 agent (anakinra) have also been tested in small trials and failed to show significant efficacy. However, some individual patients have shown sustained responses to anakinra and sarilumab (P. Robinson, pers. obs., 2012). In addition, the phosphodiesterase 4 inhibitor apremilast showed encouraging results in phase 2 trials. Currently in trial is the janus kinase inhibitor tofacitinib in AS, and aminopeptidase inhibitors are in preclinical development. Therefore, it is likely that several of these new therapeutics will make it to the clinic in the next 5–10 years.

**MRI**

MRI is the technological advance that enables the recognition of axSpA at an early stage or in those who do not have erosive disease. Research has shown that T1 and short tau inversion recovery (STIR) sequences are best to demonstrate axSpA and that gadolinium contrast is not additive in making the diagnosis and is therefore not justified. Definitions of a positive sacroiliac joint scan have been proposed and include two discrete STIR lesions on the same slice or one STIR lesion that is observed on more than one slice. A positive spinal MRI is currently defined as three or more corner inflammatory lesions (osseitis), with each lesion having to be present on at least two slices. Work on including structural lesions like erosions in the ASAS definition is in progress. Finally, research examining the value of scanning the entire spine in addition to the sacroiliac joints in the diagnosis of nr-axSpA has shown that there is little additive value in the spine imaging. However, it should be noted that in daily clinical practice, the purpose of an MRI is not only to include or exclude SpA, but to diagnose chronic back pain.

**Referral strategies**

Referral strategies aimed at effective identification and referral of suspected axSpA have been trialled in multicentre randomised trials. These have shown in those patients with chronic back pain the presence of one item such as inflammatory back pain or HLA-B27 identifies 25–42% of patients. Increasing the complexity the referral algorithm did not significantly improve identification rates in one large German trial. Large-scale campaigns aimed at the public are also effective at increasing referral and diagnosis rates.

**Biomarkers**

Several biomarkers have shown some promise in identification of both axSpA from non-axSpA and poor prognosis disease in those with axSpA. These include vascular
endothelial growth factor, matrix metalloprotein 3, sclerostin, citrullinated vimentin, dikkopf-1 and antibodies to MHC class II-associated invariant chain.\textsuperscript{54–60} While identification of individual biomarkers is important, evaluating the capacity of panels of multiple biomarkers is required. Evaluation of these biomarker panels in several independent and longitudinal cohorts is required to determine their prognostic value in the clinical setting.

**Radiographic progression and the potential window of opportunity**

Observational cohort studies have shown that smoking, an elevated C-reactive protein (CRP), pre-existing syndesmophytes and being male all increase the risk of radiographic progression.\textsuperscript{61}

First described in 1973 with a drug called phenylbutazone, the potential for non-steroidal anti-inflammatory drugs (NSAIDs) to reduce radiographic progression has gained more credence with the increasing evidence base.\textsuperscript{62}

A 2-year randomised trial of celecoxib noted a significant difference in radiographic progression of the spine in those who took celecoxib regularly compared with those who took it as required. Supporting this is an additional observational report of NSAID’s ability to retard radiographic damage from the GESPIC cohort.\textsuperscript{63} A re-analysis of the celecoxib trial demonstrated that those with an elevated CRP had the most benefit from continuous NSAID therapy in regard to radiographic progression.\textsuperscript{64}

There is substantial circumstantial evidence that early effective treatment of inflammatory disease in axSpA could reduce radiographic progression – analogous to the ‘window of opportunity’ in rheumatoid arthritis.\textsuperscript{65} This stems from the substantial longitudinal MRI studies of anti-TNF drug therapy. In addition, two observational studies have suggested that anti-TNF reduces radiographic progression over the long term.\textsuperscript{66,67} Therefore, combined NSAID and anti-TNF therapy may be effective at significantly slowing or halting radiographic progression in patients. However, definitively demonstrating this is challenging, primarily because of the very slow baseline rate of radiographic progression. This is demonstrated by the difference observed in the 2-year celecoxib trial in the PRN dosing group (those that progressed the fastest); they progressed a mean of 1.5 modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) units, although the standard deviation was 2.5 mSASSS units.\textsuperscript{68} One mSASSS unit is erosion of one corner of a vertebrae, sclerosis or squaring of a vertebrae.\textsuperscript{69} This demonstrates the low average progression rate but a high level of variance between individuals, thereby requiring large sample sizes over a long time. The effect of newer agents on radiographic progression is unknown but will be of substantial interest. Their effect will help determine whether it is just suppression of inflammation or a specific biological action that helps reduce radiographic progression.

**Conclusion**

The advances in therapeutics have brought back to rheumatology clinics a huge cohort of patients who often felt there was little to be gained from visiting a rheumatologist. There are also several additional novel agents in the pipeline that may also join TNF inhibitors in the clinic in the near future. With huge recent gains made in both genetics research and in basic mechanisms of pathogenesis, coupled with improved classification criteria and diagnostic tools, the future looks bright.

**References**


Ankylosing spondylitis and HLA-A 27. 


43. de Hooge M, van den Berg R, Navarro-Compan V, van Gaalen F, van der Heijde D, Huizinga T et al. Magnetic resonance imaging of the sacroiliac joints in the early detection of spondyloarthritits: no added value of gadolinium compared with short tau...


© 2014 Royal Australasian College of Physicians
Deep brain stimulation for Parkinson disease in Australia: current scientific and clinical status

P. C. Poortvliet,1,2 P. A. Silburn,1 T. J. Coyne1 and H. J. Chenery1

1Asia-Pacific Centre for Neuromodulation, Centre for Clinical Research, 2Centre for Sensorimotor Performance, School of Human Movement and Nutrition Sciences, The University of Queensland, Brisbane, Queensland, Australia

Key words
deep brain stimulation, Parkinson disease, early stim, pedunculopontine nucleus, motor symptom, non-motor symptom.

Abstract
There is currently no cure for Parkinson disease (PD). Disease management is directed primarily at motor symptom relief, but the impact of non-motor symptoms associated with PD should not be underestimated. Medical and surgical treatment options aim to increase functional independence and quality of life. Deep brain stimulation (DBS) has proven to be a safe, effective and cost-efficient surgical treatment option. In 2009, the Australian referral guidelines, developed to provide a synopsis of DBS therapy for PD, were introduced, and since then novel findings have been reported regarding the timing of intervention, target selection and symptom management. Our aim is to provide an update of DBS for PD in Australia. Intervention at earlier stages of the disease can potentially improve quality of life over a longer period with greater possibilities for meaningful social and professional contributions. For less responsive motor symptoms (e.g. freezing of gait, postural instability), the pedunculopontine nucleus has emerged as a promising new surgical target. Traditional PD treatment is focused on improvement of motor symptoms, but the disorder is also characterised by non-motor symptoms, often undiagnosed or undisclosed, that have the potential to impact quality of life to a greater extent than motor symptoms. It is essential to identify and routinely monitor for non-motor symptoms as they can emerge at all stages of the disease or can result from treatment. Many of these current advances require long-term monitoring of treatment outcomes to improve future clinical practice, refine patient selection and ensure best patient outcomes.

Introduction
Parkinson disease (PD) is a progressive, neurodegenerative disorder, resulting in tremor, rigidity and bradykinesia as well as causing postural and gait disturbances. As such, PD reduces quality of life and functional status and increases dependence on care and assistance.1 Although commonly considered primarily a movement disorder, several significant non-motor symptoms are associated with the primary disease or are therapy induced, which collectively may impact on patient health and functional status. Prevalence reports of PD vary considerably, possibly due to a lack of definitive diagnostic tools and consequent underreporting of the disorder or differences in methodological estimation approaches. The latest report from 2011 estimated that around 64 000 Australians were affected by PD (approximately one in every 350 people) of which the majority (80%) were aged over 65 years.1 This number is predicted to double over the next two decades with the ageing Australian population. Even though PD is associated with older age, up to 19% of affected individuals were diagnosed between the working ages of 15 to 64 years, which led to a high risk of premature withdrawal from the workforce due to the increasing disease burden.1

Many of the cardinal symptoms of PD can be reduced by pharmacological or surgical treatment, thus greatly improving functional status and quality of life. Although dopaminergic medications have proven to be effective,
long-term treatment is associated with motor fluctuations, characterised by unpredictable responsiveness to medication (e.g. end of dose wearing off, longer ‘off’ times and delays in ‘on’ response), which may limit the therapeutic window and the eventual development of non-motor and motor complications as well as dyskinesias.2 These disabling effects not only affect the quality of life and wellness of the patient, but also have a significant impact on the caregiver as well as the community, due to the increasing dependence and need of care. In 2011, the total economic burden of disease was valued at $8.3 billion per year.2 For an overview of these costs by barer, see Table 1.

Introduced in Australia in 2001 as an non-destructive and reversible stereotactic procedure, deep brain stimulation (DBS) has evolved as a well-established, safe and effective surgical treatment option for advanced stage PD.2,3 The procedure consists of implantation of electrodes into specific uni- or bilateral deep brain targets, through which electrical stimulation is delivered (Fig. 1). The strength and frequency of stimulation can be flexibly programmed to the individual needs of the patient, to optimise treatment efficacy. Worldwide, DBS has proven effective for treatment of several disorders, including PD, and is under investigation as a treatment option for various novel indications by targeting different brain structures (Table 2). Most recently, DBS has received regulatory approval in Australia for refractory epilepsy and in most, but not all states for treatment-resistant obsessive-compulsive disorder. Since DBS for psychiatric disorders is considered psychosurgery under the state-based mental health legislation, it is prohibited in New South Wales and strictly regulated in Victoria for these purposes.4

In 2009, a panel of Australian neurosurgeons and neurologists developed the Australian referral guidelines for DBS, providing assistance for identification of potential patients with PD for DBS treatment.2 Several studies have since reported novel findings regarding new targets, timing of intervention and symptom management. Our aim is to provide an update of the current clinical status of DBS for the treatment of PD in Australia that considers recent scientific advances.

### Current status of DBS in Australia

Over 100,000 people have received DBS worldwide for a variety of indications,5 with growth projections for the global DBS market estimating that it will nearly double to $800 million from 2012 to 2016.6 In 2013, between 300 and 350 Australians were estimated to have received DBS for a variety of indications, although, at present PD remains the most common disorder for DBS intervention. Compared to conventional medical treatment, the initial cost of DBS treatment might seem substantial due to the cost of the surgical procedure and implanted device. However, Class 1 evidence has demonstrated that long-term DBS treatment for PD is more cost-effective than standard long-term medical treatment due to

<table>
<thead>
<tr>
<th>Barer</th>
<th>% of total financial cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Federal government</td>
<td>39</td>
</tr>
<tr>
<td>State government</td>
<td>16</td>
</tr>
<tr>
<td>Employers</td>
<td>2</td>
</tr>
<tr>
<td>Society</td>
<td>22</td>
</tr>
<tr>
<td>Household</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 1 The financial cost of Parkinson disease in 2011 by barer of the cost2

<table>
<thead>
<tr>
<th>Approved indications</th>
<th>Emerging indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson disease</td>
<td>Depression</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>Cluster headache</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Chronic pain syndromes</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>Obesity</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td></td>
<td>Tourette’s syndrome</td>
</tr>
</tbody>
</table>

Table 2 Overview of currently approved and novel indications for treatment with deep brain stimulation (DBS)
a decrease or discontinuation of PD medication and a reduction in symptoms and comorbidities leading to a decreased reliance on care, assistance and hospitalisation.7 There are currently 16 DBS clinics across Australia responsible for over 3000 DBS procedures since 2001.1 Many of the procedures are performed bilaterally with most implantations (including the pulse generators) performed during a single procedure.

**Advances in DBS over the last five years**

**Patient selection: intervention at earlier stages of the disease**

Although accuracy of electrode placement is necessary for the success of DBS treatment, it is alone insufficient for beneficial treatment outcomes. As indicated by the Australian referral guidelines, patient selection criteria are perhaps the first and the most crucial step in determining the success of DBS treatment for improving quality of life and alleviating symptoms.2 There are no age standards for DBS treatment; however, studies investigating intervention outcomes commonly report a mean patient age of 60 years and a mean disease duration of 12 years. Seminal studies reported successful outcomes of patients with advanced PD presenting with reduced responsiveness to medications, considerable fluctuations in ‘on-off’ times and severe motor complications.8,9 Furthermore, cognitive state and neuropsychological functioning, which can be more affected in older rather than younger patients, are routinely considered in the selection process.2 In addition, patients must be willing and able to attend regular clinical consultations for monitoring/programming of stimulation settings to optimise treatment efficacy. Patients are generally assessed on an individual basis to provide a tailored approach in maximising treatment outcomes and minimising (post) operative risks or negative outcomes.2 In general terms, potential candidates are considered for DBS when symptoms and/or quality of life are inadequately improved by medications, but are excluded when cognitive or psychiatric impairments or uncontrolled significant medical or surgical comorbidities are present.

One of the most important recent advances in DBS for PD is the shift to earlier stages of the disease. Recent Class I trials have reported beneficial patient outcomes when treated with DBS in the earlier stages of the disorder (mean age 52.5 years, disease duration >4 years).6–10 The rationale for a shift to earlier intervention is that patients benefit longer before the disease reaches a state in which neither DBS nor medications can improve symptoms.10 Further, earlier intervention could allow patients and their caregivers to return to meaningful social and productive professional participation.1 DBS has already proven to be a cost-effective treatment for advanced PD, and scenario analyses have shown that intervention at earlier stages could result in even greater cost-effectiveness due to reductions in pharmaceutical costs, reliance on professional care, therapy and specialist consultations.11 Long-term data from early-phase intervention are lacking, and therefore patients need to be monitored over prolonged periods to assess the long-term therapeutic outcomes in relation to quality of life and financial benefit.9,11

**Identification of new target structures**

The 2009 referral guidelines highlight that the decision to target a specific structure largely depends on the disease, type of symptoms and comorbidities.2 Three well-established targets were described for implantation of DBS electrodes in PD (Fig. 1). These include the subthalamic nucleus (STN), the globus pallidus internus (GPi) and the ventral intermediate nucleus of the thalamus (VIM). Some of these targets have proven more beneficial in effectively treating PD symptoms, resulting in fewer adverse treatment effects and/or reduced requirements for additional medication. For instance, the VIM has been used successfully to alleviate tremor dominant PD, but is less suitable as a target for bradykinesia and rigidity. Further, medication is rarely reduced with VIM DBS.2 Reduction in medication is advantageous when patients present with persistent medically refractory symptoms and/or medically induced adverse effects (e.g. dyskinesias, motor fluctuations, disabling ‘off’ periods and/or a variety of non-motor symptoms) despite optimal medical therapy. In a randomised control trial, STN stimulation was shown to be superior to standard medical PD therapy alone, reducing many symptoms with a concurrent significant reduction or even discontinuation of medications.12 There has been an ongoing debate whether GPi or STN is the more preferable target for treatment of PD symptoms, and several small studies have reported results favoring either target. Recently, results from three large randomised controlled trials have shown comparable maintained improvements of motor function as assessed by the Unified Parkinson Disease Rating Scale (UPDRS)13,14 and a generic disability scale (Academic Medical Center Linear Disability Score)15 when directly comparing bilateral stimulation for both targets. In addition, no difference in adverse events was observed between targets. Differences between targets were mainly observed in secondary outcomes, with two studies reporting significant reductions in medication, as
well as lower stimulation settings (amplitudes and pulse widths) following STN DBS, while dyskinesias were more effectively reduced following 1 year of GPi DBS without change to medication. Further, the risk of neuropsychological complications was reported no worse or slightly higher for STN DBS than GPi DBS after 2 years. However, after 3 years, no differences between targets were observed. In general, the results from these three studies show that both STN and GPi are effective targets for improving motor outcomes. However, the selection of one or the other depends on the combination of symptoms, their impact on quality of life, the desired treatment goals and long-term disease management plan. In Australia, STN is the preferred target for treatment of many of the symptoms of PD.

Although effective for many symptoms, both DBS and medications have shown variable effectiveness for treatment of freezing of gait and falls. A fourth structure, the pedunculopontine nucleus (PPN; Fig. 1), was also mentioned in the 2009 referral guidelines as possible target for symptoms of postural instability and freezing of gait. To date, the PPN is the deepest part of the brain targeted for DBS stimulation. The indistinct borders of this structure and the lack of a characteristic neuropsychological activity make this structure a particularly challenging target. In 2009, studies investigating the effects of stimulating this target had not been completed, but several studies have since reported on the effects of PPN stimulation for these difficult to treat symptoms. Double-blinded objective assessments of freezing of gait, start hesitancy and gait and falls showed significant improvements in both studies. These improvements were more pronounced with bilateral than unilateral stimulation. The effects of PPN stimulation were not directly reflected in changes in motor assessment scores (Movement Disorder Society (MDS)-UPDRS) and medication levels over a 2-year follow up nor in improved step length and step variability when comparing ‘on’ and ‘off’ DBS states. It is important to mention that although the MDS-UPDRS is suitable to assess motor function, it is less sensitive to detect subtle changes in gait and posture. Another distinction that sets this target apart from the other three targets is that low rather than high frequency stimulation seems to be more beneficial in improving motor activity. To date, complete elimination of freezing of gait and start hesitancy following PPN stimulation have not been reported, and the impact of the reported improvements on quality of life remains to be determined. However, initial results from the recent small studies are promising, and more extensive studies are required to understand the full potential of PPN as a new individual target or as a supplementary target.

### Table 3 Non-motor symptoms associated with Parkinson disease

<table>
<thead>
<tr>
<th>Behavioural dysfunction</th>
<th>Autonomic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression†,§</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Anxiety†,§</td>
<td>Gastric dysfunction†</td>
</tr>
<tr>
<td>Apathy§</td>
<td>Intestinal dysfunction†</td>
</tr>
<tr>
<td>Obsessive behaviour§</td>
<td>Urological dysfunction†</td>
</tr>
<tr>
<td>Impulse control disorder†,§</td>
<td>Impaired sexual functions†</td>
</tr>
<tr>
<td>Cognitive impairment (demential)§</td>
<td>Cardiovascular autonomic dysfunction</td>
</tr>
<tr>
<td>Hallucinations†,§, psychosis§, delusions§</td>
<td>Thermoregulatory dysfunction</td>
</tr>
<tr>
<td>Panic attacks§</td>
<td>Respiratory dysfunction</td>
</tr>
<tr>
<td>Sleep-related dysfunction</td>
<td>Sensory dysfunction</td>
</tr>
<tr>
<td>Insomnia†</td>
<td>Visual dysfunction (blurred vision, diplopia)†</td>
</tr>
<tr>
<td>REM sleep behaviour disorder†</td>
<td>Pain</td>
</tr>
<tr>
<td>Excessive daytime sleepiness†,‡</td>
<td>Olfactory dysfunction</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>Sensorimotor dysfunction</td>
</tr>
<tr>
<td>Restless legs syndrome‡</td>
<td>Fatigue (central and peripheral)</td>
</tr>
</tbody>
</table>

†Potentially treatable. ‡Showed improvement. §Potentially worsen. REM, rapid eye movement.

### Focus on non-motor symptoms

While traditional PD treatment has mainly focused on improvement of the overt motor symptoms, the disorder is characterised by at least one (90% of patients) and often more non-motor symptoms (Table 3), depending on the disease duration. Although only briefly mentioned in the 2009 referral guidelines, it is now internationally recognised that non-motor symptoms can potentially have a greater impact on quality of life than motor symptoms. Identification of these non-motor symptoms is therefore essential, especially since some non-motor symptoms can emerge well before any motor symptoms, and their numbers increase as the disease advances. Furthermore, non-motor symptoms can be attributed to or worsened by the actual treatment (e.g. by high doses of medications and/or potential unwanted electrical stimulation of surrounding brain tissues with DBS) adversely affecting patient treatment and quality of life (Table 3). Many of the non-motor symptoms are often inappropriately identified or unidentified in routine clinical evaluations and therefore are not always included in treatment considerations. Further, identification of non-motor symptoms can be challenging since patients do not always relate their non-motor symptoms to PD or are embarrassed to address their symptoms during clinical visits. However, several non-motor symptoms are...
treatable (Table 3) or at least manageable if properly identified.24 It is therefore important to provide a clinical environment in which patients and their caregiver(s) are educated and informed about all symptoms, and communication between clinicians and patients is facilitated. Long-term management of PD requires a multidisciplinary approach involving routine patient assessments to monitor changes in or emergence of a broad range of associated symptoms. In recent years, several clinical tools have been adapted to accommodate identification of non-motor symptoms, such as the MDS-UPDRS and the Scales for Outcomes in PD. Several other tools have been developed and validated in recent years capable of measuring the impact of non-motor symptoms on quality of life. Aimed at subjective symptom detection (e.g. the Non-Motor Symptoms Questionnaire)25 and objective rating of symptom severity and frequency (the Non-Motor Symptoms Scale),26 both tools have been used in several recent studies and were successful in identifying and assessing changes in non-motor symptoms in patients following DBS surgery targeting the STN.27–29 The results showed a significant reduction in the number and/or severity of several non-motor symptoms following DBS (Table 3), which was related to increased quality of life. Several reasons were proposed for the observed improvements following DBS, including direct stimulation effects on non-motor symptoms, increased mobility and sense of well-being and also significant reductions in medication.28

No current data are available for the extent of assessment of non-motor symptoms in the Australian PD population, nor is there evidence of clinical consideration of these symptoms as standard practice in DBS treatment plans. It is essential to keep in mind that for patients, functional status and independence are important treatment outcomes, and quality of life also involves non-motor, social and emotional factors that can outweigh the motor factors in DBS outcomes.30 Clinical awareness of the broad range of motor and non-motor symptoms associated with PD is important, but the priorities for long-term management of PD and improvement of quality of life are early identification and appropriate consideration in subsequent treatment plans.

The efficacy and safety of DBS as treatment for PD as well as other indications is well established. Advances in the past 5 years have seen a shift to DBS intervention at early stages of the disease, investigation of new targets for less responsive symptoms and the recognition that PD is more than just a movement disorder and subsequent treatment has to take into consideration a range of motor and non-motor symptoms. Long-term monitoring of symptom changes or emergence and their impact on quality of life is essential for increasing our understanding of the effects of DBS and improving clinical practice for treatment of PD and many emerging indications.31

References

12 Deuschl G, Schade-Brittinger C, Krack P, Volkman J, Schaafer H, Boetzela K et al.


Early and late changes in markers of aortic stiffness with breast cancer therapy

S. Grover,1,2,3,4 P. W. Lou,1 C. Bradbrook,4 K. Cheong5,6, D. Kotasek,5,6 D. P. Leong,2,7 B. Koczwara2,8 and J. B. Selvanayagam1,2,3,4

1Cardiology Department and 4Flinders Cardiac Cardiovascular Magnetic Resonance Department, Flinders Medical Centre, 2Health Sciences, Flinders University, 3Heart Health, South Australian Health and Medical Research Institute, 5Oncology Department, Adelaide Cancer Centre, 6Department of Medicine, University of Adelaide and 8Department of Medical Oncology, Flinders Centre for Innovation in Cancer, Adelaide, South Australia, Australia and 7Population Health Research Institute, Hamilton General Hospital, McMaster University, Hamilton, Ontario, Canada

Key words
cardiotoxicity, chemotherapy, aortic distensibility, pulse wave velocity, anthracyclines, trastuzumab.

Correspondence
Joseph Selvanayagam, Department of Cardiovascular Medicine, Flinders Medical Centre, Adelaide, SA 5042, Australia.
Email:joseph.selva@health.sa.gov.au

Received 10 June 2014; accepted 4 November 2014.
doi:10.1111/imj.12645

Abstract

Background: Anthracyclines and trastuzumab are well recognised to cause cardiac toxicity. Further to their effects on left ventricular (LV) function, anthracyclines in particular are considered to cause negative arterial remodelling. Whether these changes reverse is unknown. In addition, whether trastuzumab causes specific effects on arterial remodelling is yet undetermined.

Methods: Patients receiving these agents for treatment of breast cancer and healthy volunteers prospectively underwent clinical evaluation and cardiovascular magnetic resonance (CMR) imaging at baseline, 1, 4 and 14 months post-therapy, including functional assessment, measurement of aortic pulse wave velocity (PWV) using velocity encoded imaging and distensibility at ascending aorta (AA) and proximal descending aorta (PDA).

Results: Twenty-nine patients pretherapy and 12 volunteers demonstrated no differences in PWV, distensibility and LV function. Among cancer subjects, PWV increased acutely, \( P = 0.002 \) (4 months), then decreased by 14 months (\( P < 0.001 \)). In addition, a decrease was observed in distensibility at the AA within 1 (\( P = 0.001 \)) and 4 months (\( P < 0.001 \)) of commencing therapy. At the PDA, only significant reduction was observed at 14 month distensibility when compared with baseline, \( P < 0.001 \). Patients with anthracycline exposure only had a greater reduction in aortic distensibility in the AA with time, \( P = 0.005 \) at 1 month, \( P < 0.001 \) at 4 months and \( P = 0.009 \) at 14 months.

Conclusion: Acute changes are observed in PWV and distensibility at the AA following contemporary breast cancer chemotherapy and partially reverse a year after therapy is discontinued, with more severe effects seen with anthracyclines.

Introduction

Anthracyclines and trastuzumab are commonly used for the treatment of breast cancer and are well recognised for their potential for cardiotoxicity. These agents can cause injury to the left ventricular (LV) myocardium, reduction in global ventricular function and lead to clinical heart failure1–5; both early and late after administration, however, the exact mechanism remains unclear. Anthracyclines induce generation of toxic oxygen free radicals, which can potentially lead to cardiovascular (CV) injury. The heart in particular is significantly susceptible to oxidative stress. Trastuzumab, responsible for inhibiting HER 2 protein, blocks repair pathways, which leaves the myocardium vulnerable to injury and failure to repair efficiently.

Negative arterial remodelling (reflected by changes in aortic stiffness, such as rise in pulse wave velocity (PWV) and decline in distensibility) has been linked to increase in CV events.6,7 Indeed, presence of increased aortic stiffness is an independent predictor of all cause mortality in patients with hypertension.6,9 Increase in aortic stiffness has been implicated as one of the potential mechanisms...
for the observed CV morbidity in chemotherapy, particularly when combined with other CV risk factors, such as hypertension, diabetes and age.\textsuperscript{6,7,9} Although changes in aortic compliance and stiffness following anthracylines have been evaluated, little is known whether these changes reverse after cessation of therapy. Furthermore, the effects of trastuzumab on aortic compliance and stiffness remain unstudied. Our primary aim was therefore to study the acute (within 1 and 4 months) effects of both cardiotoxic drugs (anthracylines and trastuzumab) on aortic remodelling and whether they reverse in patients undergoing treatment for breast cancer. Our secondary aim was to differentiate between the two drugs in terms of their effects on arterial remodelling. We measured CV magnetic resonance (CMR) aortic PWV, which represents a regional functional measurement of arterial stiffness over a particular arterial length. We also measured CMR aortic distensibility, which refers to local elastic properties of the vessel.

**Methods**

Patients were eligible for enrolment if they had early or metastatic breast cancer and had chemotherapy with anthracylines and/or trastuzumab prescribed (although not concurrently). In the metastatic disease group, the patients were required to be chemotherapy naive for 5 years and not to have received either of these drugs previously. Exclusion criteria included age less than 18 years, previous diagnosis of coronary artery disease, cardiomyopathy, severe valvular heart disease or myocarditis. In addition, patients with permanent pacemakers, implantable cardioverter defibrillators or glomerular filtration rate of <30/mL/min were excluded from participation. All patients provided written informed consent to the study protocol (24/10), which was approved by the clinical research and ethics committee of each participating institution, and conforms to the Declaration of Helsinki.

**Study procedures**

From July 2011 to October 2012 inclusive, female patients from three oncology centres in Adelaide were prospectively recruited into the study. Participants underwent clinical evaluation and CMR, pretreatment and at 1, 4 and 14 months post-treatment. Furthermore, a control group of women from the community underwent baseline investigations, including clinical evaluation, CMR aortic PWV, aortic distensibility and LV function.

All participants provided clinical information with regards to history of CV risk factors, including family history, hypertension, diabetes, smoking history and hypercholesterolaemia. A complete history of current medications at the time of commencement of the study was recorded. Patients were asked to report any new medications during the course of the study.

**CMR imaging**

CMR was performed with a 1.5 T scanner (Aera, Siemens, Erlangen, Germany). Transverse and sagittal images were acquired with a dark blood half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence (repetition time (TR) 600 ms, echo time (TE) 33 ms, 6 mm slice thickness, 1.8 mm interslice gap, matrix 256 x 151). Cine breath-hold balanced steady-state free precession sequence (TR 48 ms, TE 1.2 ms, fractional anisotropy 70\(^\circ\), 7 mm slice thickness, matrix 192 x 156) was used to acquire 4 chamber, 2 chamber and left ventricular outflow tract (LVOT) views, and subsequently these images were used to plan the short-axis images that encompassed the entire LV from the base to the apex (stack of 8–10 sequential short-axis slices). Using transverse and sagittal HASTE localisers, cine images with the following parameters (TR = 3.1 ms, TE = 1.5 ms, matrix size = 256 x 204 interpolated to 512 x 512, field of view varied from 330 to 400 mm according to the subject, slice thickness = 5 mm, number of lines in k-space per excitation = 19). One breath-hold acquisition provides images at different phases of the cardiac cycle, and 32 images were acquired in order to cover the whole cardiac cycle. The temporal resolution varied according to the RR interval (RR/32). Images of the ascending and proximal descending aorta (PDA) were acquired in the sagittal plane, and then axial cross-sectional images were planned to determine the maximum and minimum aortic lumen area for the ascending aorta (AA) and PDA. A non-ferromagnetic brachial blood pressure (BP) cuff was applied to record BP during the aortic cross-sectional image acquisitions. Phase-contrast CMR (PC-CMR) images were performed according to previous published techniques,\textsuperscript{10} in the same plane to determine PWV in AA and PDA. PC-CMR imaging parameters included a 34- to 36-cm field of view, a 256 x 192 matrix, a TR 23 ms, a 3–5-ms TE, a 15–20\(^\circ\) flip angle, an 8-mm thick slice and a through plane velocity encoding of 150 cm/s.

**CMR image analysis**

**Aortic distensibility and PWV**

All images were analysed offline using CMR-42 software (Circle Cardiovascular Imaging, Calgary, Canada). Using the cine image, the aortic lumen was magnified 400–800% and manually traced to determine the maximum
and minimum area. Ascending and PDA distensibility (Fig. 1) and PWV through the thoracic aorta were determined using previously published criteria (Fig. 2).10,11 Specifically, PWV (m/s) was calculated as the ratio of distance between levels and time difference between arrival of the pulse wave at these levels. The pulse wave was considered to ‘arrive’ at a certain level when the mean velocity reached half of its maximum value. Aortic root measurements were determined using cine imaging of LVOT and LVOT cross-cut views. Measurements were performed by manual planimetry at the aortic annulus, sinus and sinotubular junction.

Figure 1 The aorta was demonstrated in a saggital plane (A) and cross-sectional images were planned at the level of the middle pulmonary artery (solid black line) to generate ascending aorta (AA) and proximal descending aorta (PDA). Image B and C represent the minimum and maximum areas in AA and PDA; the difference between the two and aortic pulse pressure were subsequently used to calculate aortic distensibility at AA and PDA. Distensibility was calculated as $\frac{(A_{\text{max}} - A_{\text{min}})}{A_{\text{min}} \times PP}$, where $A_{\text{max}}$ and $A_{\text{min}}$ represent the maximum and minimum areas and PP represents the pulse pressure measured at the time.

LV volumes, function and mass

Functional data were assessed using the cine images. Endocardium and epicardium were contoured using standard criteria previously published.12 End-diastolic and end-systolic volumes were measured from which LV stroke volume, ejection fraction (EF) and myocardial mass were calculated.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (where normally distributed) or median (25th–75th percentile) and compared between groups at baseline using analysis of variance or the Kruskal–Wallis test as appropriate. Categorical data are summarised as frequencies and percentages, and compared using the $\chi^2$ or Fisher’s exact test.

For repeated-measures analysis of outcome variables of interest (distensibility of ascending and PDA; and PWV from ascending to PDA), mixed effects modelling was employed. The significance of predictor variables (baseline LVEF, hypertension, diabetes, hypercholesterolaemia, smoking, family history of ischaemic heart disease, pulse pressure, systolic BP, age, body surface area, use of anthracycline, trastuzumab, left-sided radiotherapy) of interest was evaluated by including them in a mixed effects model as part of an interaction term with subjects’ visit time (i.e. baseline vs follow up). If this predictor–time interaction term was significant, it implied that the candidate predictor variable’s influence on the outcome variable was time dependent. Post-hoc testing was then performed to determine whether the candidate predictor
variable’s association with the outcome variable was significant at both baseline and follow-up visit. All statistical tests were two sided, and a $P$-value $< 0.05$ was considered statistically significant.

Observer reproducibility of parameters was assessed in 12 patients using the approach of Bland and Altman. All analyses were undertaken using STATA software, Version 12 (Stata Corp., College Station, TX, USA).

**Results**

Twenty-nine women (mean age 54 ± 11 years) requiring anthracycline and/or trastuzumab containing chemotherapy regimens for breast cancer were enrolled from July 2011 to October 2012. Two patients were excluded because of detection of undiagnosed cardiomyopathy on baseline investigations in one and refusal to follow up after baseline investigations in the other. Hence, 27 patients proceeded with the study (25, early breast cancer; 2, metastatic breast cancer). These patients received either three to six cycles of epirubicin at 100 mg/m² or three to six cycles of doxorubicin at 50 mg/m², and/or trastuzumab in combination with taxanes or on its own with a loading dose of 8 mg/kg followed by 6 mg/kg every 21 days for 12 months. Five patients (three in the anthracycline group and two in the trastuzumab group) received left-sided radiotherapy as part of their treatment regimen. Fourteen patients received anthracyclines and 12 patients received trastuzumab. One patient received both, although not concurrently, and hence was analysed in the anthracyline group until 4 months (period of anthracyline exposure) and then removed from further analysis. The control group (12 volunteers, age 54 ± 10) had similar CV risk factors as our study group (Table 1) and no previous history of malignancy or chemotherapy.

**Baseline parameters**

Specifically, five patients had a history of hypertension, from which one received angiotensin converting enzyme inhibitors. No new medications were begun during the course of the study period. We found no difference in PWV or distensibility at the ascending and PDA between pretreatment study patients and volunteers (Table 1).

**Feasibility**

Functional and aortic PWV CMR imaging was feasible in all 27 cancer patients, and aortic distensibility calculation was feasible in 26/27 (96%) patients. One patient had BP measurements missing, and hence calculation of distensibility was not feasible. All parameters were measured in the control group.

**Aortic PWV and distensibility measurements in study patients**

Significant changes were observed in aortic distensibility and PWV at 4 months (Table 2). While the PWV

---

**Table 1 Baseline characteristics of study and volunteer populations**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study population</th>
<th>Volunteer population</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>27</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 11</td>
<td>54 ± 13</td>
<td>0.47</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.1</td>
<td>0.49</td>
</tr>
<tr>
<td>Comorbidities (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4, 15</td>
<td>0, 0</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5, 19</td>
<td>4, 33</td>
<td>0.42</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>10, 37</td>
<td>3, 25</td>
<td>0.71</td>
</tr>
<tr>
<td>Smokers – current</td>
<td>2, 7</td>
<td>2, 17</td>
<td>0.57</td>
</tr>
<tr>
<td>Smokers – ex</td>
<td>11, 41</td>
<td>4, 33</td>
<td>0.73</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>7, 26</td>
<td>1, 8</td>
<td>0.39</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic/diastolic BP (mmHg)</td>
<td>115 ± 17/68 ± 11</td>
<td>122 ± 14/73 ± 9</td>
<td>0.13/0.08</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>48 ± 11</td>
<td>49 ± 14</td>
<td>0.41</td>
</tr>
<tr>
<td>Parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic pulse wave velocity (m/s)</td>
<td>6.8 ± 3.2</td>
<td>7.5 ± 2.8</td>
<td>0.25</td>
</tr>
<tr>
<td>Aortic distensibility – AA, per mm² mercury</td>
<td>8.1 ± 3.6</td>
<td>8.4 ± 3.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Aortic distensibility – PDA, per mm² mercury</td>
<td>7.8 ± 4.4</td>
<td>8.6 ± 3.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>72 ± 5</td>
<td>71 ± 7</td>
<td>0.30</td>
</tr>
<tr>
<td>Myocardial mass indexed (g/m²)</td>
<td>46.1 ± 8.9</td>
<td>46.1 ± 8.8</td>
<td>0.50</td>
</tr>
</tbody>
</table>

-, not applicable. AA, ascending aorta; BP, blood pressure; BSA, body surface area; CAD, coronary artery disease; PDA, proximal descending aorta.
increased, paralleled decrease was seen in aortic distensibility at the AA (Fig. 3). Furthermore, partial improvement was noted in PWV at 14 months, yet aortic distensibility at the AA failed to demonstrate a significant return to normal. At the PDA, only significant changes were observed in distensibility from prechemotherapy to 14 months.

We examined whether baseline age, body surface area, pulse pressure, systolic BP, LVEF, comorbidities (hypertension, diabetes mellitus, hypercholesterolaemia and smoking), use of anthracyclines, trastuzumab or left-sided radiotherapy were significantly associated with change in PWV over time. We found that baseline patient age, pulse pressure and systolic BP were predictive of change in PWV. The older the patient, the more they demonstrated an increase in PWV with time (age–time interaction \( P = 0.004 \)). The wider the pulse pressure and higher the systolic BP, the greater the increase in PWV with time (pulse pressure–time interaction \( P = 0.002 \) and systolic BP–time interaction \( P = 0.04 \)).

We were able to demonstrate similar relationships between aortic distensibility at the AA and body surface area, systolic BP and pulse pressure. Patients with increased body surface area had greater reduction in aortic distensibility at the AA with time (body surface area–time interaction \( P = 0.001 \)). Furthermore, higher systolic BP was associated with greater reduction in distensibility (systolic BP–time interaction \( P = 0.001 \)), and a trend towards interaction between pulse pressure and distensibility at the AA were also established (pulse pressure–time interaction \( P = 0.08 \)). Importantly, we found a significant interaction between patients that received anthracyclines (\( n = 14 \)) and aortic distensibility at the AA (anthracycline–time interaction \( P = 0.02 \)). Therefore, in comparison with the group that did not receive anthracyclines, patients with anthracycline exposure had a greater reduction in aortic distensibility in the AA with time, \( P = 0.005 \) at 1 month, \( P < 0.001 \) at 4 months and \( P = 0.009 \) at 14 months. In the anthracycline group, aortic distensibility at the AA decreased from \( 9.2 \pm 2.8 \) to \( 6.8 \pm 2.5 \) per mm\(^3\) mercury at 14 months. In contrast, in the trastuzumab group, the distensibility changed from \( 6.7 \pm 4.0 \) to \( 7.1 \pm 2.2 \) per mm\(^3\) mercury.

### Table 2: Changes in aortic pulse wave velocity, aortic distensibility in study patients and volunteers with time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study patients</th>
<th>Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PWV (m/s)</td>
<td>AA Aortic distensibility (per mm(^3) mercury)</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>6.8 ± 3.2</td>
<td>8.1 ± 3.6</td>
</tr>
<tr>
<td>1 month f/u</td>
<td>7.8 ± 4.3</td>
<td>6.0 ± 3.2*</td>
</tr>
<tr>
<td>4 months f/u</td>
<td>8.9 ± 6.4*</td>
<td>5.7 ± 3.2**</td>
</tr>
<tr>
<td>12 months f/u</td>
<td>8.2 ± 4.2*</td>
<td>6.9 ± 2.3</td>
</tr>
</tbody>
</table>

\*\( P < 0.05 \), \**\( P < 0.001 \). AA, ascending aorta; f/u, follow up; ND, not done; PDA, proximal descending aorta; PWV, pulse wave velocity.
With respect to the aortic distensibility of the PDA, a trend was observed between aortic distensibility and pulse pressure (pulse pressure–time interaction \( P = 0.06 \)).

Aortic PWV and distensibility measurements in volunteers

Six volunteers underwent repeat imaging at median time of 4 months. There were no significant changes observed in PWV and aortic distensibility at the ascending and PDA at follow up (Table 2).

Aortic root and BP measurements in study patients

There were no changes observed at the aortic annulus, sinus or sinotubular junction from prechemotherapy to follow up (Table 3). We also evaluated whether there were changes in BP during the study period. Overall, the only significant change was a drop in the systolic and diastolic BP pretreatment to 4 months \( (P = 0.05) \). Pulse pressure remained unchanged (Table 3).

LV function

There were no significant differences in LV volumes, mass or EF between study patients at baseline and normal volunteers (Table 1). Significant LV functional changes were seen among cancer patients from baseline \( (\text{EF} \ 72 \pm 5) \) to 4 months \( (\text{EF} \ 66 \pm 7, \ P = 0.001) \). These changes persisted at 14 months \( (\text{EF} \ 67 \pm 7, \ P = 0.001) \). At 4 months, immediately after completion of anthracyclines or completion of six cycles of trastuzumab, 27% patients \( (7/26) \) showed a decline in LVEF by >10%. By 14 months, 19% \( (5/26) \) of the cohort examined had persistent LV dysfunction; however, none had LVEF below the normal range \( (<55\%) \). A decline of >10% was considered significant based on recent evidence, suggesting that it warrants treatment in patients receiving trastuzumab.\(^{11}\)

**Discussion**

Our principal findings show that adverse aortic remodelling occurs early (within 4 months) of commencement of chemotherapy. At 14 months, 1 month after completion of trastuzumab and 10 months after completion of anthracyclines, only PWV remained reduced suggesting potential improvement in negative arterial remodelling. All parameters (PWV and aortic distensibility) remained elevated at the PDA at 14 months.

Aortic remodelling has been demonstrated acutely with anthracyclines, yet whether these return to normal or remain persistently elevated is not evident from previous work. Chaosuwannakit and colleagues demonstrated significantly increased PWV and parallel decrease in aortic distensibility in patients receiving anthracyline chemotherapy as measured by CMR.\(^{10}\) These changes were evaluated over 4 months and were greater in magnitude than seen in our study. However, whether they remained persistently elevated or returned to baseline was not demonstrated in this study as they did not report a 12-month follow up. In addition, an ultrasound-based study evaluated patient pre-anthracycline chemotherapy, and 6 months post and showed lasting elevations in aortic stiffness and decrease in aortic compliance, suggesting persistent negative arterial remodelling at least to 6 months post-anthracycline therapy.\(^{14}\) We did not demonstrate persistent changes in all our parameters of aortic remodelling. Specifically, aortic PWV decreased at the 14-month mark, although not to baseline. We hypothesise that acute changes in aortic remodelling parameters following chemotherapy with anthracycline or trastuzumab are partially reversible. One of the potential reasons that we were not able to demonstrate return of all our CMR parameters to baseline may be related to the fact that half our patients received anthracyclines while the other half were given trastuzumab. We found significant interaction between greater decline in aortic distensibility at the AA and anthracyclines. We propose that in our overall group, most of the changes observed were driven by patients receiving anthracyclines and that trastuzumab does not cause significant changes in negative arterial remodelling. This may explain why the magnitude of overall changes in our group were smaller than work by Chaosuwannakit and colleagues who predominantly only evaluated anthracyclines.

In a large study of hypertensive patients, it was demonstrated that an absolute PWV of 11.3 ms was associated...
with a 1.5 times increased odds ratio of CV mortality over 9 years.8 The mean PWV in our group was 8.2 ± 0.1 m/s at the end of 14 months, and only 23% of our patients had PWV greater than 11.3 m/s at that time point. Furthermore, none of our patients dropped their LVEF below normal at 14 months. Whether our patients represent a group that by far had limited abnormalities in pulse wave velocities and hence likely to remain free of significant CV mortality is unclear. There are some distinct differences between the two studies. First, this initial study performed by Laurent and colleagues evaluated a stable cohort of hypertensive patients while ours examined PWV following administration of potentially cardiotoxic drugs. Second, the methodologies utilised differed, with Laurent employing carotid-femoral PWV while ours was measured between ascending and PDA using MRI.

At 14 months, we found that only PWV began to regress while the increase in aortic distensibility at the AA was not significant. At the PDA, distensibility remained reduced at 14 months. Whether with larger numbers or further imaging at 2–3 years post-chemotherapy, the changes in distensibility become significant remains to be seen.

The mechanism by which chemotherapy or hormonal therapy agents cause negative arterial remodelling remains unclear. Anthracyclines in particular have been extensively evaluated and are thought to cause an increase in oxidative stress because of production of toxic oxygen free radicals.1,2 This in turn leads to structural changes in the vascular matrix and interferes with endothelin regulation of vascular tone, thereby increasing aortic stiffness. Doxorubicin has been demonstrated to suppress endothelin production, which in turn may make the myocytes susceptible to apoptosis.15

Trastuzumab on the other hand is a recombinant DNA-derived monoclonal antibody that binds to extracellular domain of the Her2 protein in breast cancer cells. Its cardiotoxicity is due to its effect in nulling the beneficial effects of erbB2 derived repair pathways in the heart. This specifically impacts how myocytes respond to stress. Experimental animal work using trastuzumab and high-dose radiation has been shown to demonstrate greater effect on vessel relaxation and electron microscopic evidence of endothelial damage on thoracic aorta.16 Our patients showed greater decline in aortic distensibility in the anthracycline group rather than the trastuzumab group. This may potentially reflect the acute endothelial derived insult of the anthracyclines. The patients that received trastuzumab potentially require accumulation of further toxicity and failure of repair processes to undergo negative remodelling. Long-term follow up of these patients may clarify whether trastuzumab on its own causes limited effects, or with time, it mirrors similar changes in aortic stiffness as seen with anthracyclines.

Limitations

Our study has several limitations. First, our patient numbers are small and hence our findings need to be replicated in larger multicentre studies. Most importantly, we lack power to perform separate analysis between the anthracycline and trastuzumab patients individually. Second, we were only able to follow up half of our control group over a period of 4 months. Therefore, it is theoretically possible that these changes are due to time (14 month older patient) rather than chemotherapy. Against this are the lack of difference between baseline characteristics of study patients and normal volunteers and the minimal change observed in the followed up control group. Furthermore, previous studies have evaluated normal volunteers and found no difference in PWV and distensibility over 4 months.10 Recently, evaluation of the Multi-Ethnic Study of Atherosclerosis cohort showed absolute changes in PWV of 1 m/s over 10 years in a normal cohort.17 Hence, it is unlikely that the temporal changes seen in the anthracycline group are due to time. Finally, as our proposed changes in aortic distensibility may have been driven by endothelin derived effect, we should have specifically evaluated flow-mediated dilatation after reactive hyperaemia to elucidate better the aetiology of changes observed in our study patients.

Conclusion

Acute changes are observed in PWV and distensibility at the AA following contemporary breast cancer chemotherapy. These changes partially reverse a year after chemotherapy is discontinued. Anthracyclines have more severe effects on arterial remodelling than trastuzumab therapy.
References


Enteric fever in the Pacific: a regional retrospective study from Auckland, New Zealand

R. J. Lane,1,2 D. Holland,1 S. McBride,1 S. Perera,3 I. Zeng,1 M. Wilson,4 K. Read,5 T. Jelleyman6 and R. J. H. Ingram2

1Infectious Diseases Department, Middlemore Hospital, 4Medicine, North Shore Hospital, 6Department of Paediatrics, Waitakere Hospital, 2Infectious Diseases Department, Auckland City Hospital and 3Auckland Regional Public Health Service, Auckland and 5Environmental Science and Research, Christchurch, New Zealand

Abstract

Background: There are limited clinical data on enteric fever in the Pacific and New Zealand (NZ) compared with the Indian subcontinent (ISC) and South-East Asia (SEA). Our objective was to describe enteric fever in Auckland – a large Pacific city, focusing on disease acquired in these regions.

Methods: We reviewed enteric fever cases hospitalised in Auckland from January 2005 to December 2010.

Results: Microbiologically confirmed EF was identified in 162 patients. Travel regions: Pacific, 40 cases (25%) (Samoa, 38; Fiji, two), ISC, 72 (44%), SEA, seven (4%), other, three (2%), no travel, 40 (25%). Enteric fever rates for Auckland resident travellers were: India 50.3/100 000; Samoa 19.7/100 000. All Pacific cases were Salmonella Typhi. Of local isolates (without travel history), 38 were S. Typhi (36 fully susceptible, one multi-drug resistant (MDR) + nalidixic acid resistant (NAR), one unknown) and two S. Paratyphi (both NAR). Of non-Pacific travel, 56/82 (69%) isolates were S. Typhi, the remainder S. Paratyphi (15 isolates were fully susceptible, only 1% were MDR). Significant associations of serotype and antibiotic resistance with different travel regions and similarity of phage types (local and Pacific) were observed.

Headache, vomiting and acute kidney injuries were more frequent with Pacific travel, while abdominal distension and cholecystitis with local disease. Shorter duration of treatment in the Pacific group was seen despite length of stay in hospital not being reduced. Local cases were associated with longer hospital admissions.

Conclusions: One half of cases in Auckland are acquired either from Pacific or locally. Similarities mean that disease acquired locally is likely of Pacific origin.

Introduction

Typhoid, also known as enteric fever, is caused by infection by Salmonella enterica serotypes Typhi and Paratyphi. Both are obligate human pathogens, typically food and water borne, that cause a clinically indistinguishable disease.

Globally, typhoid infects approximately 22 million people annually with about 200 000 deaths.1 The Indian subcontinent (ISC) and South-East Asia (SEA) have the greatest burden of disease.1 Cases typically occur in returning travellers from these regions.2 The New Zealand (NZ) notification rate for typhoid fever was 1 per 100 000 in 2011, but higher in the Auckland region at 2 per 100 000.3

Auckland is the largest city in NZ with a population of 1 303 068 based on the 2006 National Census.4 It has one of the largest populations of Pacific residents in the world behind only Port Moresby5 and Honolulu county.6 In Auckland there are 177 933 Pacific peoples and a total of 265 974 in NZ.7

Between NZ and the Pacific, there is frequent commuting – both to visit friends and relatives and also to holiday. There are limited data on enteric fever in this region, which is reported to have a medium incidence (10–100 cases per 100 000).8 Typhoid cases have increased in Samoa since 2002. A projected burden of disease

Funding: None.
Conflict of interest: None.
assessment performed from July 2010 to 2011 found a very high incidence in Samoa of 270 cases (range 134–460) per 100 000,9 similar to rates in the ISC.1

Our objective was to describe the epidemiology and clinical features of confirmed cases of enteric fever admitted to hospitals in Auckland from 2005 to 2010 and to compare the features of cases acquired in different geographical regions.

Methods

We conducted a retrospective review of microbiologically confirmed cases of enteric fever (either Salmonella Typhi or Salmonella Paratyphi) hospitalised in Auckland over the period 1 January 2005 to 31 December 2010. Ethical approval was obtained from the Ethics Committees of the Ministry of Health and subsequently from the Health and Disability Commission of New Zealand.

Cases of S. Typhi or S. Paratyphi infection from blood or stools were identified from hospital microbiological databases. The two community laboratories in the region provided information on community isolates, and this was cross-referenced with notifications from Auckland Regional Public Health Service (ARPHS). From December 2007, all cases of enteric fever were legally notifiable to ARPHS by laboratories and clinicians. Prior to that, only clinician notification occurred.

After case identification, all inpatient hospital records were reviewed by a single author (RJL). Residency status was determined from hospital records gathered by revenue departments. Travel history involved review of the 6 months prior to admission. In cases of travel to multiple countries, the main region was defined by where the most time was spent. For interpretation of antibiotic susceptibility results, Clinical and Laboratory Standards Institute breakpoint criteria were utilised.

Crude rates of enteric fever for specific regions and ethnicity were calculated with data from Statistics New Zealand. This included reports on the number of Auckland travellers to destinations from airport departure cards from 2005 till 2010, and ethnicity data from the 2006 national census.

Statistics

For statistical analysis, associations between categorical variables were determined using the Chi-squared or Fisher’s exact test. Comparisons of continuous variables were performed using analysis of variance (ANOVA) or the Kruskal–Wallis test where the assumption of ANOVA was not met. Multiple comparisons were not adjusted. Poisson regression was applied for testing if there were significant trends in the number of cases across admission year, adjusted for overall number of New Zealand travellers. Age adjusted incidence rate of typhoid of Auckland residents is reported by using the World Health Organisation standard population and New Zealand 2006 census information. SAS Copyright 2002–2010 by SAS Institute Inc., Cary, NC, USA, was used for the analysis.

Results

There were 162 microbiologically confirmed cases of enteric fever in Auckland with a hospital admission dated from 1 January 2005 to 31 December 2010. Figure 1 shows 40 (25%) had a history of travel to the Pacific region, 82 (50%) non-Pacific travel, and 40 (25%) had disease acquired locally (no travel history). Within the
Pacific region, the only two destination countries of disease acquisition were Samoa (38) and Fiji (2).

As shown in Figure 2, the number of cases diagnosed per year was stable over the 6-year period, apart from an almost doubling of cases in the last quarter of 2006 and the first quarter of 2007 associated with a spike in locally acquired cases. This remained stable after adjustment for the total number of travellers in NZ. Thirteen (32%) of the locally acquired cases were diagnosed in the last quarter of 2006. Travel-acquired cases occurred mainly in first quarter peaks. There were two peaks associated with Pacific acquisition, one in 2007 and the other in 2010.

Table 1 documents patient characteristics. Ethnicity and country of birth data showed significant associations with the region of disease acquisition. Most cases (92%) that acquired enteric fever in the Pacific were Samoan ethnicity, and also the majority with locally acquired disease were also Samoan (55%). Of the cases of enteric fever acquired in non-Pacific travel regions, 58 (72%) were of Indian ethnicity.

Of the 58 cases where reason for travel was known (both travel from and visitors to Auckland); 40 (69%) had been visiting friends or relatives (VFR) (14 cases acquired in the Pacific, 26 in non-Pacific regions), 12 were new arrivals to NZ and 6 had travelled overseas for holiday or work (one acquired with Pacific travel, 5 acquired with non-Pacific travel). Among those for whom this data was known, and excluding immigrants, there were seven times more VFR travellers than non-VFR travellers.

Only two patients were known to have received the injectable polysaccharide typhoid vaccine; one contracted S. Typhi infection, the other S. Paratyphi.

Of 40 locally acquired cases, 12 had a history of enteric fever contacts, while four had a history of ingestion of imported Pacific food. Two cases occurred after laboratory exposure to S. Typhi. Exposure was unknown for the remainder.

The duration of travel was shorter in those who travelled to the Pacific compared with other regions (mean duration 25 vs 50 days, \( P = 0.002 \)). Time from arrival in NZ to admission was a median of 14 days in all travel groups. The duration of symptoms prior to admission in days was 9 days in the locally acquired group compared with 12 days in the Pacific and 15 days in the non-Pacific travel groups. The difference was not statistically significant (\( P = 0.31 \)).

Auckland residents who traveled to India had the highest rate of enteric fever with 50.3 cases per 100 000 travellers. Samoa had a rate of 19.7 cases/100 000, while Fiji had 0.3 cases/100 000. There were insufficient data to determine rates for other countries or rates dependent on travel duration.

Locally acquired disease occurred at a rate of 0.51 cases per 100 000 Auckland residents. By ethnicity of Auckland residents, Samoans had a rate of 4.2 cases per 100 000 compared with 17.3 cases per 100 000 Tongans, 0.7 cases per 100 000 NZ Maori and 0.1 cases per 100 000 NZ Europeans.

Clinical details of cases of enteric fever are documented on Table 2. The most frequent presenting symptoms were fevers and sweats (91%) followed by diarrhoea (61%). Headache and vomiting were only present in 40% and 36% of all cases respectively, but varied by region, being seen less frequently in non-Pacific and locally acquired.
disease. The sign seen most frequently on admission was fever (83%). Abdominal distension was the only sign for which there was a significant variation by region (local 15%, Pacific 10%, non-Pacific 2%, \( P = 0.02 \)).

The most common antibiotic prescribed after diagnosis was ciprofloxacin (55%) followed by amoxicillin (21%). Length of treatment analysis showed there was a trend (\( P = 0.061 \)) to shorter duration of treatment in the Pacific acquired (mean 11 days) compared with locally acquired disease (13 days) and non-Pacific travel (14 days). The median length of stay was longer for those with disease acquired locally.

Complications are listed in Table 3. The most frequently observed complication was acute renal failure in 10% of cases. The frequency of pneumonia, acute renal failure and shock varied by region with all three seen more frequently in disease acquired in the Pacific. There were no differences in relapse rate or chronic carriage between regions. No deaths occurred over the study period.

Isolate information is documented on Table 4. Fifty-eight per cent of cases were diagnosed by blood culture, 8% from stool culture and 34% from both. In one patient, \( S. \) Typhi grew from urine in addition to blood. \( S. \) Typhi represented 83% of cases. \( S. \) Paratyphi was identified more frequently in those who acquired enteric fever from non-Pacific regions (\( P < 0.0001 \)). Resistance was seen more in this region with only 18% of isolates being fully susceptible. Pacific-acquired disease was only caused by \( S. \) Typhi. All but one case was fully susceptible (one Nalidixic acid resistant (NAR) isolate). Among the locally acquired cases, 38 were \( S. \) Typhi (one combined multi-drug resistant and NAR, one with unknown susceptibilities, while the remainder were fully susceptible) and two were \( S. \) Paratyphi (both NAR). Of those two cases, one was associated with laboratory exposure.

The E1a phage type (\( S. \) Typhi) was the most commonly isolated over all groups. Aside from the single cases of Paratyphi A and B isolated in the locally acquired disease, only two phage types (E1a and E7) were seen in this region and the Pacific. In non-Pacific travel, Paratyphi A was seen in 32%, but nine different phage types were noted.

**Discussion**

This is the largest descriptive study of enteric fever from the Pacific and describes the features associated with disease from this region. A prior study\(^{19} \) of enteric fever from Auckland reviewed an 8-year period from 1977 to 1984 and found only 23 cases, of which 10 were determined to be of Pacific origin. Our study shows a
Table 2  Clinical characteristics of patients by region of disease acquisition

<table>
<thead>
<tr>
<th>Region of acquisition</th>
<th>Total, n = 162</th>
<th>Pacific, n = 40</th>
<th>Local, n = 40</th>
<th>Non-Pacific, n = 82</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms on admission, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever or sweats</td>
<td>147 (91)</td>
<td>37 (93)</td>
<td>34 (85)</td>
<td>76 (93)</td>
<td>0.40</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>98 (61)</td>
<td>37 (90)</td>
<td>24 (60)</td>
<td>50 (61)</td>
<td>0.90</td>
</tr>
<tr>
<td>Rigors</td>
<td>49 (30)</td>
<td>11 (28)</td>
<td>14 (35)</td>
<td>24 (29)</td>
<td>0.74</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>77 (48)</td>
<td>21 (53)</td>
<td>32 (39)</td>
<td>24 (30)</td>
<td>0.07</td>
</tr>
<tr>
<td>Headache</td>
<td>64 (40)</td>
<td>21 (53)</td>
<td>19 (48)</td>
<td>24 (29)</td>
<td>0.02</td>
</tr>
<tr>
<td>Anorexia</td>
<td>48 (30)</td>
<td>9 (23)</td>
<td>14 (35)</td>
<td>27 (33)</td>
<td>0.50</td>
</tr>
<tr>
<td>Vomiting</td>
<td>58 (36)</td>
<td>20 (50)</td>
<td>17 (43)</td>
<td>21 (26)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cough</td>
<td>50 (31)</td>
<td>15 (38)</td>
<td>10 (25)</td>
<td>25 (31)</td>
<td>0.48</td>
</tr>
<tr>
<td>Signs on admission, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>134 (83)</td>
<td>35 (88)</td>
<td>33 (83)</td>
<td>66 (81)</td>
<td>0.63</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>84 (52)</td>
<td>25 (63)</td>
<td>23 (58)</td>
<td>36 (44)</td>
<td>0.11</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>13 (8)</td>
<td>2 (5)</td>
<td>4 (10)</td>
<td>7 (9)</td>
<td>0.70</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>12 (7)</td>
<td>4 (10)</td>
<td>6 (15)</td>
<td>2 (2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>39 (24)</td>
<td>10 (25)</td>
<td>11 (28)</td>
<td>18 (22)</td>
<td>0.79</td>
</tr>
<tr>
<td>Number of admissions prior to diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>117 (72)</td>
<td>35 (88)</td>
<td>33 (83)</td>
<td>66 (81)</td>
<td>0.63</td>
</tr>
<tr>
<td>1</td>
<td>40 (25)</td>
<td>13 (32)</td>
<td>12 (30)</td>
<td>15 (18)</td>
<td>0.84</td>
</tr>
<tr>
<td>2</td>
<td>5 (3)</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Median hospital stay in days, n (IQR)</td>
<td>6 (4–8)</td>
<td>6 (5–9)</td>
<td>8 (5–9)</td>
<td>5 (3–7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Definitive antibiotic treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>34 (21)</td>
<td>6 (15)</td>
<td>7 (18)</td>
<td>21 (26)</td>
<td>0.12</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>89 (55)</td>
<td>24 (60)</td>
<td>28 (70)</td>
<td>37 (45)</td>
<td>0.84</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>23 (14)</td>
<td>6 (15)</td>
<td>1 (3)</td>
<td>16 (20)</td>
<td>0.49</td>
</tr>
<tr>
<td>Other†</td>
<td>16 (10)</td>
<td>4 (10)</td>
<td>4 (10)</td>
<td>8 (10)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

†Other antibiotic choices include: co-trimoxazole, cefotaxime, azithromycin, ertapenem and unknown. IQR, interquartile ranges.

Table 3  Complications by region of acquisition

<table>
<thead>
<tr>
<th>Region of acquisition</th>
<th>Total, n = 162</th>
<th>Pacific, n = 40</th>
<th>Local, n = 40</th>
<th>Non-Pacific, n = 82</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>4 (2)</td>
<td>0</td>
<td>3 (8)</td>
<td>1 (1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Jaundice</td>
<td>5 (3)</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>2 (2)</td>
<td>0.84</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (5)</td>
<td>4 (10)</td>
<td>4 (10)</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>16 (10)</td>
<td>10 (25)</td>
<td>3 (8)</td>
<td>3 (4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Shock</td>
<td>6 (4)</td>
<td>4 (10)</td>
<td>1 (3)</td>
<td>1 (1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Decreased level of consciousness</td>
<td>3 (2)</td>
<td>2 (5)</td>
<td>0</td>
<td>1 (1)</td>
<td>0.30</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>5 (3)</td>
<td>0</td>
<td>5 (13)</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>Relapsed disease, n (%)</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>0.99</td>
</tr>
<tr>
<td>Clinical</td>
<td>3 (2)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1 (1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Microbiological</td>
<td>8 (5)</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>5 (6)</td>
<td>0.99</td>
</tr>
<tr>
<td>No relapse</td>
<td>151 (93)</td>
<td>37 (93)</td>
<td>38 (95)</td>
<td>76 (93)</td>
<td>0.99</td>
</tr>
<tr>
<td>Chronic carriage, n (%)</td>
<td>4 (3)</td>
<td>0</td>
<td>2 (5)</td>
<td>2 (2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Follow-up stools, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance (two negative samples)</td>
<td>83 (51)</td>
<td>19 (48)</td>
<td>23 (58)</td>
<td>41 (50)</td>
<td>0.64*</td>
</tr>
<tr>
<td>No clearance</td>
<td>13 (8)</td>
<td>1 (3)</td>
<td>4 (10)</td>
<td>8 (10)</td>
<td>0.10</td>
</tr>
<tr>
<td>No samples submitted</td>
<td>57 (35)</td>
<td>19 (48)</td>
<td>12 (30)</td>
<td>26 (32)</td>
<td>0.32</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (6)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>7 (8)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Fisher-Freeman–Halton exact test.
A significant increase in the numbers of enteric fever reflecting population growth, increased travel frequency and reporting frequency.

As with other developed countries, enteric fever in Auckland mostly follows travel to countries with endemic disease. In contrast with other large reviews where 67% to 70% of cases were travellers to the Indian subcontinent or Southern Asia, only 45% had travelled to these regions in our study. Twenty-five per cent of our cases acquired disease in the Pacific, a region not featured in the other series. This reflects our geographic location and our large Pacific population. In 2010, 12% of short-term (<12 months) NZ resident departures were to Pacific countries.

Our estimated enteric fever rates among travellers to India of 50 per 100 000 and Samoa of 20 per 100 000 were high. This compares with rates of 14 per 100 000 visits to India found during enhanced surveillance of enteric fever in England, Wales and Northern Ireland during 2006 and 2007. US studies have rates of nine to 16.7 cases per 100 000 travellers.

The burden of locally acquired disease was not insignificant at 25% of cases, but was similar to the domestic typhoid proportion in the US study from 1999–2006 at 19%. Our definition of travel history encompassing the preceding 6 months may have classified disease as travel acquired when it was actually acquired locally. In contrast, the US study defined domestic acquisition as occurring in a person who had not traveled outside the United States in the 6 weeks before onset of symptoms. This seems conservative as the incubation period of typhoid may be up to 60 days. Other series do not specify time since travel nor assess local or domestically acquired disease. The similarity of resistance patterns and phage types to locally acquired cases suggest the Pacific is the likely source, imported by contacts, carriers or food sources.

Both locally acquired and imported disease has important public health implications. There is clear evidence of a local outbreak in late 2006. ARPHS is responsible for source attainment and contact identification and management. Both cases and contacts in high-risk groups, such as childcare staff and attendees, food handlers and healthcare workers, must provide two negative faecal specimens before returning to work in order to exclude the carrier state and prevent local transmission. ARPHS has also communicated warning regarding travel and privately imported food in response to elevated disease rates occurring in Pacific groups.

Most resistant disease, particularly to nalidixic acid and fluoroquinolones arises from the ISC. In this study, only S. Typhi was acquired in the Pacific, and virtually all these isolates were fully susceptible. As with many worldwide centres, laboratories within Auckland did not always test ciprofloxacin minimum inhibitory concentrations (MIC) in the absence of acid resistance. Therefore, clear evidence of the trend of fluoroquinolone MIC is not available. Anecdotally, the emergence of resistance, particularly decreased fluoroquinolone susceptibility, has significant increase in the numbers of enteric fever reflecting population growth, increased travel frequency and reporting frequency.

As with other developed countries, enteric fever in Auckland mostly follows travel to countries with endemic disease. In contrast with other large reviews, where 67% to 70% of cases were travellers to the Indian subcontinent or Southern Asia, only 45% had travelled to these regions in our study. Twenty-five per cent of our cases acquired disease in the Pacific, a region not featured in the other series. This reflects our geographic location and our large Pacific population. In 2010, 12% of short-term (<12 months) NZ resident departures were to Pacific countries.

Our estimated enteric fever rates among travellers to India of 50 per 100 000 and Samoa of 20 per 100 000 were high. This compares with rates of 14 per 100 000 visits to India found during enhanced surveillance of enteric fever in England, Wales and Northern Ireland during 2006 and 2007. US studies have rates of nine to 16.7 cases per 100 000 travellers.

The burden of locally acquired disease was not insignificant at 25% of cases, but was similar to the domestic typhoid proportion in the US study from 1999–2006 at 19%. Our definition of travel history encompassing the preceding 6 months may have classified disease as travel acquired when it was actually acquired locally. In contrast, the US study defined domestic acquisition as occurring in a person who had not traveled outside the United States in the 6 weeks before onset of symptoms. This seems conservative as the incubation period of typhoid may be up to 60 days. Other series do not specify time since travel nor assess local or domestically acquired disease. The similarity of resistance patterns and phage types to locally acquired cases suggest the Pacific is the likely source, imported by contacts, carriers or food sources.

Both locally acquired and imported disease has important public health implications. There is clear evidence of a local outbreak in late 2006. ARPHS is responsible for source attainment and contact identification and management. Both cases and contacts in high-risk groups, such as childcare staff and attendees, food handlers and healthcare workers, must provide two negative faecal specimens before returning to work in order to exclude the carrier state and prevent local transmission. ARPHS has also communicated warning regarding travel and privately imported food in response to elevated disease rates occurring in Pacific groups.

Most resistant disease, particularly to nalidixic acid and fluoroquinolones arises from the ISC. In this study, only S. Typhi was acquired in the Pacific, and virtually all these isolates were fully susceptible. As with many worldwide centres, laboratories within Auckland did not always test ciprofloxacin minimum inhibitory concentrations (MIC) in the absence of acid resistance. Therefore, clear evidence of the trend of fluoroquinolone MIC is not available. Anecdotally, the emergence of resistance, particularly decreased fluoroquinolone susceptibility, has

Table 4 Microbiological characteristics by regions of acquisition

<table>
<thead>
<tr>
<th>Region of acquisition</th>
<th>Total, n = 162</th>
<th>Pacific, n = 40</th>
<th>Local, n = 40</th>
<th>Others, n = 82</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolate source, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stool</td>
<td>13 (8)</td>
<td>2 (5)</td>
<td>4 (10)</td>
<td>7 (5)</td>
<td></td>
</tr>
<tr>
<td>blood</td>
<td>94 (58)</td>
<td>23 (58)</td>
<td>22 (55)</td>
<td>49 (60)</td>
<td></td>
</tr>
<tr>
<td>both</td>
<td>55 (34)</td>
<td>15 (38)</td>
<td>14 (35)</td>
<td>26 (32)</td>
<td>0.90</td>
</tr>
<tr>
<td>Serotype, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>typhi</td>
<td>134 (83)</td>
<td>40 (100)</td>
<td>38 (95)</td>
<td>56 (82)</td>
<td></td>
</tr>
<tr>
<td>paratyphi</td>
<td>27 (17)</td>
<td>0 (0)</td>
<td>2 (5)</td>
<td>26 (32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Susceptibility pattern, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fully susceptible</td>
<td>89 (55)</td>
<td>38 (95)</td>
<td>36 (92)</td>
<td>15 (18)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>NAR + QS</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAR + UQS</td>
<td>23 (14)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>21 (26)</td>
<td></td>
</tr>
<tr>
<td>NAR + DQS</td>
<td>44 (27)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>42 (51)</td>
<td></td>
</tr>
<tr>
<td>MDR</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR + NAR + DQS</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Phage type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1a</td>
<td>80 (49)</td>
<td>27 (68)</td>
<td>25 (63)</td>
<td>28 (34)</td>
<td>0.004</td>
</tr>
<tr>
<td>E7</td>
<td>22 (14)</td>
<td>10 (25)</td>
<td>9 (23)</td>
<td>3 (4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Paratyphi A</td>
<td>27 (17)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>26 (32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unknown</td>
<td>19 (12)</td>
<td>3 (8)</td>
<td>4 (10)</td>
<td>12 (7)</td>
<td></td>
</tr>
<tr>
<td>Paratyphi B</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Phage type A</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>W form</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>E9</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Other (D1, D9)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (4)</td>
<td></td>
</tr>
</tbody>
</table>

*Fisher–Freeman–Halton exact test. DQR, decreased quinolone susceptibility; MDR, multi-drug resistant (Amoxicillin, Chloramphenicol, Co-trimoxazole); NAR, nalidixic acid resistant; UK, unknown; UQS, unknown quinolone susceptibility.
been reported on Pacific isolates obtained after our study period. Environmental Science and Research Ltd, the national public health surveillance service, had 41 cases of S. Typhi in 2012. Of these, a total of 20 were nalidixic acid resistant, six of which came from Samoa.18 In other areas of the world, S. Paratyphi is causing an increasing burden of disease.11,12,15,19 Our results show this trend is not seen in the Pacific region or in local cases.

Disease acquired in the Pacific occurred after a shorter travel duration, likely reflecting the ease of travel – in terms of both cost and time. Despite less resistance among the Pacific isolates, there were no clear differences in antibiotic treatment. A shorter duration of treatment in the Pacific group was noted, but length of hospitalisation was not reduced. This may be due to delays in diagnosis, but time from admission until diagnostic confirmation was not assessed. The median length of hospital stay in our series was similar to reviews in the UK and United States.11,14

Weaknesses of this study are its retrospective nature, leading to missing data and our inability to adjust for confounding effects; missing cases; potential misclassification of travel or local acquisition and variable resistance testing.

Consistent with other studies, there was limited documentation on vaccination status.15 Similarly, the reason for travel was unknown in 41% of our cohort and VFR-related travel rates could not be calculated. However, among those for whom purpose of travel was known, there were seven times more VFR travellers than non-VFR travellers, indicating a significantly higher rate in VFR travellers, similar to other studies.15

This study may underestimate the burden of enteric fever within the Auckland. First, only cases admitted to hospital were included. Community laboratory data suggested that during the time of the study, 29 patients were found who were culture positive for either S. Typhi or Paratyphi without an admission to hospital. A similar review in the United States14 noted only three quarters of cases of typhoid was hospitalised. Second, legal notification of laboratory and clinical cases to ARPHS was not introduced until December 2007 and prior to that some cases would have been missed as they relied solely on clinician-led notification.

The strength of this study is that it is a comprehensive, city-wide study providing the largest ever reported cohort of enteric fever acquired in the Pacific, and for the first time provides comparative data for Pacific-acquired versus Asian-acquired enteric fever.

Conclusion
More information on enteric fever in the Pacific, particularly Samoa, is required, particularly in view of concerns about increasing resistance and changes to antibiotic practice within this region. Further molecular research on locally acquired disease would confirm Pacific clonality. There are public health implications related to preventing local transmission within NZ from imported cases and privately imported contaminated products. VFR, especially those visiting India and Samoa, are particular targets for pre-travel care and vaccination.

References
14 Health Protection Agency. Final Report and Evaluation of Pilot of Enhanced Enteric
Characteristics favouring a delayed disposition decision in the emergency department

L. Perimal-Lewis,1 P. H. Hakendorf2 and C. H. Thompson3

1School of Computer Science, Engineering and Mathematics, Flinders University, 2Clinical Epidemiology Unit, Flinders Medical Centre, and 3Clinical Studies, University of Adelaide, Adelaide, South Australia, Australia

Abstract

Background: The working hours of a hospital affects efficiency of care within the emergency department (ED). Understanding the influences on ED time intervals is crucial for process redesign to improve ED patient flow.

Aim: To assess characteristics that affect patients’ transit through an ED.

Methods: Retrospective cohort study from 2004 to 2010 of 268 296 adult patients who presented to the ED of an urban tertiary-referral Australian teaching hospital.

Results: After adjustment for Australasian Triage Scale (ATS) category, every decade increase in age meant patients spent an additional 2 min in the ED waiting to be seen (P < 0.001) and an extra 29 min receiving treatment (P < 0.001). For every additional 10 patients in the ED, the ‘waiting time’ (WT) phase duration increased by 20 min (P < 0.001) and the ‘Assessment and Treatment Time’ (ATT) phase duration increased by 26 min (P < 0.001). When patients arrived outside working hours, the WT phase duration increased by 20 min (P < 0.001). When seen outside working hours, the ATT phase duration increased by 34.5 min (P < 0.001).

Conclusion: Extrinsic to the patients themselves and in addition to ED overcrowding, the working hours of the hospital affected efficiency of care within the ED. Not only should the whole of the hospital be involved in improving efficient and safe transit of patients through an ED, but the whole of the day and every day of the week deserve attention.

Introduction

A prolonged stay for a patient within the emergency department (ED) can adversely affect their outcome.1-3 Therefore, there is considerable effort directed towards facilitating the timely transit of patients through a hospital’s ED. The excessive time that admitted patients wait in the ED for an inpatient bed (access block) has received attention,4,5 but it takes time to decide to admit or discharge an acutely unwell patient in the first place. Once
the patient is triaged, a doctor must then attend to the patient, assess them, commence treatment if necessary and then decide whether the patient requires admission to hospital. Initial triage of the patient allows ED staff to prioritise their workload and categorise patients according to a scale. The time ED staff take to initiate their bedside clinical assessment of the patient is closely monitored with significant governmental oversight of this time period. The National Emergency Access Target requires 90% of ED presentations at public hospitals to be admitted to the hospital, transferred to another hospital or discharged within 4 h. The subsequent parts of the disposition–decision process (admit, discharge or transfer the patient) are less well studied.

We can divide the time a patient spends in ED into three distinct phases. The first phase is the time it took for triaged patients to be seen by an ED doctor. We classify this phase as ‘waiting time’ (WT) phase. The second phase is the time it subsequently took for the patients to undergo investigations and receive treatment prior to a disposition decision being made. We classify this phase as the ‘assessment and treatment time’ (ATT) phase. The third phase starts when the admitted patient awaits a bed in the hospital itself. We classify this phase as ‘admission delay time’ (ADT) phase.

The relative importance of the triage-to-admit time (= WT phase + ATT phase) and ADT phase has recently been addressed in a study restricted to general medical patients9 where a short triage-to-admit time was associated with an increase in mortality if coupled with a prolonged ADT. Another study also restricted to general medical patients7 found prolonged triage-to-admit time for presentations outside of working hours and for those patients with less urgent Australasian Triage Scale (ATS) categories. However, these studies have not distinguished between WT phase and ATT phase.

A recent comprehensive review done on ED overcrowding measures identified time interval and patient count to be the most promising measures.6,9 The aim of this study was to define the characteristics of patients presenting to the ED in the context of WT phase and ATT phase. A greater understanding of the influences upon the duration of the disposition decision processes should inform new strategies to address ED overcrowding. Process redesign can thus be targeted better, and an integrated ED- or hospital-wide process improvement approach can be facilitated.

Aims

The aim of this study was to assess characteristics that affect patients’ transit through an ED.

Methods

Study design and setting

We performed a retrospective study of all adult patients who presented to the ED at Flinders Medical Centre (FMC). FMC is an urban Australian tertiary-referral teaching hospital. The data cover a wide variety of patients with varied comorbidities and disease severities.

Incoming patients were identified and triaged upon presentation into ATS categories; these scores are used as a measure of the urgency of review necessary for each patient. Each patient presenting to the ED had three recorded timestamps indicating (i) when they were triaged, (ii) when they were seen by a doctor/nurse and (iii) when a disposition decision had been made (usually to admit them, transfer them to another hospital or discharge them to their home with or without outpatient follow up). Accordingly, the time a patient spent in the ED awaiting a disposition decision was divided into two phases: a WT phase and an ATT phase. The WT phase therefore is the elapsed time between triage date/time and date/time seen by the ED doctor. The ATT phase is the elapsed time between the date/time seen by the ED doctor and the disposition date/time. The number of patients in the ED when a patient started each of these ED phases and the time of day (whether within working hours or not) were also derived for each patient journey. The time any admitted patient might spend in the ED awaiting a bed, the ADT phase, can be delineated but was removed temporarily from our consideration. The time a patient spends during their WT phase in the ED and their overall length of stay (LOS) in the ED are routinely measured and reported by hospitals.

The patient characteristics assessed in our study were age and ATS category. The ED characteristics that were assessed included the time of day and the number of patients in the ED when each ED phase started for each patient. Working hours were defined as 0800–1800 h Monday to Friday. The outcome measures of most interest were the durations of the WT and ATT phases.

Data

Administrative data were extracted from the hospital’s patient electronic health records. The data set contained patients who presented to the hospital’s ED between the 1 January 2004 and the 1 January 2011. These data were merged with the ED patient count data set to gather information about the number of patients in the ED at the time of patient presentation, at the time of initiation of doctor assessment and at the time of disposition decision. Further exclusion of data was necessary for a model.
that reflected the main behaviour of the system. Therefore, data were analysed only from patients for whom all variables were included, whose WT phase duration was ≥20 and ≤24 h, whose ATT phase duration was ≥0 and ≤48 h and, if admitted, who spent ≥20 and ≤48 h awaiting an inpatient ward bed. Records with an uncommon time-stamp sequence were also removed. These criteria led to the exclusion of 4735 sets of data.

Statistical analysis

Data analysis was performed using Microsoft Office Access, Microsoft Office Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and statistical analysis was performed using STATA 13.1 (STATA Corp., College Station, TX, USA).

Multiple regression analysis was performed to model the relationship between the explanatory variables and the outcome variables (WT phase and ATT phase). As the sample size is large and satisfies the central limit theorem, none of the outcome/dependent variables was transformed. The F-value for all models had a P-value of <0.0001 indicating the independent variables were reliable for predicting the dependent variables. Variables in all models were checked for multicollinearity using the variance inflation factor. There were no variables with standard errors for the b coefficient that were greater than 2.0 suggesting that there were no numerical problems with any of the independent variables. A P-value of <0.05 was considered as statistically significant.

Ethics approval

Ethics approval was granted by the local Health Service/University Human Research Ethics Committee for the use of data from the patient journey database.

Results

A total of 268 296 patients, aged 18 years or older, was triaged in the ED over the 7 years of our study. Of these, 9434 did not wait to be seen subsequently by any ED doctor and another 28 were pronounced dead on arrival. This meant that over the duration of the study, 255 640 adult patients started to receive treatment in the ED. Of these patients, 316 died in the ED, 132 966 (52.0%) were discharged from the ED, 106 071 (41.5%) were admitted to that index hospital, and 16 266 (6.4%) were transferred to another hospital. Of those 106 071 admitted to the index hospital, 85 520 had to wait in the ED for an inpatient hospital ward bed to become available for them. Some of the characteristics of these patients and their stay in the ED are presented in Table 1.

Of the patients who presented to the ED, fewer than half (44.9%) presented inside working hours. Of the patients who were assessed by a doctor in the ED, 41.2% were initially assessed within working hours. The average number of patients in the ED at the time of any person’s triage was 48.3 (±12.2 standard deviation (SD)) inside working hours and 43.2 (±12.0 SD) outside working hours.

Multiple linear regression analysis (Table 2) demonstrated several characteristics that, even after adjustment for ATS category, were significant influences (P < 0.001) upon WT phase duration including patient age, the number of patients in the ED at triage time and whether triage occurred within or outside working hours. More explicitly, for every decade increase in age, the WT phase duration rose by 2.2 min. For every additional 10 patients in the ED at the time of triage, the WT phase duration rose by 2.2 min. If triage occurred outside working hours, then WT phase duration was 20.3 min longer than for a similar patient seen inside working hours. Discharged patients spent about 11 min longer waiting to be seen than admitted patients.

The same characteristics and more were identified that significantly influenced (P < 0.001) the ATT phase of a patient’s stay in the ED. These characteristics included the ATS category for the patient, their age, their WT phase duration, the number of patients in the ED at the time of initial doctor assessment and whether the time of that assessment was within working hours or outside working hours (Table 3). For every decade increase in age, the ATT phase duration rose by 29 min. For every additional 10 patients in the ED at the time of initial assessment, the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Presenting patients n = 255 640</th>
<th>Admitted patients n = 106 071</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.9 (22.3)</td>
<td>59.8 (21.8)</td>
</tr>
<tr>
<td>WT phase duration (h)</td>
<td>1.5 (1.3)</td>
<td>1.4 (1.4)</td>
</tr>
<tr>
<td>ATT phase duration (h)</td>
<td>5.8 (6.9)</td>
<td>9.9 (8.1)</td>
</tr>
<tr>
<td>Time awaiting bed (h)</td>
<td>4.6 (5.9)</td>
<td>2.3 (4.9)</td>
</tr>
<tr>
<td>Total ED length of stay (h)</td>
<td>9.1 (10.4)</td>
<td>15.6 (12.4)</td>
</tr>
</tbody>
</table>

ATS, Australasian Triage Scale; ATT, assessment and treatment time; ED, emergency department; IQR, interquartile range; SD, standard deviation; WT, waiting time.

© 2014 Royal Australasian College of Physicians
duration of the ATT phase rose by 25.9 min. If that initial assessment occurred outside working hours, then ATT phase duration was 34.5 min longer than the ATT phase duration for a similar patient seen inside working hours. The duration of the WT phase had a negligible effect upon the ATT phase duration. Every hour increase in the duration of the WT phase was associated with an increase in the ATT phase duration of only about 10 min. Discharged patients spent about 8 h less in the ATT phase compared with patients who were admitted.

Discussion

We have shown that the time a patient spends in the ED awaiting a disposition decision depends in part not only upon factors inherent to each patient, but also upon independent factors associated with the ED environment and the time of day and day of the week of the ED presentation. Also, the relative importance of all these factors can be gauged by our results.

As might be expected, age-dependent factors prolong the time a patient spends being diagnosed and receiving treatment despite patients having a similar ATS category and being in the ED at the same time. Age has a small effect on the time that patients wait to be seen in the first place. The prevalence of many diseases rises with age. Co-morbidity is present in many older people\textsuperscript{12} and more investigations and ‘sorting’ are required for older patients than for younger patients.\textsuperscript{6}

ED overcrowding impairs ED function.\textsuperscript{4,11} Our data suggest that ED overcrowding lengthens the time it takes until a patient is seen almost as much as it lengthens the time taken to reach a disposition decision on that patient. Strategies to decongest the ED clearly remain critical to efficient patient care. Reducing the transit times for patients attending the ED should reduce ED overcrowding\textsuperscript{13,14} and improve patient outcomes.\textsuperscript{13} The eventual disposition of the patient in the ATT phase was higher as expected for those patients to be admitted.

The time taken to reach a disposition decision for a patient is severely affected by the time of day or day of the week they present and this is independent of any overcrowding in the ED, the age of the patient and their ATS category. In our study, over half the workload of the ED was initiated outside working hours and about an hour can be added on average to patients’ ED stay if presentation occurs outside working hours. Compared with within working hours, outside hours may be associated with a reduction in the seniority of ED and hospital staff, greater staff fatigue and reduced

Table 2 Regression parameters for the duration of the WT phase

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (95% CI)</th>
<th>Effect of unit change in parameter on WT phase (min) (95% CI)</th>
<th>Robust standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>0.0037 (0.0035–0.0039)</td>
<td>0.2220 (0.2100–0.2340)</td>
<td>0.0001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATS categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATS category 2</td>
<td>0.5038 (0.4810–0.5175)</td>
<td>30.2280 (28.8600–31.0500)</td>
<td>0.0070</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATS category 3</td>
<td>1.8094 (1.7950–1.8238)</td>
<td>108.5640 (107.7000–109.4280)</td>
<td>0.0074</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATS category 4</td>
<td>1.7760 (1.7613–1.7907)</td>
<td>106.5600 (105.6780–107.4420)</td>
<td>0.0075</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATS category 5</td>
<td>1.3739 (1.3502–1.3976)</td>
<td>82.4340 (81.0120–83.8560)</td>
<td>0.0121</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presentation to triage outside working hours†</td>
<td>0.3381 (0.3289–0.3473)</td>
<td>20.2860 (19.7340–20.8380)</td>
<td>0.0047</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient count in ED at time of presentation to triage</td>
<td>0.0331 (0.0327–0.0335)</td>
<td>1.9860 (1.9620–2.0100)</td>
<td>0.0003</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†Working hours = 0800–1800 h from Monday to Friday. ATS, Australasian Triage Scale; CI, confidence interval; ED, emergency department; WT, waiting time.

Table 3 Regression parameters for the duration of the ATT phase

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (95% CI)</th>
<th>Effect of unit change in parameter on ATT phase (min) (95% CI)</th>
<th>Robust standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>0.0483 (0.0470 to 0.0495)</td>
<td>2.8980 (2.8200 to 2.9700)</td>
<td>0.0016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATS Categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATS category 2</td>
<td>0.7209 (0.4923 to 0.9495)</td>
<td>43.2540 (29.5380 to 56.9700)</td>
<td>0.1166</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATS category 3</td>
<td>−0.3770 (−0.5996 to −0.1543)</td>
<td>−22.6200 (−35.9760 to −9.2580)</td>
<td>0.1136</td>
<td>0.001</td>
</tr>
<tr>
<td>ATS category 4</td>
<td>−2.7192 (−2.9414 to −2.4970)</td>
<td>−163.1520 (−176.4840 to −149.8200)</td>
<td>0.1134</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATS category 5</td>
<td>−4.7306 (−4.9574 to −4.5037)</td>
<td>−283.8360 (−297.4440 to −270.2220)</td>
<td>0.1158</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment initiation outside working hours†</td>
<td>0.5752 (0.5202 to 0.6303)</td>
<td>34.5120 (31.2120 to 37.818)</td>
<td>0.0281</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient count in ED at time of treatment initiation</td>
<td>0.0432 (0.0410 to 0.0455)</td>
<td>2.5920 (2.4600 to 2.7300)</td>
<td>0.0012</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waiting to be seen (WT) phase duration (h)</td>
<td>0.1665 (0.1440 to 0.1890)</td>
<td>9.9900 (8.6400 to 11.3400)</td>
<td>0.0115</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†Working hours = 0800–1800 h from Monday to Friday. ATS, Australasian Triage Scale; ATT, assessment and treatment time; CI, confidence interval; ED, emergency department; WT, waiting time.
staff support for the provision of timely laboratory-based and radiological investigations. There may also be reduced availability of in-hospital medical staff to process imminent admissions because they are contemporaneously responsible for in-patients already on the wards. Our study was not designed to explain these observed variations in the duration of phases of patient care within the ED. Our study does suggest that a round-the-clock, 7-day-a-week hospital-wide approach to emergency care is critical to efficient ED processing of all patients. Also, particular attention should be paid not only to reduction of ED overcrowding, but also to the older patient in the ED. Again, the hospital as a whole has much to offer the ED in these regards. There is some evidence that too short a time spent reaching a disposition decision can be harmful so further work in this area of ED-located patient care is clearly required.

**Limitations**

This was a retrospective study performed at a single site. Data collection quality was affected resulting in the removal of records that did not record all variables needed for the analysis. Mapping the patient journey and the processes that occur within the WT and ATT phase of patient care is critical to a greater understanding of how to reduce waste during this important and sometimes lengthy period of initial patient care. Charlson co-morbidity index, as modified by Quan and colleagues, was only recorded for those admitted patients in the administrative data set. The analysis includes all ED presentations, as such it was not possible to include co-morbidity index in the models.

**Conclusion**

The age of a patient, their ATS category and the number of patients within the ED all contribute to slow transit for patients through the ED. Independent of these influences, patient presentation within or outside working hours was a major influence upon the time taken to reach a disposition decision. Our work suggests that hospitals need to provide a similar level of service to support their ED at 10 p.m. as at 10 a.m. every day of the week.

**References**

Epidemiology, disease burden and outcomes of cirrhosis in a large secondary care hospital in South Auckland, New Zealand

J. C. Hsiang,1 W. W. Bai,1 Z. Raos,1 W. Stableforth,1 A. Upton,1 S. Selvaratnam,1 E. J. Gane2 and S. J. Gerred1

1 Counties Manukau District Health Board, Middlemore Hospital and 2 New Zealand Liver Transplant Unit, Auckland District Health Board, Auckland City Hospital, Auckland, New Zealand

Key words cirrhosis, liver complication, cirrhosis mortality, viral hepatitis, hepatocellular carcinoma, non-alcoholic liver disease.

Correspondence John C. Hsiang, Counties Manukau District Health Board, Gastroenterology Department, Middlemore Hospital, Hospital Road, Otahuhu, Manukau, Auckland, New Zealand.

Email: jchsiang@gmail.com

Received 27 June 2014; accepted 28 October 2014.
doi:10.1111/imj.12624

Abstract

Background: Liver cirrhosis is an important cause of morbidity and mortality; however, little is known about its impact in New Zealand.

Aims: We aim to determine the disease burden, epidemiology and outcomes of cirrhotic patients.

Methods: This is a retrospective study of cirrhosis patients under secondary public hospital care in a geographically defined region, between the years 2000 and 2011. Cirrhosis complications and mortality was recorded. Poisson log-linear regression analysis was performed for incidence rate ratio (IRR) and Cox regression analysis was used to analyse time-related events.

Results: Seven hundred and forty-six cirrhotic patients were analysed; most were European/Other (39.9%), Pacific islanders (21.6%), Southeast Asian/Chinese (17.8%) and Maori (12.3%). 68.4% were male. The common primary aetiologies for cirrhosis were chronic hepatitis B (CHB) cirrhosis (37.3%), alcoholic liver disease (ALD) cirrhosis (24.1%), chronic hepatitis C (CHC) cirrhosis (22.3%) and non-alcoholic fatty liver disease (NAFLD) cirrhosis (16.4%). The hepatocellular carcinoma (HCC) mortality rates were highest in NAFLD and CHB cirrhosis groups (3.0 and 3.1 per 100 patient-year respectively), compared with ALD and CHC groups (2.2 and 1.4 per 100 patient-year, all \( P < 0.05 \) respectively). Patients with ALD and NAFLD cirrhosis had the highest all-cause and non-HCC mortality rate compared with viral hepatitis cirrhosis groups. The IRR for HCC incidence, liver-related mortality and HCC mortality were 1.087, 1.098 and 1.114, respectively (all \( P < 0.001 \)), suggesting increasing incidence and disease burden over the study period.

Conclusion: The number of cirrhotic patients in secondary care is increasing steadily. Cirrhosis complications and mortality rates are also rising, particularly the incidence and mortality of HCC.

Introduction

Liver cirrhosis is a major cause of morbidity and mortality among individuals with viral hepatitis, non-alcoholic fatty liver disease (NAFLD) and hazardous alcohol use. Overall, liver cirrhosis contributes to 31 027 disability-adjusted life years (DALY) worldwide in 2010 increased by 27.5% since 1990 as shown in the Global Burden of Disease Study. However, these figures did not take into account the DALY from hepatocellular carcinoma (HCC) for which cirrhosis and viral hepatitis are major aetiologies.

South Auckland, New Zealand (NZ) is served by Counties Manukau District Health Board (CMDHB), with a population of 512 130 (2013 population projection). It consists of a multi-ethnic mix of patients. Compared with the rest of NZ, South Auckland consists of less Europeans (40.5% vs 67.6%), more Maori and Pacific people (40%
vs 20.6%) and more Asians (21% vs 9.2%). Among the CMDHB population, the prevalence of risk factors for chronic liver disease including chronic hepatitis B (CHB), hazardous alcohol consumption, and obesity and type 2 diabetes (both risk factors for NAFLD) is high. In addition, the diagnosis of NAFLD and its cirrhosis are often delayed and underrecognised. Currently, chronic hepatitis C (CHC) infection is estimated to affect about 1% of New Zealanders and CMDHB rates are believed to be similar to the population as a whole with much remaining undiagnosed.

While cirrhosis and its complications may be preventable, the incidence and the impact of cirrhosis are not known in NZ or the South Pacific region. Therefore, our aim was to describe the epidemiology and disease burden of the four most common known causes of cirrhosis in the CMDHB area (alcoholic liver disease [ALD], NAFLD, CHC and CHB infection) over a 12-year period.

Methods

Patients

CMDHB located in the South Auckland, NZ, provides health service to residents within the defined geographic area of districts within South Auckland. Middlemore Hospital, the sole secondary care hospital, provides liver-related healthcare to the residents in the region. There are three other public hospitals in the rest of Auckland region with linkage of the hospital computer database containing comprehensive information on demographics, hospital admissions and important clinical data. All residents will attend liver-related health services at Middlemore Hospital and cannot engage with nearby public hospital services unless referred by specialists. Any patients with HCC or liver failure require assessment for orthotopic liver transplantation (OLT) will be referred to the NZ Liver Transplant Unit, Auckland City Hospital, located 20 km to the north. Following interventions for HCC or OLT, patients would return to the CMDHB clinic for follow up. Given the comprehensiveness of the clinical data available in a defined region of health service coverage, we therefore carried out a retrospective review of cirrhosis patients under our hospital follow up.

Data collection

We performed retrospective review of all patients diagnosed with cirrhosis over the 12-year period from January 2000 to 31 December 2011. Data were collected from patients’ electronic system for all patients identified on the cirrhosis database. The diagnosis of cirrhosis was made on clinical, biochemical, histological, transient elastographic or radiological evidence (nodular liver surface, dilated portal vein (>12 mm) and enlarged spleen (>12 cm)) accompanied by clinical signs of cirrhosis such as oesophageal varices, ascites, hepatic encephalopathy and thrombocytopenia. Where transient elastography (FibroScan; EchoSens, Paris, France) was used to assess degree of fibrosis, liver stiffness measurement cut-off for cirrhosis was 11 kPa, 14.5 kPa for hepatitis B and hepatitis C, and 19.5 kPa and 10.3 kPa for ALD and NAFLD primary aetiologies respectively.

Clinical features and complications of cirrhosis (oesophageal or gastric variceal bleeding, spontaneous bacterial peritonitis, ascites, hepatic encephalopathy and HCC) were defined and recorded according to international guidelines. Child-Pugh-Turcotte stage is used to assess the prognosis of cirrhosis based on five clinical measure of liver disease such as total bilirubin, serum albumin, INR, ascites and hepatic encephalopathy. Each measure is score between one to three points. Model for End-Stage Liver Disease (MELD) score is a scoring system for assessing the severity of chronic liver disease. The formula is: MELD = 3.78 [Log serum bilirubin (mg/dL)] + 11.2 [Log INR] + 9.57 [Log serum creatinine (mg/dL)] + 6.43.

Symptomatic presentation was defined as an acute presentation with complications of cirrhosis at the time of cirrhosis diagnosis. The primary end-points are cirrhosis complications and death or OLT. Ethnicity was defined by ethnicity codes used by the NZ Ministry of Health: European, Other, Maori, Pacific People, Indian and Asian. The end-point of the study was death, OLT, last follow-up date or up to 31 January 2011.

Aetiology

The primary aetiology of cirrhosis was determined by the senior hepatologists. The diagnosis of viral hepatitis was based on positive hepatitis serology (positive hepatitis B surface antigen for more than 6 months or positive hepatitis C virus [HCV] RNA). ALD was diagnosed based on history of significant alcohol intake (more than 21 units of alcohol per week for males, and 14 units per week for females) in the absence of other significant risk factors for chronic liver disease as the main aetiology. Non-alcoholic fatty liver aetiology was diagnosed by liver histology, transient elastography or radiological suspicion of fatty liver (without significant history of alcohol intake, methotrexate, corticosteroid use, viral hepatitis or positive autoimmune antibodies), in the presence of metabolic syndrome features such as obesity, and type 2 diabetes.

Secondary causes or co-factors for cirrhosis were determined as an important but minor aetiology in the cause.
of patients’ progression to cirrhosis. In addition to viral serology, routine investigations included liver autoimmune serology, iron studies, ceruloplasmin and alpha-one antitrypsin levels.

Statistical analysis

The data were analysed using SPSS (IBM, version 21; IBM, Armonk, NY, USA). Comparison between categorical variables was carried out using Chi-square test or Fisher’s exact test and between continuous variables using student t-test or Mann–Whitney test where appropriate. Log-rank test was used to compare time-dependent variables. The crude age- and ethnic-adjusted incidence rates for age stratified groups (15–29, 30–44, 45–59, 60–79, >80 years) and ethnic groups were calculated by dividing age-specific and ethnicity-specific liver events by age- and ethnic-specific (weighted) CMDHB population sizes data from the NZ Health Statistics (Ministry of Health). Projected cirrhosis incidence per year was calculated by dividing the year-specific number of total cirrhosis patients under active follow up by the year-specific CMDHB population data from NZ Health Information Services and using results from year 2000–2011 to extrapolate the cumulative cirrhosis patients under active follow up until 2023. Cox regression survival analysis was used to determine the predictors associated with mortality. Logistic regression analysis was used to examine the predictors of symptomatic HCC at cirrhosis diagnosis. Poisson log-linear regression model was used to examine the incidence rate ratio (IRR) looking for trends in liver event incidence and mortality and significance between time-dependent variables (where appropriate). IRR estimated from the model larger than 1.0 indicate that the event has a higher incidence than the preceding year. A two-sided P value <0.05 was considered significant.

Results

Demographics and aetiology

Over the 12-year study period between year 2000 to 2011, 832 patients were identified. Seven hundred and forty-six patients had either CHB, CHC, ALD or NAFLD as the primary aetiology of the cirrhosis with a follow up of 2792.5 patient-years and were analysed further. Eighty-six patients (10.3%) had cirrhosis from autoimmune hepatitis (32 patients), primary biliary cirrhosis (9 patients), primary sclerosing cholangitis (8 patients) and other causes (12 patients). This group was not analysed further. Patient demographics and characteristics at baseline are shown in Table 1. The majority of patients were male (68%) and the mean age at baseline was 56 ± 13 years. Maori patients were younger at baseline (52 ± 11 years) compared with non-Maori (57 ± 13 years, P < 0.05). Overall, 9.7% (72/746 patients) were lost in follow up during the study with a follow-up period of 2.6 ± 2.6 years, compared with 3.9 ± 3.4 years of follow up in patients who were followed up until death or census date.

CHB accounted for 37.2% of the cohort, followed by ALD (24.1%), CHC (22.3%) and NAFLD (16.4%). The patients were predominantly male except for the NAFLD cohort where the gender ratio was 1:1. The aetiology of cirrhosis varied strongly according to patient ethnicity. Asian cirrhosis were much more likely to have viral (CHB/CHC) related cirrhosis than ALD/NAFLD (91.7% vs 8.3%, P < 0.001) compared with non-Asians. Hepatitis B was also the leading cause of cirrhosis in Maori compared with other causes (49 of 92 patients, 53.3% vs 46.7%, P = 0.001) and also in Pacific people, compared with other causes (123 of 161 patients, 76.4% vs 23.6%, P < 0.001). However, cirrhosis due to CHB infection was an uncommon aetiology among Europeans (16/298 patients, 5.4%) and Indians (5/62 patients, 8.1%) as ALD was the most aetiology identified in 42.6% of Europeans and 35.5% of Indians. Among the Pacific people, CHC cirrhosis was a rare cause of cirrhosis compared with other aetiologies (2.4%, P < 0.05 in all group comparisons). Hazardous (significant) alcohol consumption was the most common secondary cause of cirrhosis in 56 of 746 (7.5%) patients and 18.7% (31/166) of all CHC patients had significant alcohol use as the secondary cause of their cirrhosis (P < 0.001, compared with other aetiologies). Patients with ALD were more likely to present with cirrhosis complications at diagnosis compared with other groups (P < 0.05) and presented with a higher model for end-stage liver disease (MELD) score and more Child-Pugh C cirrhosis at diagnosis compared with other groups (all P < 0.05).

The majority (68.0%) of the CHB cirrhotic patients were HBeAg negative at diagnosis. Anti-viral therapy was initiated in 67.6% (188 of 278 patients) at diagnosis and the remainder had low or undetectable HBV DNA level. Among the patients with CHC cirrhosis, 63.9% (106 of 166 patients) received interferon or pegylated interferon/ribavirin treatment. Of these, 29.2% (31/106) were cured while 18.9% were responder/relapsers and 50.9% were null responders.

Incidence and outcome

The crude age- and ethnicity-adjusted incidence rate of different cirrhosis aetiologies was calculated for the four groups (Fig. 1) over the study period. Given the incidence ratio of cirrhosis of different aetiology varies with
Table 1: Baseline characteristics of 746 cirrhosis patients in South Auckland, New Zealand (year 2000–2011)

<table>
<thead>
<tr>
<th></th>
<th>ALD (group 1) n = 180</th>
<th>NAFLD (group 2) n = 122</th>
<th>CHB (group 3) n = 278</th>
<th>CHC (group 4) n = 166</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis (years ± SD)</strong></td>
<td>59 ± 12</td>
<td>63 ± 12</td>
<td>52 ± 12</td>
<td>54 ± 11</td>
<td>*</td>
</tr>
<tr>
<td><strong>Follow-up duration (years ± SD)</strong></td>
<td>3.7 ± 3.5</td>
<td>3.9 ± 3.4</td>
<td>4.1 ± 3.4</td>
<td>4.4 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Male gender (%)</strong></td>
<td>143 (79.4%)</td>
<td>62 (50.8%)</td>
<td>191 (68.7%)</td>
<td>114 (68.7%)</td>
<td>*</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>6 (3.3%)</td>
<td>5 (4.1%)</td>
<td>85 (30.6%)</td>
<td>37 (22.3%)</td>
<td>**</td>
</tr>
<tr>
<td>European/Other</td>
<td>127 (70.6%)</td>
<td>70 (57.4%)</td>
<td>16 (5.8%)</td>
<td>85 (51.2%)</td>
<td>**</td>
</tr>
<tr>
<td>Maori</td>
<td>14 (7.8%)</td>
<td>6 (4.9%)</td>
<td>49 (17.6%)</td>
<td>23 (13.9%)</td>
<td>**</td>
</tr>
<tr>
<td>Indian</td>
<td>22 (12.2%)</td>
<td>18 (14.8%)</td>
<td>5 (1.8%)</td>
<td>17 (10.2%)</td>
<td>**</td>
</tr>
<tr>
<td>Pacific people</td>
<td>11 (6.1%)</td>
<td>23 (18.9%)</td>
<td>123 (44.2%)</td>
<td>4 (2.4%)</td>
<td>*</td>
</tr>
<tr>
<td><strong>Secondary cause</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>NA</td>
<td>10 (8.2%)</td>
<td>15 (5.4%)</td>
<td>31 (18.7%)</td>
<td>****</td>
</tr>
<tr>
<td>NAFLD</td>
<td>13 (7.2%)</td>
<td>NA</td>
<td>7 (2.5%)</td>
<td>5 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>CHB</td>
<td>9 (5%)</td>
<td>2 (1.6%)</td>
<td>NA</td>
<td>4 (2.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>CHC</td>
<td>6 (3.3%)</td>
<td>NA</td>
<td>1 (0.4%)</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>HDV</td>
<td>NA</td>
<td>NA</td>
<td>9 (3.2%)</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.7%)</td>
<td>3 (2.5%)</td>
<td>0</td>
<td>1 (0.6%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Method of diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>9 (5.0%)</td>
<td>35 (28.7%)</td>
<td>94 (33.8%)</td>
<td>20 (12.0%)</td>
<td>*</td>
</tr>
<tr>
<td>Transient elastography</td>
<td>22 (12.2%)</td>
<td>6 (4.9%)</td>
<td>41 (14.7%)</td>
<td>86 (51.8%)</td>
<td>*</td>
</tr>
<tr>
<td>Radiological</td>
<td>45 (25%)</td>
<td>6 (4.9%)</td>
<td>78 (28.1%)</td>
<td>36 (21.7%)</td>
<td>*</td>
</tr>
<tr>
<td>Cirrhosis complications</td>
<td>104 (57.3%)</td>
<td>75 (61.5%)</td>
<td>65 (23.4%)</td>
<td>24 (14.5%)</td>
<td>*</td>
</tr>
<tr>
<td>MELD score at diagnosis</td>
<td>13 ± 6</td>
<td>10 ± 4</td>
<td>10 ± 6</td>
<td>8 ± 3</td>
<td>*</td>
</tr>
<tr>
<td>Child-Pugh-Turcotte Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class A</td>
<td>76 (42.3%)</td>
<td>79 (64.3%)</td>
<td>198 (71.2%)</td>
<td>144 (86.7%)</td>
<td>*</td>
</tr>
<tr>
<td>Class B</td>
<td>65 (36.1%)</td>
<td>35 (28.7%)</td>
<td>61 (21.9%)</td>
<td>16 (9.6%)</td>
<td>*</td>
</tr>
<tr>
<td>Class C</td>
<td>39 (21.7%)</td>
<td>8 (6.6%)</td>
<td>19 (6.8%)</td>
<td>6 (3.6%)</td>
<td>*</td>
</tr>
<tr>
<td>Platelet count (×10^3/mm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;150</td>
<td>73 (41%)</td>
<td>56 (45.9%)</td>
<td>146 (52.7%)</td>
<td>79 (47.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>100–150</td>
<td>63 (35.4%)</td>
<td>43 (35.2%)</td>
<td>61 (21.9%)</td>
<td>49 (29.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;100</td>
<td>42 (35.4%)</td>
<td>23 (18.9%)</td>
<td>19 (6.8%)</td>
<td>38 (22.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;35</td>
<td>70 (38.9%)</td>
<td>63 (51.6%)</td>
<td>175 (62.9%)</td>
<td>123 (74.1%)</td>
<td>**</td>
</tr>
<tr>
<td>28–35</td>
<td>67 (37.2%)</td>
<td>42 (34.4%)</td>
<td>58 (20.9%)</td>
<td>33 (19.9%)</td>
<td>**</td>
</tr>
<tr>
<td>&lt;28</td>
<td>43 (23.9%)</td>
<td>17 (13.9%)</td>
<td>45 (16.2%)</td>
<td>10 (6.1%)</td>
<td>*</td>
</tr>
</tbody>
</table>

χ² test, P value <0.05: *Group 1 versus 2; **Group 1 versus 3; ***Group 1 versus 4; ****Group 2 versus 3; *****Group 2 versus 4; ******Group 3 versus 4. ALD, alcoholic liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; HDV, hepatitis delta virus; NA, not available; NAFLD, non-alcoholic fatty liver disease; MELD, model for end-stage liver disease; NS, not significant.
time, Poisson regression analysis of the crude IRR was performed to determine the trend of the incidence rate changes over the 12 years (Table 2). For NAFLD cirrhosis, there is a small but significant increase in incidence over time, 4.9% increase compared with the previous year (IRR = 1.049, 95% confidence interval (CI): 1.039–1.060, \( P < 0.001 \)). Both the crude IRR for ALD cirrhosis (IRR = 0.976, 95% CI: 0.969–0.983, \( P < 0.001 \)) and CHB cirrhosis (IRR = 0.929, 95% CI: 0.923–0.936, \( P < 0.001 \)) indicated 2.4% and 7.1% reduction, respectively, in incidence per annum compared with the previous year. The crude IRR for cirrhosis outcomes showed significant increase in the rate of symptomatic HCC at cirrhosis diagnosis, HCC incidence, and liver-related and HCC-related mortality over the study period (Table 2).

The total number of patients with documented liver cirrhosis under active follow up was increased by more than fivefold over the past decade from 33 patients per 100 000 in 2001 to 169 per 100 000 in 2011. This trend projection would indicate that the cumulative number of active cases of cirrhosis patients would reach an estimated 300 per 100 000 by year 2023, all things being equal (Fig. 2).

Patients with ALD cirrhosis had the highest annual risk of developing cirrhosis complications over time (43.1 per 100 patient-year) compared with CHB cirrhosis (17.4 per 100 patient-year) and CHC cirrhosis (15.5 per 100 patient year, all \( P < 0.05 \) in group comparisons). The rates of cirrhosis complications were also higher in NAFLD cirrhosis compared with the viral hepatitis groups (31.1 per 100 patient-years, \( P < 0.05 \)). ALD patients were also more

**Figure 1** Crude age- and ethnicity-adjusted incidence rate of cirrhosis (per 100 000 people) by aetiology for year 2000 to 2011. ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C.

**Table 2** Crude age- and ethnicity-adjusted incidence rate ratio of cirrhosis aetiologies and cirrhosis outcomes, for the CMDHB population (year 2000–2011)

<table>
<thead>
<tr>
<th>Aetiology of cirrhosis</th>
<th>Incidence rate ratio (IRR)</th>
<th>Lower range</th>
<th>Upper range</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol liver disease</td>
<td>0.976</td>
<td>0.969</td>
<td>0.983</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-alcoholic liver disease</td>
<td>1.049</td>
<td>1.039</td>
<td>1.060</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>0.929</td>
<td>0.923</td>
<td>0.936</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>1.004</td>
<td>0.996</td>
<td>1.012</td>
<td>0.355</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC incidence during follow up</td>
<td>1.087</td>
<td>1.076</td>
<td>1.098</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incidence of symptomatic HCC at baseline diagnosis</td>
<td>1.01</td>
<td>0.995</td>
<td>1.03</td>
<td>0.17</td>
</tr>
<tr>
<td>Liver-related mortality</td>
<td>1.098</td>
<td>1.087</td>
<td>1.108</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCC-related mortality</td>
<td>1.114</td>
<td>1.099</td>
<td>1.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Crude incidence rate ratio by Poisson log-linear regression analysis. CMDHB, Counties Manukau District Health Board; HCC, hepatocellular carcinoma.
likely to develop variceal bleeding and hepatic encephalopathy compared with the other three groups (all $P < 0.05$). With regards to HCC, CHB cirrhosis patients had significantly higher rate of HCC during follow up compared with ALD and CHC groups (6.1 vs 3.3 vs 3.0 per 100 patient-year, respectively; all $P < 0.05$) but similar rate to those with NAFLD cirrhosis (6.1 vs 4.5, $P = 0.10$).

Both NAFLD and CHB patients had a high rate of HCC presentation at baseline (2.7 and 2.9 per 100 patient-year) compared with ALD and CHC groups respectively (1.0 and 0.7, respectively, all $P < 0.05$). Patients with ALD had the highest all-cause mortality and non-HCC-related liver mortality compared with the viral hepatitis groups (Table 3). Despite having a lower HCC incidence rate per 100 patient-year, the HCC related mortality in ALD patients was comparable to those of NAFLD and CHB patients (2.2, 3.0 and 3.1 per 100 patient-year, respectively; all $P > 0.05$).

Given the significant incidence of HCC at cirrhosis diagnosis, we performed logistic regression analysis to

| Table 3 Risk of cirrhosis complications and death in the CMDHB cirrhosis cohort (year 2000–2011) |
|---------------------------------|---------------|-------------|---------------|---------------|-------------|
|                                | ALD group 1  | NAFLD group 2 | CHB group 3  | CHC group 4   | $P$ value    |
| Follow-up duration (patient-year)  | 579.9         | 334.2        | 1187.3        | 691.1         |             |
| All liver-related complications (per 100 patient-year) | 43.1          | 31.1         | 17.4          | 15.5          | **, ***, *****, ***** |
| Variceal bleeding | 7.9 | 6.9 | 1.7 | 2.5 | **, ***, ** |
| Spontaneous bacterial peritonitis (SBP) | 3.6          | 2.1          | 1.3           | 1.6           | **, *** |
| Hepatic encephalopathy (HE) | 10.9          | 5.1          | 2.6           | 3.2           | **, ***, ** |
| Ascites | 17.4          | 12.6         | 5.7           | 5.2           | **, ***, ** |
| Hepatocellular carcinoma (HCC) | 3.3 | 4.5 | 6.1 | 3.0 | **, ** |
| Cirrhosis complication at first diagnosis (per 100 patient-year) | 16.6 | 14.4 | 5.4 | 2.9 | **, ***, *****, **** |
| HCC at cirrhosis diagnosis (per 100 patient-year) | 1.0 | 2.7 | 2.9 | 0.7 | **, ****, **** |
| Liver transplantation (per 100 patient-year) | 0.7 | 1.5 | 1.8 | 1.3 | NS |
| All-cause mortality (per 100 patient-year) | 15.0 | 12.9 | 6.4 | 4.6 | **, ***, **** |
| Non-HCC related | 4.8 | 3.0 | 1.4 | 1.6 | **, ** |
| HCC related | 2.2 | 3.0 | 3.1 | 1.4 | ** |
| Cardiovascular | 1.6 | 1.8 | 0.3 | 0.1 | **, ***, **** |
| Non-HCC malignancy | 1.1 | 1.5 | 0.3 | 0.1 | **, ***, **** |
| Non-SBP sepsis | 1.9 | 0.3 | 0.7 | 0.1 | **, ** |
| Other/unknown | 3.4 | 3.3 | 0.6 | 1.3 | **, **, **** |

Comparison by Poisson log-linear or Cox regression analysis where appropriate, $P$ value $< 0.05$: *Group 1 versus 2; **Group 1 versus 3; ***Group 1 versus 4; ****Group 2 versus 3; *****Group 2 versus 4; ******Group 3 versus 4. ALD, alcoholic liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CMDHB, Counties Manukau District Health Board; NAFLD, non-alcoholic fatty liver disease; NS, not significant.

© 2014 Royal Australasian College of Physicians
examine the risk factors for this; CHB and NAFLD cirrhosis when compared with ALD cirrhosis (odds ratio (OR) 6.58, 95% CI: 1.42–30.39; OR 4.78, 95% CI: 1.05–21.29, respectively). Maori and Pacific ethnicity (compared with European) were risk factors of HCC presentation at cirrhosis diagnosis (OR 3.47, 95% CI: 1.11–10.83 and OR 6.09, 95% CI: 2.14–17.37, respectively) after adjusting for host factors and severity of cirrhosis at baseline. On Cox regression analysis, Asian, Maori and Pacific people were ethnic predictors of HCC-related mortality or liver transplant (hazard ratio (HR) 2.41, 95% CI: 1.04–5.54; HR 4.13, 95% CI: 1.85–9.25; and HR 3.02, 95% CI: 1.35–6.75, respectively) when compared with European after adjusting for gender, age, significant alcohol use, cirrhosis aetiology, MELD score, albumin and platelet count at baseline (Table 4). Maori, Asian and Pacific people were associated with earlier HCC development after cirrhosis diagnosis compared with European ethnicity (Cox regression HR 2.46, 95% CI: 1.30–4.67 for Maori; HR 1.88, 95% CI: 1.001–3.64 for Asian, and HR 2.89, 95% CI: 1.60–5.25 for Pacific people) after adjusting for gender, baseline age, MELD score, albumin levels, cirrhosis aetiology and significant alcohol use (data not shown).

### Discussion

This study underpins the impact of chronic liver disease in NZ. We described the epidemiology, liver complications and mortality of a South Auckland cohort of cirrhosis patients with four most common causes. To our knowledge, this is the first cohort study from the South Pacific on the incidence and outcomes of cirrhosis of different aetiology, and it highlights several important and changing epidemiological aspects of cirrhosis disease burden our region.

The incidence of CHB cirrhosis has decreased over last decade as shown by the IRR and is likely to be the result of several important interventions: the introduction of universal hepatitis B vaccination in 1990s into NZ, the introduction of lamivudine in year 2000 which reduced cirrhosis progression and complications, and finally,
there was a large cohort of hepatitis B carriers detected through the national hepatitis B screening programme in early 2000s8 which identified a large number of hepatitis B carriers. This decrease in CHB cirrhosis incidence was however not associated with a decrease in the complication rate or mortality rate in these patients. CHB cirrhosis was found to be a predictor of symptomatic HCC at cirrhosis diagnosis (along with NAFLD cirrhosis) suggesting many undiagnosed cases of CHB cirrhosis in the NZ population; in particular, there has been considerable immigration from HBV endemic regions (Pacific and Asia) in the last two decades. Of concern, the incidence rate of HCC (a major complication of CHB patients) among cirrhotic patients at diagnosis has not changed over 12 years. These findings highlight the ongoing importance of hepatitis B screening for at-risk ethnic groups facilitating appropriate follow up and referral.

Consistent with the rising trend of the obesity epidemic, there is an increase in the incidence of NAFLD cirrhosis. In the South Auckland community (and NZ as a whole), 28–29% of adults in NZ are obese.9 Obesity disproportionately affects Maori (~45%) and Pacific people (~62%); however, we saw relatively low rates of NAFLD cirrhosis in these groups, suggesting NAFLD cirrhosis may be underdiagnosed. The impact of NAFLD cirrhosis is significant among our study cohort, with the second highest rate of cirrhosis complications as well as high rates of all-cause, cardiovascular- and malignancy-related mortality. The high rate of NAFLD cirrhosis diagnosis by cirrhosis complication in our study also supported the notion that NAFLD cirrhosis is often underrecognised and diagnosis delayed.10 In other parts of the world, NAFLD is the third commonest indication for OLT in 2009 and will become the most common indication for OLT in the future.29 The disease burden of NAFLD liver disease is likely to continue to impact on the NZ community significantly and the NAFLD cirrhosis patients are likely to be younger over the next three to four decades with the increasing prevalence of childhood obesity.9

High rates of hazardous alcohol consumption and the increasing rates of obesity with the associated metabolic complications are likely to contribute to an ongoing rise in the numbers of those with non-viral cirrhosis over the next two decades.30 Abstinence is the most important intervention that improves survival in ALD patients but is seldom achieved long term.31 In the present study, ALD patients were the mostly likely to present with symptomatic complications at cirrhosis diagnosis (baseline), and have the highest mortality from non-HCC liver complications, cardiovascular causes. At the primary care level, clinicians should be vigilant in taking a thorough alcohol history by screening with CAGE question32 as well as checking for clinical and biochemical signs of cirrhosis which would predict the cirrhosis outcomes and mortality (Table 4). At the population level, health promotion and public health policies are required to reduce the harm of alcohol.

Our current study showed similar incidence of HCC and liver complications in CHC cirrhosis patients to the study by Sangiovanni and colleagues, of 17-year follow-up.33 To date, there has been little therapeutic impact on the burden of CHC, either globally or in NZ. Many CHC cirrhotic patients are not suitable for interferon-based therapy and cure rates are poor.34 With the advent of non-interferon oral-base direct antiviral agents (DAA) for hepatitis C Infection on the horizon, it is likely that many CHC cirrhotic patients will be successfully treated in the future. Studies have already established the effectiveness of DAs in CHC patients with cirrhosis, with or without previous exposure to interferon therapy.35,36 With these treatments, we will certainly see the impact of risk reduction in liver complications, liver-related mortality and OLT in the future; however, it is likely to be many years before we see a large reduction in CHC cirrhosis prevalence due to the high cost barrier.

The incidence of symptomatic HCC presentation at baseline has not changed significantly over the 12-year period. Furthermore, the mortality rates associated with cirrhosis patients increased over the study period. The rising incidence of HCC is a concern in the South Auckland region. In terms of ethnicity, Maori and Pacific people were the predictors of symptomatic HCC at presentation, compared with Europeans. These two ethnic groups (Maori and Pacific people) were significant predictors of HCC-related mortality even after adjusting for age, gender, aetiology and severity of cirrhosis. There are several possible explanations for these findings: among the Maori and Pacific people, obesity and metabolic syndrome are much more prevalent, which is also a predictor of cirrhosis morbidity and mortality.37 Furthermore, poorer health and healthcare access are likely to contribute to the disparity in liver disease outcomes.38 In addition, the increasing incidence of symptomatic HCC at cirrhosis diagnosis suggests screening for advanced liver disease and HCC is important in specific risk groups.

There are several limitations to our study. First, 9.7% of the patients were lost to follow up. In addition, some patients with stable cirrhosis may have their follow up under private specialists therefore not included in the CMDHB database. Notwithstanding this, all cirrhosis patients with complications were referred or admitted to our hospital or the wider Auckland region for further care, which would be captured on the hospital computer database. Given the retrospective nature of the study, we do not have the complete data for
anthropometry or metabolic syndrome for the whole cohort or specifically for the NAFLD group. Furthermore, we have not assessed HCC tumour stage or therapy, which are all important clinical factors in survival of HCC patients.

**Conclusion**

The burden of advanced liver disease is steadily rising in South Auckland, NZ and is associated with rising morbidity and mortality. CHB, ALD, CHC and NAFLD are the common aetiologies. Public health strategies focusing on risk factors such as excessive alcohol use and obesity are required to reduce the impact of non-viral liver disease. Targeted screening for at-risk groups will facilitate early detection of liver disease allowing early and effective intervention and may have an impact on the development of cirrhosis and its complications.

---

**References**


Gastroenterology 2011; 141: 1249–53.


Dose tailoring of anti-tumour necrosis factor-alpha therapy delivers useful clinical efficacy in Crohn disease patients experiencing loss of response

S. Ghaly,1,2 S. Costello,3 L. Beswick,4 A. Pudipeddi,3 A. Agarwal,3 A. Sechi,5 S. Antoniades,1 B. Headon,4 S. Connor,5 I. C. Lawrance,2 M. Sparrow,4 A. J. Walsh1 and J. M. Andrews3, on behalf of AIBDA*

1Department of Gastroenterology, St Vincent’s Hospital and 2Department of Gastroenterology, Liverpool Hospital, University of NSW, Sydney, New South Wales, 3IBD Service, Department of Gastroenterology and Hepatology, School of Medicine, University of Adelaide at Royal Adelaide Hospital, Adelaide, South Australia, 4Department of Gastroenterology, The Alfred Hospital, Melbourne, Victoria and 5Centre for Inflammatory Bowel Disease, Fremantle Hospital, Fremantle, Western Australia, Australia

Key words
Crohn disease, infliximab, adalimumab, anti-TNF-α, dose escalation.

Abstract
Background: ‘Dose tailoring’ of anti-tumour necrosis factor alpha (TNF-α) therapy in Crohn disease (CD), by dose escalation, or shortening of dosing intervals, has been suggested to regain clinical response following a flare in a proportion of patients. However, reported outcome data are sparse and none exists from Australia.

Method: In an observational multicentre, retrospective study, the impact of anti-TNF-α dose tailoring on corticosteroid use, the need for surgery and physician perception of clinical efficacy was examined in a real-world setting at six Australian adult teaching hospitals. Demographics, disease characteristics, medications, indication for and duration of dose tailoring were documented.

Results: Fifty-five CD patients were identified as requiring dose tailoring and secondary loss of response was the indication in 96%. Either adalimumab (64%) or infliximab (36%) was dose escalated for a median of 5 months (range 1–47), with a median of 20 months follow up (range 3–65). At 3 months, dose tailoring reduced the mean number of days on high-dose corticosteroids (45 vs 23, \(P = 0.01\)). Most (78%) patients remained resection free, and 73% of physicians reported good clinical efficacy of dose tailoring. Of those who de-escalated therapy due to induction of remission, long-term (>12 months) follow up and complete data on steroid use were available in 15/28, with 12/15 (80%) remaining steroid free at 1 year.

Conclusion: Short-term dose tailoring regains disease response in the majority of patients with CD. Of these, most will remain free of corticosteroids at 1 year after de-escalating therapy.

Introduction
The monoclonal anti-tumour necrosis factor alpha (TNF-α) antibodies, infliximab (IFX) and adalimumab (ADA), are effective in the treatment of both luminal and fistulising Crohn disease (CD).1–4 The original registration studies reported remission rates of 33–36%, and clinical trial data demonstrated that in the first year of

*Australian Inflammatory Bowel Disease Association.

Funding: S. Ghaly has received lecture fees and/or research support from AbbVie, Janssen, Ferring and Shire. S. Connor has consulted for, received research funding, lecture fees and/or research support from AbbVie, Janssen, Ferring, Shire and Orphan; she also sits (sat) on Advisory Boards for AbbVie, Janssen and Vifor. I. C. Lawrance has consulted to AbbVie, Pharmatel Fresenius Kabi, Janssen-Cilag Pharmaceuticals, Shire, GlaxoSmithKline and Takeda Pharmaceuticals Australia, received speaker’s honoraria from AbbVie, Fresenius Kabi, Janssen-Cilag Pharmaceuticals and Shire, and received educational grants and research grants from AbbVie. M. Sparrow has received educational grants or research support from AbbVie, Ferring and Janssen; he also sits (sat) on Advisory Boards for Janssen. A. J. Walsh has consulted for, received research funding, lecture fees and/or research support from AbbVie, Abbott, Janssen, Ferring, Shire, MSD, Orphan and Takeda; she also sits on advisory boards for AbbVie, Janssen, Abbott and Takeda. J. M. Andrews has consulted for, received research funding, lecture fees and/or research support from AbbVie, Abbott, Janssen, Ferring, Nycomed, AstraZeneca, Shire, Fresenius Kabi, MSD, Orphan & Takeda; she also sits (sat) on Advisory Boards for AbbVie, Janssen, Abbott, MSD, Ferring and Takeda.

Conflict of interest: None.
maintenance treatment with IFX, 42–60% of responders lost response. However, once these agents were used in usual clinical settings, it became clear that higher initial response rates (>80%) and lower rates of long-term loss of response could be achieved (33% over 18 months). Primary loss of response (LOR) is the failure to achieve a meaningful clinical response with induction therapy. Secondary loss of response refers to increased CD activity in a patient with previously good response during anti-TNF-α therapy. This may occur for a number of reasons, including the development of anti-drug antibodies, other factors that increase drug clearance (decreased circulation half life and possible high consumption in severe disease), concurrent true increased disease activity or emerging disease resistance (as some postulate inflammatory mechanisms to change over time).

There are now emerging data that secondary LOR can be effectively managed by dose tailoring. This can be either temporary or permanent and can involve either increasing the dose, or shortening dosing intervals. However, current funding restrictions in many countries, including Australia, do not allow for any flexibility in either the dosing or shortening of the dosing interval. Moreover, to date, all of the data on dose tailoring comes from countries outside Australia, where the access to anti-TNF therapy varies, and thus the relevance of the current data, to our clinical setting is uncertain. A systematic review determined that dose intensification with adalimumab permitted 71.4% of patients to regain response to therapy and achieve remission in 39.9%; however, follow up in the majority was limited to 12 months or less. Data on the long-term efficacy of dose escalation (≥1 year) are lacking.

Anti-TNF-α therapy is expensive and is generally only available via third party payer schemes. For third party payment, a demonstrable level of cost-efficacy is demanded and appropriate. These data usually come from registration trials, which set the funded dose and schedule. However, once a drug is licensed for use, formal trials to examine the cost efficacy of alternative dosing regimens are not usually performed due to their significant cost and lack of commercial imperative. Given the difference in both initial response rates to anti-TNF therapy and also in longer term loss of response rates between registration studies and real world experience, it is important to collect local data on the clinical outcomes of dose tailoring. In the absence of funding for a strategy trial to access therapy, observational cohort studies are necessary to inform care and support evidence-based adjustments to funding schemes.

The aim of this study was to review retrospectively the indications and outcomes of TNF-α dose tailoring outside the Pharmaceutical Benefits Scheme (PBS) criteria in Australia.

Methods

Patients and design

Patients were recruited from six tertiary centres in Australia with dedicated inflammatory bowel disease (IBD) services between February 2007 (the first year anti-TNF-α therapy became widely used in Australia) and June 2013. The inclusion criteria were; patients’ age 17–70 years at CD diagnosis, with CD being diagnosed according to standard clinical, endoscopic, histological and radiological criteria. In Australia, IFX and ADA are subsidised by the PBS for patients with CD failing standard therapy (minimum 6 weeks corticosteroids with an appropriate dose of an immunomodulator (IM) for a minimum of 12 weeks). Those responding to induction therapy, qualify for maintenance IFX funded at 5 mg/kg every 8 weeks and ADA as 40 mg every other week. Dose tailoring defined as either increasing the medication dose or decreasing the dosing interval is not funded by the PBS and requires funding by the individual, local hospital or on compassionate grounds by the drug distributor.

Patients included in the study must have had previous exposure to standard PBS dosing anti-TNF-α therapy for a minimum of 3 months followed by dose tailoring with a minimum of 3 months follow-up post-dose tailoring.

The human research ethics committee of the Royal Adelaide Hospital primarily approved the study, with second level approvals by participating units. As it was retrospective with no influence on patient care and only used de-identified data, specific patient consent was deemed unnecessary.

Data and definitions

Data were collected from the medical records and included demographics, smoking history, Montreal classification, CD treatment history and surgery.

Corticosteroid therapy prior to dose tailoring was recorded in detail: the number of episodes of continuous therapy of greater than 6 months duration in the previous 5 years, the cumulative months of corticosteroids in the prior 5 years and the number of days on high-dose corticosteroids (greater than 20 mg of prednisolone or equivalent), in the 90 days pre- and post-dose tailoring.

The indications for dose tailoring were recorded as primary or secondary loss of response. Primary loss of response was defined as failure to achieve clinical remission after induction therapy with IFX (weeks 0, 2 and 6)
and ADA (160 mg week 0, 80 mg week 2 then 40 mg every other week) assessed between weeks 6 and 12. Secondary loss of response was defined as further active CD in a patient previously in anti-TNF-α induced clinical remission, preferably supported by laboratory parameters, imaging or endoscopy.14

To assess response, short and long-term outcomes were assessed. Corticosteroid use was recorded as described above. The physician assessment was also recorded at routine clinical review between 10 and 16 weeks after dose tailoring was commenced. If the physician and patient appeared to be satisfied with the response, this was recorded as ‘Good’; if there were guarded comments about the response, this was recorded as ‘Partial response’; and if there was no improvement in clinical symptoms this was recorded as ‘No real benefit’. For long-term outcomes, the response, this was recorded as ‘Partial response’; and if there was no improvement in clinical symptoms this was recorded as ‘No real benefit’. For long-term outcomes, the longest period for which patients remained free of any corticosteroid therapy or need for surgery were recorded. The ongoing use of IM and anti-TNF-α therapy at last follow up were also recorded.

Statistical analysis
All data were entered in a central database using Excel (Microsoft, Redmond, WA, USA) and analysed statistically using SMSTATA 12.0 software package (StataCorp, College Station, TX, USA). The statistical analysis compiled descriptive statistics, including percentages for discrete variables, and means, medians and ranges for continuous variables. To compare mean days of high-dose corticosteroids before and after dose tailoring paired student t-tests were used where the differences were found to be approximately normally distributed. Univariate analysis and logistic regression analysis were performed to look for factors predicting response to dose tailoring. The results from univariate analysis were expressed as an odds ratio (OR) with 95% confidence intervals (CI) and the corresponding P-value. Two-sided tests were used and P-values <0.05 were considered significant.

Results
One hundred patients with CD who received additional, non-PBS funded anti-TNF-α therapy were identified. Of these, 45 were excluded as outlined in Figure 1. Full demographic details of the remaining 55 eligible patients are displayed in Table 1.

Previous treatment
Data on corticosteroid use were available in 52/55 (96%) patients. Forty-nine of these (94%) were exposed to corticosteroid therapy at some stage during the 5 years preceding dose tailoring of anti-TNF-α therapy. Of these 49, 25 (51%) had received corticosteroids for more than 12 months cumulatively, but not necessarily continuously. Twenty-four (49%) had episodes of continuous corticosteroids for greater than 6 months during the 5-year period (Table 1). In the 3 months prior to tailoring anti-TNF-α therapy, 24/55 (44%) were on corticosteroids, and of these 24 patients required a mean of 45 ± 35 days on high-dose corticosteroids. Fifty-three (96%) had been on one IM, and half (n = 27, 49%) had been on a second IM during their disease history.

Secondary loss of response was the indication for tailoring of therapy in 53/55 (96%) patients. Of these, 31/53 (58%) patients were on their first anti-TNF-α (IFX 14, ADA 17) and 22/53 (42%) patients were receiving a second (or subsequent) agent and again lost response (IFX 4, ADA 18). Two patients were classified as primary non-responders. In one, ADA was administered weekly due to a failure of improvement in perianal fistulising disease with the initial induction therapy with ADA. The second patient already had secondary loss of response to IFX for luminal disease and had been switched to ADA on PBS, but after initial induction did not have sufficient reduction in CDAI so was trialled on weekly ADA for 6 months.

Tailoring of anti-TNF-α therapy
Of the 55 patients, IFX was dose tailored in 20 (36%) patients and ADA in 35 (64%) patients. Dose tailoring of IFX therapy was variable. The dosing interval was shortened to 6 weeks in 11 patients. Of these 11 patients, the dose was maintained at 5 mg/kg in nine patients and escalated to 10 mg/kg in two. One patient had the dosing interval shortened to 4 weeks. Eight patients had re-induction of IFX at 5 mg/kg at weeks 0, 2 and 6 and then returned to 8-weekly dosing. Dose tailoring of ADA was given as a weekly dose (40 mg) in all patients.

Anti-TNF-α therapy was tailored for a median of 5 months (range 1–47 months). The most common reason to stop tailored therapy was successful induction of remission in 28/43 (65%) patients, inability to access further therapy in five (12%), and lack of response in eight (19%). In two (4%) patients, the reason for ceasing additional dosing was not adequately documented. Dose-tailored therapy was still ongoing at the last follow up in 12 (21%) patients at a median of 60 months (range 3–60 months).

Outcomes
Corticosteroid use
Thirty-five patients (64%) did not require any corticosteroids in the 90 days after dose tailoring compared to 31
Of the 24 requiring corticosteroids, there was a significant reduction in the mean number of days on high-dose steroids compared to the 3 months immediately prior (23 ± 27 vs. 45 ± 36 days respectively, \( P = 0.01 \)). In the 33 (60%) patients with ≥ 12 months of follow-up and complete data on steroid use, 18 (55%) patients remained steroid free at 12 months.

**Surgery**

During the follow-up period, 12 (22%) patients required bowel resection surgery and an additional two (4%) requiring perianal surgery for management of perianal fistulae or abscesses.

**Physician assessment at 3 months**

In 40 (73%) patients, the physician deemed the patient to have had a good response to the additional anti-TNF therapy. In 10 (18%) patients, a partial response and in four (7%) patients, no real benefit was perceived. The physician assessment could not be elucidated from the medical records in one patient (Table 2).

**Predictors of outcomes**

The only predictor of durable steroid-free remission over the 12 months following dose tailoring was the absence of prolonged continuous use of corticosteroids for ≥ 6 months in the 5 years prior to dose tailoring (OR 3.5, 95% CI 1.05–12.05, \( P = 0.042 \)) (Table 3).

The same variables were also examined to assess their association with reduction in corticosteroid use in the 3 months after dose tailoring, the need for surgery during follow up and achieving good physician assessment (data not shown). Those who had an episode of continuous corticosteroids for ≥ 6 months in the 5 years prior to tailoring of therapy were more likely to require surgery during follow up (OR 16.2, 95% CI 1.87–140.51, \( P = 0.01 \)). Furthermore, age less than 30 years was associated
with an increased chance of requiring surgery during follow up (OR 5.4, 95% CI 1.27–23.0, \( P = 0.02 \)). There were no significant predictors of a good physician assessment, and a good physician assessment did not predict other clinical outcomes, such as remaining free of corticosteroids or surgery.

**Follow up**

The median follow up after initiation of tailored anti-TNF-\( \alpha \) therapy was 20 months (range 3–65 months, data not shown). At last follow up, 46/55 (84%) patients remained on an anti-TNF-\( \alpha \) agent (IFX 18, ADA 28) with 34/46 (74%) receiving it in combination with an IM, while 12/46 (26%) remained on an anti-TNF-\( \alpha \) agent without an IM. In those continuing anti-TNF-\( \alpha \) therapy, 35 (75%) patients continued on standard PBS dosing alone, while 11 (25%) remained on dose-tailored therapy accessed through the PBS for standard dose and the additional dosing from compassionate access.

Nine patients were no longer receiving any anti-TNF-\( \alpha \) therapy. Of these, five patients were receiving neither anti-TNF nor an IM. The physician assessment at 3 months after dose tailoring was good in 7/9, some response in one and no real benefit in one. The reason of stopping tailored therapy was successful induction of remission in five patients, unable to access in two, failure in one and the reason not established in one. The treatment was well tolerated in all patients. Thus, the reason for cessation could not be attributed to treatment failure or intolerance in the majority. Of note, 5/9 required bowel resection surgery during follow up, and in these five subjects, the physicians had assessed response to dose tailoring at 3 months to be good in four.

In 28 patients, therapy was de-escalated back to standard dosing due to successful induction of remission after a median of 4 months (range 1–15) of dose-tailored therapy. Follow up was available for \( \geq 12 \) months after

### Table 1 Patient demographics

<table>
<thead>
<tr>
<th>n = 55</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>34 (61.8)</td>
</tr>
<tr>
<td>Age at dose tailoring (median years)</td>
<td>33 (range 18–65)</td>
</tr>
<tr>
<td>Disease duration at dose tailoring (median years)</td>
<td>9 (range 0.8–33.5)</td>
</tr>
<tr>
<td>Location Montreal % (L1/L2/L3/L1 + 4)</td>
<td>14/36/28/2</td>
</tr>
<tr>
<td>Behaviour Montreal % (B1/B2/B3)</td>
<td>58/18/24</td>
</tr>
<tr>
<td>Prior surgery for CD</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Bowel resection</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Perianal</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (66)</td>
</tr>
<tr>
<td>Smoking (% never, current, former, missing)</td>
<td>60, 13, 15, 13</td>
</tr>
<tr>
<td>Cumulative months on corticosteroids in 5 years prior to dose tailoring</td>
<td>3 (6)</td>
</tr>
<tr>
<td>6 months or less</td>
<td>12 (22)</td>
</tr>
<tr>
<td>7–12 months</td>
<td>12 (22)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>25 (46)</td>
</tr>
<tr>
<td>Missing data</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Episodes of corticosteroids &gt; 6 months in 5 years prior</td>
<td>24 (44)</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (51)</td>
</tr>
<tr>
<td>No</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Mean days of Pred &gt; 20 mg/day in 3 months pre</td>
<td>45 ± 36</td>
</tr>
<tr>
<td>First previous IM</td>
<td>53 (96)</td>
</tr>
<tr>
<td>Second previous IM</td>
<td>27 (49)</td>
</tr>
<tr>
<td>First previous(or current) anti-TNF (n = 55)</td>
<td>34 (62)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>18 (33)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>18 (33)</td>
</tr>
</tbody>
</table>

### Table 2 Dose tailoring and outcomes

<table>
<thead>
<tr>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>Primary non-response</td>
</tr>
<tr>
<td>Secondary loss of response</td>
</tr>
<tr>
<td>Type</td>
</tr>
<tr>
<td>Adalimumab</td>
</tr>
<tr>
<td>Infliximab</td>
</tr>
<tr>
<td>Duration months (median)</td>
</tr>
<tr>
<td>Reason stop dose tailoring (n = 43)</td>
</tr>
<tr>
<td>Induction of remission</td>
</tr>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>Unable to access</td>
</tr>
<tr>
<td>Missing data</td>
</tr>
<tr>
<td>Physician assessment 3 months post</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Some response</td>
</tr>
<tr>
<td>No real benefit</td>
</tr>
<tr>
<td>Missing data</td>
</tr>
<tr>
<td>Mean days of Pred &gt; 20 mg/day in 3 months post-dose tailoring (±SD)</td>
</tr>
<tr>
<td>Steroid-free during follow up</td>
</tr>
<tr>
<td>6 months</td>
</tr>
<tr>
<td>12 months</td>
</tr>
<tr>
<td>36 or more months</td>
</tr>
<tr>
<td>Surgery post-dose tailoring (bowel resection, perianal, other, none)</td>
</tr>
</tbody>
</table>

CD, Crohn disease; IM, immunomodulator; TNF, tumour necrosis factor.
Table 3: Univariate logistic regression: remaining steroid free for more than 12 months

<table>
<thead>
<tr>
<th></th>
<th>n = 18</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>1.04</td>
<td>0.98–1.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.33</td>
<td>0.42–4.28</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>1</td>
<td>0.99–1.01</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1.89</td>
<td>0.36–10.02</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.89</td>
<td>0.36–10.02</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single/divorce/separated</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/de facto</td>
<td>0.89</td>
<td>0.37–2.15</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perianal</td>
<td>2.40</td>
<td>0.52–10.99</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Penetrating</td>
<td>0.50</td>
<td>0.04–6.02</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.69</td>
<td>0.41–6.88</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Episodes corticosteroids &gt;6 months in 5 years prior CA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3.5</td>
<td>1.05–12.05</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel resection</td>
<td>0.35</td>
<td>0.08–1.56</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Second PBS TNF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.82</td>
<td>0.24–2.79</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Type CA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.11</td>
<td>0.35–3.51</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1</td>
<td>0.95–1.07</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Months of CA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CA, compassionate access; PBS, pharmaceutical benefits scheme; TNF, tumour necrosis factor.

De-escalation in 17/28 (61%), and 15/17 (88%) had data available for long-term steroid use. There was no requirement for any corticosteroids 1 year after dose de-escalation in 12/15 (80%). Only 1/15 (7%) required bowel resection surgery, but none of those who maintained a steroid-free remission for 1 year or more required surgery.

Discussion

This study represents a longer term, ‘real-life’ experience of anti-TNF-α dose tailoring in a national cohort of patients with CD refractory to at least one if not two previous anti-TNF-α agents. We demonstrate that dose intensification for a median of 5 months can achieve a good clinical response in 73% of patients and maintain a steroid-free remission beyond 12 months in 55% of patients, with many able to be de-escalated back to standard dose therapy while maintaining good disease control.

International guidelines suggest intensifying anti-TNF-α therapy by dose escalation or dose interval reduction in the event of treatment failure. These recommendations are based on large registration studies (usually of 12 months or less duration) where patients are carefully selected and do not necessarily reflect real clinical practice. Few groups have reported their ‘real-life’ experience. A recent systematic review reported on the loss of response and need of ADA dose intensification. Within this only 120 patients from seven small studies are found to report on the results of dose escalation. A multicenter retrospective study from Europe, United States and Israel examined the impact of doubling IFX dose versus halving the infusion intervals. They found dose doubling led to a sustained response at 12 months in 47% of CD patients, and this was not different to halving of infusion intervals. Outcomes beyond 12 months were not detailed.

The precise clinical utility of serum drug trough and anti-drug antibody levels in the setting of LOR is still evolving. Dynamic changes in antibody levels and the lack of standardised assays are limiting factors. It has also emerged that dose intensification even in those with ‘therapeutic’ drug trough levels and anti-drug antibodies may regain response in a proportion of patients, and this strategy is as effective as following algorithms based on drug trough and anti-drug antibody level algorithms. A reimbursed commercial assay to measure serum trough levels and anti-drug antibody levels is currently not available in Australia.

Few studies provide clinicians with guidance about de-escalation of therapy, with patients in large registration studies continuing dose escalation for the duration of the study (usually 12 months). The cost associated with indefinite dose escalation precludes the use of this strategy in many countries. Encouragingly, in our study, 78% of patients de-escalated anti-TNF-α therapy during the follow-up period with the majority doing so because they achieved clinical remission. In a large real-life cohort study, Belgian investigators found dose escalation with ADA was required in 208/605 for secondary LOR. Dose de-escalation back to fortnightly dosing was attempted in 75/139 (54%) patients after a median of 3 months, and this was successful in 47/75 (63%). Success was defined by maintaining a durable response for at least 6 months after de-escalation. In our study, 77% of those who had de-escalation of therapy were still free of corticosteroid therapy after 1 year.

The current study identified a number of factors that may predict those least likely to benefit from dose escalation of therapy. Predictably, these factors were markers for difficult to treat disease. In particular, long-term steroids prior to dose tailoring predicted the
need for steroids and surgery during follow up after dose tailoring. Furthermore, age less than 30 years was associated with an increased chance of requiring surgery during follow up (OR 5.4, 95% CI 1.27–23.0, P = 0.02). Therefore, we feel that younger patients who have required prolonged corticosteroids are likely to require surgery or further corticosteroid therapy despite dose escalation. This may be due to more aggressive disease and fibrostenotic complications.

There are several limitations to this retrospective study. We did not have a validated measure of disease activity, such as Harvey–Bradshaw Index or the Crohn Disease Activity Index available to define LOR, response and remission. As a result, LOR was defined as the physician documenting a flare of symptoms while the patient was compliant with therapy. While a subjective measure, physician assessment of response to dose tailoring however appeared to be at odds with subsequent outcomes in some cases, for example in the five patients who stopped dose tailoring therapy and went on to have surgery, physicians had assessed response to therapy as ‘good’ in four cases. This may perhaps be because these subjects were subsequently determined to have fibrostenotic disease with the anti-TNF therapy having controlled inflammation – although this could not be clarified from case notes. These discrepancies emphasise the need for accurate and complete case notes and for the objective assessment of the inflammatory state with radiology, endoscopy or faecal inflammatory markers where appropriate.

**Conclusion**

In this difficult to treat population, many of whom have failed two anti-TNF agents, dose escalation is a useful therapeutic strategy that not only reduces short-term corticosteroid use, but also appears to lead to low rates of surgery during follow up and high rates of being steroid-free beyond 1 year. Encouragingly, more than half of the patients are able to return to standard dose therapy after a median of 4 months while maintaining remission. Older age, longer disease duration and not previously requiring prolonged courses of high-dose steroids are factors associated with more favourable outcomes with dose tailoring of anti-TNF-α therapy.

**References**

Management and outcomes of axial isolated distal deep vein thrombosis at North Shore Hospital, New Zealand: a retrospective audit

A. Y. Li, T. Woulfe, V. Rolfe-Vyson, V. Rowland, D. Simpson and E. Merriman
Haematology Department, North Shore Hospital, Auckland, New Zealand

Key words
distal deep vein thrombosis, calf vein thrombosis, management, DVT, anticoagulation.

Correspondence
Acrane Yihe Li, Haematology Department, North Shore Hospital, Private Bag 93503, Takapuna, North Shore City 0740, New Zealand.
Email: acranel@adhb.govt.nz

Received 17 March 2014; accepted 20 November 2014.
doi:10.1111/imj.12664

Abstract

Background: It is standard of care to treat proximal vein deep vein thrombosis (DVT) for a minimum of 3 months. Conversely, management of isolated distal DVT (IDDVT) is controversial, with options including observation and repeat ultrasound scan within 1 week to detect and anticoagulate those with proximal propagation, or anticoagulation for periods of up to 3 months.

Aim: The aim was to assess the rates of proximal propagation and venous thromboembolism (VTE) recurrence within 3 months of diagnosis of IDDVT, and to examine how the duration of treatment might influence this.

Methods: Study patients were identified by retrospective audit of data from the North Shore Hospital VTE database. All patients presenting with established axial vein distal DVT from July 2007 to June 2012 were included. A 6-week treatment duration cutoff was used to separate the treatment arms (<6 weeks vs ≥6 weeks), and Fisher’s exact or Pearson’s Chi-squared tests were used to assess between-group comparisons.

Results: Five hundred and seven patients were included in the study, mean age 59.7 years; 53% female. There were three cases of proximal propagation, all occurring in those receiving ≤6 weeks treatment. There were six VTE recurrences, three in the <6 week and three in the ≥26 week treatment groups respectively. Malignancy was the only significant predictor of VTE recurrence (P = 0.001).

Conclusion: A 6-week duration of anticoagulation appears to be an effective and safe treatment for isolated axial distal DVT, with low rates of VTE recurrence and proximal propagation.
Introduction

Most pulmonary embolii (PE) originate from thrombi in the proximal veins of the legs. Approximately 10% of PE are rapidly fatal, with an additional 5% causing death at a later time point, despite diagnosis and treatment.\(^1\) Treatment of proximal DVT with full-dose anticoagulant therapy for a minimum of 3–6 months is therefore the standard of care. Anticoagulant therapy is associated with a risk of major and fatal bleeding of 0.25–3% per year,\(^2\) and is costly and inconvenient, therefore, it is important to treat appropriately. Conversely, isolated distal deep vein thrombosis (IDDVT) carries a much lower risk of PE than proximal DVT\(^3\) and is only clinically relevant if proximal propagation occurs. It is thought that some 10–20% enlarge by propagating to the leg veins\(^1,3\); however, estimations of the proportion of distal vein DVT propagating to proximal veins vary widely in the literature, from 0% to 44%.\(^4\) This is in part due to the heterogeneity of populations included in these studies.

The management of IDDVT is therefore controversial. The American College of Chest Physicians guidelines recommend treatment of isolated distal DVT for 3 months.\(^5\) However, several studies have demonstrated low rates of venous thromboembolism (VTE) recurrence and proximal propagation with shorter durations of anticoagulation ranging from 4 to 6 weeks.\(^2,6\)

The aim of this retrospective study was to assess the rates of proximal propagation and VTE recurrence within 3 months of IDDVT diagnosis during a 5-year period at North Shore Hospital and to examine how the duration of treatment might influence this.

Methods

Study population

Study patients were identified using a prospective database of consecutive VTE patients referred to North Shore Hospital, New Zealand. Patients with an objectively confirmed diagnosis of IDDVT from July 2007 to June 2012 were included for review. Cases with isolated muscular vein (soleal and/or gastrocnemius) thrombosis, and those on permanent anticoagulation prior to diagnosis, were excluded from the analysis. Patients’ case notes were reviewed to identify demographic characteristics, aetiology of IDDVT, primary outcomes including timing of ultrasound and clot propagation rate, anticoagulation length, VTE recurrence rate, and rates of major and minor bleeding. A standardised case report form was used to collect variables and outcomes.

Definitions

IDDVT was defined as incompressible thrombus on ultrasound isolated to veins below the level of the popliteal vein. Proximal propagation was defined as ultrasonographically proven extension of thrombus into the popliteal, femoral or iliac veins. VTE recurrence was defined as the reappearance of thrombus in a previously involved vein that was demonstrated to have resolved on subsequent complete compression ultrasound (CUS), new thrombus in a different anatomical calf vein, or the presence of PE on CTPA or VQ scan within 3 months of IDDVT diagnosis. Bleeding was classified as major according to ISTH definition\(^7\); all other bleeds were classified as minor.

Study endpoints

The primary outcomes were the rates of proximal thrombus propagation and VTE recurrence (DVT, PE, other thromboembolism) within 3 months of IDDVT diagnosis in patients receiving no treatment, less than 6 weeks, 6 weeks and more than 6 weeks anticoagulation. Secondary outcomes were predictors for VTE recurrence, bleeding complications (major and minor) and all-cause mortality.

Statistical analysis

Patients’ treatment lengths were then retrospectively classified. Assessment of the dichotomous primary and secondary outcomes was by Pearson’s Chi-squared test or Fisher’s exact test. The sample population was also assessed under predefined subgroups, which included provoked only, unprovoked only and provoked without malignancy. There were no missing data. All statistical analyses were performed with SPSS Statistics for Windows Version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Study population

A total of 562 cases of IDDVT was identified by our study criteria. Twenty-three cases of muscular vein thrombosis were excluded. Of the remainder 539 cases, 13 patients died of causes unrelated to thrombosis or bleeding complications, and 19 patients were lost prior to the follow-up CUS.
Treatment groups

The consort diagram (Fig. 1) outlines the allocation of patients in their respective treatment arms. Fifty-three patients were observed initially. Three patients subsequently received 6 weeks of anticoagulation due to clot propagation in the distal calf on follow-up CUS. An additional 10 patients received greater than 6 weeks anticoagulation, again due to clot propagation (eight distal and two proximal extensions). Grouping for bleeding profiles took account of the final duration of therapy for these 13 patients.

The rest of the patients received durations of anticoagulation as follows: 54 patients received <6 weeks treatment, 97 patients received 6 weeks of treatment and 303 patients received >6 weeks treatment, with durations in the latter group ranging from 8 weeks to lifelong (median 12 weeks). Table 1 shows the demographic distribution between the treatment arms.

Table 2 shows the major outcomes of the study along with the subgroup analysis.

Proximal propagation

There were three cases of proximal propagation, all occurring in patients who were untreated (n = 2) or treated with <6 weeks of anticoagulation (n = 1) initially. There were no cases of proximal propagation in the patients treated with 6 weeks or more anticoagulation. There was a significant difference in proximal propagation between those treated with <6 weeks anticoagulation (including those who received no treatment) versus those treated with ≥6 weeks anticoagulation (2.8% vs 0%, P = 0.001).

VTE recurrence

There were six VTE recurrences in the study. These comprised two proximal DVT, three distal DVT and one PE. Four of these patients had malignancy.

VTE recurrences within 3 months occurred in two patients receiving 6 weeks of anticoagulation (2%) versus one patient receiving more than 6 weeks anticoagulation (0.3%); this difference was not statistically significant (P = 0.147) (Table 3). Similarly, there was no significant difference in VTE recurrence between those receiving <6 weeks versus ≥6 weeks treatment

Table 1 Study patient characteristics between treatments arms

<table>
<thead>
<tr>
<th></th>
<th>Study population (n = 507)</th>
<th>A (n = 53)</th>
<th>B (n = 54)</th>
<th>C (n = 97)</th>
<th>D (n = 303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60</td>
<td>49.3</td>
<td>66.7</td>
<td>63.0</td>
<td>53.6</td>
<td>42.2</td>
</tr>
<tr>
<td>Female gender</td>
<td>53.0</td>
<td>50</td>
<td>64.8</td>
<td>47.0</td>
<td>54.0</td>
</tr>
<tr>
<td>Orthopaedic surgery</td>
<td>32.9</td>
<td>25.9</td>
<td>50</td>
<td>35.1</td>
<td>30.4</td>
</tr>
<tr>
<td>Non-orthopaedic surgery</td>
<td>4.5</td>
<td>5.6</td>
<td>7.4</td>
<td>8.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Active Malignancy</td>
<td>4.7</td>
<td>11.1</td>
<td>3.7</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Trauma</td>
<td>29.1</td>
<td>13.0</td>
<td>9.3</td>
<td>27.0</td>
<td>35.6</td>
</tr>
<tr>
<td>Immobilisation</td>
<td>5.1</td>
<td>3.7</td>
<td>9.3</td>
<td>6.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Idiopathic VTE</td>
<td>23.4</td>
<td>42.6</td>
<td>20.4</td>
<td>20.0</td>
<td>21.8</td>
</tr>
<tr>
<td>Multiple veins involvement</td>
<td>43.1</td>
<td>9.3</td>
<td>33.3</td>
<td>40.2</td>
<td>51.8</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clexane</td>
<td>14.2</td>
<td>0</td>
<td>79.6</td>
<td>9.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Warfarin</td>
<td>76.0</td>
<td>0</td>
<td>16.7</td>
<td>90.7</td>
<td>94.7</td>
</tr>
<tr>
<td>Heparin</td>
<td>0.4</td>
<td>0</td>
<td>3.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fragmin</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

A: observed initially, B: treatment <6 weeks, C: treatment = 6 weeks, D: treatment >6 weeks. VTE, venous thromboembolism.
There was no significant difference in VTE recurrence once populations were stratified into provoked DVT and unprovoked DVT. When adjusted for age and sex, the only significant predictor for VTE recurrence was malignancy. Idiopathic DVT, multiple vein involvement, surgery and presence of immobility were not significant predictors of VTE recurrence.

**Bleeding**

Major bleeding rates were 1.9% in those treated with anticoagulation versus 0% in those not receiving anticoagulation. Rates of any major or minor bleeding were not significantly different between treatment groups. There were 10 cases of major bleeding, including gastrointestinal ($n = 2$), intra-articular ($n = 5$), muscular ($n = 1$), haematuria ($n = 1$) and one unexplained significant fall in haemoglobin ($n = 1$). Of the major bleeding cases, six (60%) occurred in orthopaedic surgical patients above the age 65 years. In the total population, there were 11.1% major bleeds in patients with therapy

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Study population</th>
<th>Provoked only</th>
<th>Non-provoked only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$ (%)</td>
<td>$n$ (%)</td>
<td>$n$ (%)</td>
</tr>
<tr>
<td>Proximal propagation</td>
<td>2 (3.7)</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>2 (6.7)</td>
<td>1 (2.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>$n = 53$</td>
<td>$n = 54$</td>
<td>$n = 97$</td>
</tr>
<tr>
<td></td>
<td>$n = 30$</td>
<td>$n = 43$</td>
<td>$n = 303$</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>B $n$ (%)</th>
<th>C $n$ (%)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal propagation</td>
<td>2 (3.7)</td>
<td>1 (1.9)</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>2 (6.7)</td>
<td>1 (2.3)</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>$n = 53$</td>
<td>$n = 54$</td>
<td>$n = 97$</td>
</tr>
<tr>
<td></td>
<td>$n = 30$</td>
<td>$n = 43$</td>
<td>$n = 303$</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Study population</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years</td>
<td>0.510</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.994</td>
<td></td>
</tr>
<tr>
<td>Orthopaedic surgery</td>
<td>0.600</td>
<td></td>
</tr>
<tr>
<td>Non-orthopaedic surgery</td>
<td>0.981</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>0.371</td>
<td></td>
</tr>
<tr>
<td>Immobilisation</td>
<td>0.706</td>
<td></td>
</tr>
<tr>
<td>Idiopathic IDDVT</td>
<td>0.381</td>
<td></td>
</tr>
<tr>
<td>Multiple veins involve</td>
<td>0.989</td>
<td></td>
</tr>
<tr>
<td>Residual thrombus</td>
<td>0.345</td>
<td></td>
</tr>
</tbody>
</table>

duration for <6 weeks, 0% for 6 weeks and 1.3% for >6 weeks. Subgroup analysis also yielded comparable bleeding profiles.

**Mortality**

There was one death within 3 months of IDDVT diagnosis secondary to pancreatic cancer with metastases. No thrombosis or haemorrhage associated mortality cases were identified.

**Discussion**

The majority of patients presenting with IDDVT at North Shore Hospital during the time period of this study were treated with anticoagulation (over 90%). For those receiving anticoagulation, the duration of treatment ranged from 1 week to more than 12 months, with durations often dependent on the individual preferences of the haematologists.

It would appear that a period of treatment for isolated axial distal DVT is likely to improve outcomes, as shown in a recent study of IDDVT patients receiving observation versus treatment. However, the optimal duration of treatment is not clear. We found 6 weeks of anticoagulation to be non-inferior to more than 6 weeks of anticoagulation for IDDVT, with similar rates of proximal propagation and VTE recurrence. Two previous randomised studies have reported similar findings, especially in patients without ongoing risk factors for thrombus propagation, such as malignancy. However, there was a significant difference in rates of proximal propagation between the groups receiving less than 6 weeks anticoagulation as opposed to ≥6 weeks anticoagulation. It should be noted that our numbers are small, with a heterogenous group of patients included within these groups. It is likely that a subgroup of patients with low risk factors for propagation could safely receive less than 6 weeks of treatment, with low rates of proximal propagation and VTE recurrence. There are studies currently underway to address this clinical question. The first is a prospective cohort study, Two Weeks of Anticoagulation for Isolated Symptomatic Distal Vein DVT (NCT01252420). The second is the CACTUS study, a randomised controlled trial of 6 weeks anticoagulation versus placebo for a first symptomatic isolated IDDVT (NCT00421538).

Rates of bleeding on treatment are crucial in risk-benefit consideration; this is often poorly reported in studies of patients with IDDVT. Our population had an overall major bleeding rate of 1.9% in those treated with anticoagulation, similar to bleeding rates reported in the literature. Interestingly, there was an increased rate of major bleeding in the population receiving <6 weeks course of anticoagulation (11.1%) compared with those receiving >6 weeks anticoagulation (1.3%). This can likely be explained by the fact that patients developing major bleeding would generally have had their anticoagulation stopped at the time of the bleed, resulting in a shorter period of anticoagulation. Bleeding is also more likely to occur early in the course of anticoagulation, with several studies and a recent meta-analysis attesting to the ‘front-loading’ phenomenon. In our study, the majority of major bleeds were intra-articular bleeds occurring in elderly postoperative orthopaedic patients. Patients deemed to be at high risk for bleeding were also likely to have shorter durations of, or no, anticoagulant treatment prescribed.

The thrombotic outcomes and bleeding profiles of patients with only provoked IDDVT, idiopathic IDDVT and provoked IDDVT without malignancy would suggest 6 weeks anticoagulation in these subgroups is sufficient. Malignancy is a well-known risk factor for VTE, and previous studies have shown it be a significant predictor of VTE recurrence in IDDVT. Our study has demonstrated similar findings, with malignancy present in a significant proportion (60%) of cases of VTE recurrence. This suggests that patients with malignancy require a longer course of anticoagulation, possibly indefinitely in those who have active malignancy.

Other suggested risk factors for distal DVT extension include positive D-dimer, thrombosis extensive, or close to the proximal veins (0.5 cm in length, involves multiple veins, 0.7 mm in maximum diameter), no reversible provoking factor for DVT, history of VTE and inpatient status. Idiopathic IDDVT was not a significant predictor of VTE recurrence in our study, although there was a trend towards increased VTE recurrence in those with idiopathic versus provoked IDDVT in the absence of malignancy (5% versus 0%; $P = 0.064$). The other risk factors assessed in our study were not found to be significant predictors of VTE recurrence on multivariate analysis. However, numbers are small and no firm conclusions can be drawn.

This study lends further weight to the argument that the balance of benefits and risks of anticoagulation is different in patients with isolated distal as opposed to proximal DVT, because of low rates of proximal VTE propagation and VTE recurrence in this patient group, but similar rates of bleeding on anticoagulation. A shorter period of anticoagulation would improve the benefit–risk ratio by reducing the risk of bleeding. It would also minimise inconvenience to the patient and result in less expense to the healthcare system.
Limitations
This was a single-centre retrospective observational study. The population size was moderate, and therefore the number of adverse outcomes such as VTE, bleeding or mortality was a limitation to statistical analysis. Patients were retrospectively classified into treatment groups, and an intention to treat analysis was not performed. Data were not collected on the incidence of post-thrombotic syndrome (PTS) in this population, which may influence decisions on whether to anticoagulate those with distal DVT. However, it is likely that the incidence of PTS is lower in those with distal as opposed to proximal DVT.12

Conclusion
A 6-week duration of anticoagulation appears to be an effective and safe treatment for IDDVT occurring in the absence of malignancy, with low rates of proximal propagation and VTE recurrence.

References
Prevalence of prediabetes in patients with acute coronary syndrome: impact on in-hospital outcomes

M. M. AbuShady,1 Y. Mohamady,2 B. Enany2 and W. Nammas2

1Endocrinology Unit, Department of Internal Medicine and 2Cardiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Key words
prediabetes, acute coronary syndrome, prevalence, outcome, major adverse cardiovascular event.

Correspondence
Manal M. AbuShady, Endocrinology Unit, Department of Internal Medicine, Faculty of Medicine, Ain Shams University, Abbassia, Lotfy Al-Sayyed Street, Abbassia Square, Cairo 11381, Egypt.
Email: manalabushady@gmail.com

Received 21 September 2014; accepted 25 November 2014.
doi:10.1111/imj.12651

Abstract

Background: Prediabetes is a serious condition that is associated with an increase in cardiovascular morbidity and mortality.

Aims: We sought to explore the prevalence of prediabetes in patients admitted with acute coronary syndrome (ACS) who were not known to have diabetes and to determine the impact of prediabetes on in-hospital clinical outcomes versus non-diabetic patients.

Methods: Prospectively, we enrolled 200 patients not known to have diabetes or prediabetes, admitted with ACS. Laboratory tests included fasting plasma glucose (FPG), 2-h plasma glucose (2hPG) after 75 g glucose, HbA1c and lipid profile. Electrocardiogram and echocardiography were done. The primary end-point was in-hospital major adverse cardiovascular events (MACE).

Results: Mean age was 50.9 ± 6.8 years (70.5% males). The prevalence of patients with diabetes and patients with prediabetes was 24.5% and 20% respectively. Newly discovered diabetic patients were excluded. Compared with patients without diabetes, prediabetic patients had a higher body mass index (BMI) (P = 0.002) and a longer hospital stay (P = 0.09). In-hospital MACE occurred in 10 (25%) patients with prediabetes versus six (5.4%) in patients without diabetes (P = 0.001). In-hospital MACE correlated with prediabetes (r = 0.28, P < 0.001), BMI (r = 0.14, P = 0.093), FPG (r = 0.19, P = 0.014), 2hPG (r = 0.19, P = 0.017) and HbA1c (r = 0.19, P = 0.019). Multivariate regression analysis identified prediabetes as the only independent predictor of in-hospital MACE.

Conclusions: Prediabetes is common in patients presenting with ACS who are not previously known to have diabetes. Prediabetic patients had worse in-hospital clinical outcomes compared with patients without diabetes.

Introduction

Prediabetes is associated with a significant increase in cardiovascular morbidity and mortality, and necessitates early and adequate intervention to prevent the development of complications, and progression to overt diabetes.1 Higher fasting glucose levels in patients with acute coronary syndrome (ACS) were associated with worse clinical outcomes irrespective of the presence of diabetes mellitus.2,3 Similarly, in patients without diabetes presenting with acute ST-segment elevation myocardial infarction (STEMI), higher fasting glucose was a marker of adverse outcome.4

Impaired glucose tolerance is common among non-diabetic patients admitted with ACS.5 However, evidence is controversial regarding the prognostic impact of ‘prediabetes’ on the clinical outcome of ACS. In a single-centre study, prediabetic patients admitted with the full spectrum of ACS had a 66% increase of in-hospital major adverse cardiovascular events (MACE) versus non-diabetic patients.6 In contrast, in a high-risk cohort admitted with non-ST-segment elevation ACS enrolled in the large multicentre EARLY ACS trial, patients with prediabetes had a 30-day rate of death or myocardial infarction similar to that of non-diabetic patients.7
However, the recognition of prediabetes in those two studies was performed retrospectively and was based solely on fasting blood glucose. When screening for glucose intolerance in patients with ACS, the use of fasting glucose or HbA1c alone leaves a majority of patients with impaired glucose tolerance or diabetes unrecognised compared with the oral glucose tolerance test (OGTT). Therefore, in a prospective study design, we sought to explore the prevalence of prediabetes based on the recent definition of the American Diabetes Association (that incorporates OGTT) in patients admitted with ACS who were not previously known to have diabetes and to determine the impact of prediabetes on the in-hospital clinical outcomes compared with patients without diabetes.

**Methods**

**Patient selection**

Prospectively, we enrolled 200 consecutive patients above 18 years, not known to have diabetes, admitted to our coronary care unit with the diagnosis of ACS during the period from 1 January 2014 to 5 April 2014. Before inclusion, an informed written consent was obtained from each patient after full explanation of the study protocol, and the protocol was reviewed and approved by our institutional human research committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2013.

ACS included unstable angina, non-STEMI and STEMI. All patients had persistent ischaemic-type chest pain or other acute symptoms consistent with myocardial ischaemia, at rest or with minimal exercise, lasting for more than 10 min. STEMI was defined by persistent ST-segment elevation (at least 2 mm in two contiguous precordial leads, or at least 1 mm in two limb leads), new left bundle branch block or new Q waves in two contiguous leads, with rise of biochemical markers of myocardial necrosis (creatinine kinase-MB and/or troponin) at least twice the upper limit of normal. Non-STEMI ACS was defined by the presence of new/dynamic electrocardiographic changes compatible with ischaemia, such as ST-segment depression of at least 1 mm, transient ST-segment elevation or ST segment elevation less than 1 mm, or T wave inversion more than 2 mm, in at least two contiguous leads. Non-STEMI was distinguished by rise of biochemical markers at least twice the upper limit of normal. We excluded patients with disorders that potentially impair glucose tolerance (e.g. Cushing syndrome), those on glucocorticoid therapy and those unable to comply with OGTT (e.g. cardiogenic shock).

**Diagnosis of glycaemic disorders**

Prediabetes was defined according to the recommendations of the American Diabetes Association as having impaired fasting glucose and/or impaired glucose tolerance. Impaired fasting glucose was defined as fasting plasma glucose (FPG) level of 5.55–6.94 mmol/L. Impaired glucose tolerance was defined by a 2-h plasma glucose (2hPG) level of 7.77–11.04 mmol/L after administration of 75 g of oral glucose, whereas normal glucose tolerance was defined as a FPG < 5.55 mmol/L and 2hPG < 7.77 mmol/L. Diabetes was defined as FPG ≥ 6.99 mmol/L and/or 2hPG ≥ 11.1 mmol/L. HbA1c levels were set at ≥6.5% for the diagnosis of diabetes, 5.7–6.4% for prediabetes and <5.7% for subjects without diabetes.

**Laboratory measurements**

Laboratory tests included FPG, OGTT, HbA1c and lipid profile. A fasting venous blood sample was taken on day 1 of admission after an 8-h overnight fast. A standardised OGTT (75 g of glucose in 200 mL of water) was performed after a 12-h overnight fast, between days 3 and 5 after admission. Fasting and 2-h plasma glucose after 75 g glucose were measured using an automated glucose oxidase method using Behring Diagnostics Reagents (SVR Glucose Test, Behring, La Jolla, CA, USA). HbA1c was assayed by Stanbio Procedure No. 0350 ‘Quantitative colorimetric determination of Glycohemoglobin in blood’ (Stanbio Laboratory, Boerne, TX, USA). Serum lipid concentrations were assayed by quantitative enzymatic colorimetric determination for total cholesterol, high-density lipoprotein cholesterol and triglycerides in plasma (Stanbio Cholesterol Liquicolor, Procedure NO. 1010, Stanbio Laboratory, Boerne, TX, USA). Low-density lipoprotein cholesterol was calculated using the Friedewald equation as follows: low-density lipoprotein cholesterol = (total cholesterol – high-density lipoprotein cholesterol) + triglycerides/5. The OGTT and HbA1c results were available to the treating clinicians.

**In-hospital clinical follow up**

The primary composite end-point was in-hospital MACE. MACE were defined as the first occurrence of any of the following during hospital stay: cardiac death, non-fatal re-infarction or urgent vessel revascularisation. Cardiac death was defined as death from cardiovascular causes or any death without another known cause. Re-infarction was diagnosed by a new rise of biochemical markers (creatinine kinase-MB and troponin) at least 50% above the lowest level measured previously. Urgent vessel revascularisation was defined as any unplanned intervention
(percutaneous or surgical) to the infarct-related (or culprit) vessel during hospital stay. Secondary end-points included the individual components of MACE, ventricular fibrillation, ventricular tachycardia and heart failure. Ventricular tachycardia was defined as a salvo of three or more successive ventricular premature beats. Heart failure was defined according to the standard Framingham’s criteria.

**Statistical analysis**

All continuous variables were presented as mean ± standard deviation if they were normally distributed. Data were tested for normal distribution using the Kolmogorov–Smirnov test. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between patients with prediabetes and patients without diabetes were performed using the unpaired t-test or Mann–Whitney test for continuous variables, and the Pearson χ² or Fisher’s Exact test for categorical variables, as appropriate. Pearson correlation coefficient test was used to study correlation between MACE and other variables. Finally, stepwise multivariable logistic regression analysis was performed to identify the independent predictors of MACE, as well as the independent predictors of mortality. All tests were two-sided and a probability value of P < 0.05 was considered statistically significant. Analyses were performed with SPSS version 16.0 statistical package (SPSS Inc., Chicago, IL, USA).

**Results**

**Baseline clinical characteristics**

The current study enrolled a total of 200 patients not known to have diabetes admitted with ACS. The mean age was 50.9 ± 6.8 years (70.5% males). The mean body mass index (BMI) was 28.7 ± 2.7 kg/m². One hundred and seven (53.5%) patients were diagnosed as unstable angina, 34 (17%) as non-STEMI and 59 (29.5%) as STEMI. Twenty-one (10.5%) patients developed atrial fibrillation, 34 (17%) as non-STEMI and 59 (29.5%) as STEMI. Twenty-one (10.5%) patients developed atrial fibrillation, and seven (53.5%) patients were diagnosed as unstable angina, 34 (17%) as non-STEMI and 59 (29.5%) as STEMI. Twenty-one (10.5%) patients developed atrial fibrillation, and seven (53.5%) patients were diagnosed as unstable angina, 34 (17%) as non-STEMI and 59 (29.5%) as STEMI. Twenty-one (10.5%) patients developed atrial fibrillation, and seven (53.5%) patients were diagnosed as unstable angina, 34 (17%) as non-STEMI and 59 (29.5%) as STEMI. Twenty-one (10.5%) patients developed atrial fibrillation, and seven (53.5%) patients were diagnosed as unstable angina, 34 (17%) as non-STEMI and 59 (29.5%) as STEMI. Twenty-one (10.5%) patients developed atrial fibrillation, and seven (53.5%) patients were diagnosed as unstable angina, 34 (17%) as non-STEMI and 59 (29.5%) as STEMI. Twenty-one (10.5%) patients developed atrial fibrillation, and seven (53.5%) patients were diagnosed as unstable angina, 34 (17%) as non-STEMI and 59 (29.5%) as STEMI.

Table 1. Baseline clinical characteristics of both study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-diabetic group (n = 111)</th>
<th>Prediabetic group (n = 40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51 ± 6.8</td>
<td>49.6 ± 6.9</td>
<td>0.27</td>
</tr>
<tr>
<td>Male gender</td>
<td>81 (73)</td>
<td>26 (65)</td>
<td>0.34</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.8 ± 2.4</td>
<td>29.2 ± 2.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Current smoking</td>
<td>62 (55.9)</td>
<td>25 (62.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>44 (39.6)</td>
<td>17 (42.5)</td>
<td>0.75</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64 (57.7)</td>
<td>25 (62.5)</td>
<td>0.59</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>34 (30.6)</td>
<td>13 (32.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>ACS Presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>59 (53.2)</td>
<td>22 (55)</td>
<td>0.71</td>
</tr>
<tr>
<td>Non-STEMI</td>
<td>20 (18)</td>
<td>5 (12.5)</td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>32 (28.8)</td>
<td>13 (32.5)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10 (9)</td>
<td>5 (12.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>2 (1.8)</td>
<td>1 (2.5)</td>
<td>0.61</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>2 (1.8)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Ejection fraction &lt;40%</td>
<td>14 (12.6)</td>
<td>9 (22.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>6.5 ± 2</td>
<td>7.2 ± 1.7</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as frequency (percentage). ACS, acute coronary syndrome; IHD, ischaemic heart disease; STEMI, ST-elevation myocardial infarction.

developed in-hospital re-infarction and 42 (21%) heart failure.

Based on the definition of the American Diabetes Association, 49 (24.5%) patients were classified as newly discovered diabetic patients and were excluded from analysis. Forty (20%) patients were classified as prediabetic and 111 (55.5%) as non-diabetic. Compared with patients without diabetes, patients with prediabetes had a higher BMI (P = 0.002) and tended to have a longer hospital stay (P = 0.09). The other baseline characteristics of the two groups are summarised in Table 1. Prediabetic patients had higher FPG and 2hPG (P < 0.001 for both). HbA1c was 6.2 ± 0.1% in patients with prediabetes versus 4.9 ± 0.4% in patients without diabetes (P < 0.001). The other laboratory data are summarised in Table 2.

Table 2. Laboratory data of both study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-diabetic group (n = 111)</th>
<th>Prediabetic group (n = 40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mmol/L)</td>
<td>5.12 ± 0.33</td>
<td>6.49 ± 0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2hPG (mmol/L)</td>
<td>6.66 ± 0.44</td>
<td>9.38 ± 0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.9 ± 0.4</td>
<td>6.2 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.11 ± 0.39</td>
<td>6.16 ± 0.36</td>
<td>0.50</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.24 ± 0.16</td>
<td>2.25 ± 0.17</td>
<td>0.49</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>4.04 ± 0.36</td>
<td>4.09 ± 0.21</td>
<td>0.29</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.06 ± 0.21</td>
<td>1.04 ± 0.21</td>
<td>0.61</td>
</tr>
</tbody>
</table>

2hPG, 2-h plasma glucose; FPG, fasting plasma glucose; HDX, high-density lipoprotein; LDI, low-density lipoprotein.
In-hospital clinical outcome

The primary composite end-point of in-hospital MACE occurred in 10 (25%) patients with prediabetes versus 6 (5.4%) patients without diabetes (P = 0.001). During hospital stay, five (12.5%) patients with prediabetes died and five (12.5%) developed re-infarction versus three (2.7%) and two (1.8%) patients without diabetes respectively (P < 0.05 for both). Additionally, four (10%) patients with prediabetes underwent in-hospital urgent vessel revascularisation (all of whom had in-hospital re-infarction) versus three (2.7%) patients without diabetes (two of whom had in-hospital re-infarction, and one had early post-infarction angina) (P = 0.08). Ventricular tachycardia occurred in 11 (27.5%) patients in the prediabetic group versus 10 (25%) in the non-diabetic group (P = 0.004). Heart failure occurred in 10 (25%) patients with prediabetes versus 14 (12.6%) patients without diabetes (P = 0.07), as summarised in Table 3. Interestingly, patients with prediabetes (40 patients) were statistically comparable with patients with diabetes (49 patients) for the rates of overall MACE, the individual components of MACE, as well as the secondary end-points (P > 0.05 for all) (data not shown).

In-hospital MACE correlated with prediabetes (r = 0.28, P < 0.001), BMI (r = 0.14, P = 0.093), FPG (r = 0.19, P = 0.014), 2hPG (r = 0.19, P = 0.017) and HbA1c (r = 0.19, P = 0.019). Multivariable regression analysis identified prediabetes as the only independent predictor of in-hospital MACE (P = 0.002, hazard ratio 5.8, 95% confidence Interval 1.9–17.3). Similarly, multivariable regression analysis identified prediabetes as the only independent predictor of in-hospital death (P = 0.03, hazard ratio 5.1, 95% confidence Interval 1.2–22.6).

Discussion

Main findings

We found that prediabetes is fairly common in patients presenting with ACS who are not previously known to be diabetic. Prediabetic patients had a worse in-hospital clinical outcome compared with patients without diabetes. Moreover, prediabetes was the only independent predictor of in-hospital mortality, as well as in-hospital MACE.

Prediabetes and outcome of ACS

The impact of prediabetes on the clinical outcome of patients with ACS has long been a matter of controversy. In a post-hoc analysis of the EARLY ACS trial, patients with prediabetes (defined by a FPG 6.11–6.94 mmol/L admitted with non-ST-segment elevation ACS) had a mortality rate at 30 days and at 1 year comparable with that of patients without diabetes. Two studies described a J-shaped relationship of blood glucose and adverse outcome in patients presenting with acute STEMI, both hyperglycaemia and hypoglycaemia were associated with adverse outcome. In contrast, there was a graded relation between FPG and 30-day mortality in a prospective study of patients without diabetes admitted with acute myocardial infarction. Additionally, a retrospective analysis of the GRACE registry demonstrated an odds ratio for in-hospital mortality of 1.51 in patients admitted with ACS and a FPG level of 5.55–6.94 mmol/L versus those admitted with a FPG < 5.55 mmol/L. Our findings support the latter two reports in ACS patients with prediabetes, defined according to the recent definition of the American Diabetes Association that incorporates OGTT as a prerequisite for the diagnosis of prediabetes. This makes a strong argument for our data because the identification of glucose intolerance based on FPG alone tends to underestimate the prevalence of prediabetes compared with OGTT. The divergence of results of the aforementioned studies can be explained by the different definitions used to identify prediabetes (based on FPG or OGTT) and the diversity of patients enrolled (non-ST-segment elevation ACS, acute STEMI or full spectrum of ACS).

We found a significant positive correlation between MACE on one hand, and FPG and HbA1c on the other hand. Likewise, Lenzen et al. demonstrated an association between elevated HbA1c and mortality after myocardial infarction. Similarly, Levitzky et al. reported that elevated glucose at admission and higher FPG during hospitalisation were linked to worse clinical outcomes, regardless of the presence of diabetes. Our study identified prediabetes as an independent predictor of in-hospital mortality – and MACE – in patients with ACS. Increased incidence of ventricular tachycardia (P = 0.004) and heart failure (P = 0.07) during hospital stay in patients with prediabetes versus non-diabetic patients may account for the increased in-hospital mortality.

Table 3 In-hospital clinical events in the two study groups

<table>
<thead>
<tr>
<th>Event</th>
<th>Non-diabetic group (n = 111)</th>
<th>Prediabetic group (n = 40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>6 (5.4)</td>
<td>10 (25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>3 (2.7)</td>
<td>5 (12.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Re-infarction</td>
<td>2 (1.8)</td>
<td>5 (12.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urgent revascularisation</td>
<td>3 (2.7)</td>
<td>4 (10)</td>
<td>0.08</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>17 (15.3)</td>
<td>4 (10)</td>
<td>0.59</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>10 (9)</td>
<td>11 (27.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Heart failure</td>
<td>14 (12.6)</td>
<td>10 (25)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Variables are presented as frequency (percentage). MACE, major adverse cardiac events.
Similar to our results, glucose intolerance (based on OGTT) was a strong independent predictor of MACE in patients with acute myocardial infarction at a median follow up of 34 months.4

**Prediabetes and cardiovascular risk**

The pathobiological mechanisms involved in the early adverse outcome among patients with prediabetes are still unclear. At the vascular wall level, hyperglycaemia decreases the bioavailability of nitric oxide and prosstaglandin I2, and increases the synthesis of vasoconstrictor prostanoids and endothelin through multiple mechanisms.17 In addition, endothelial dysfunction associated with chronic uncontrolled hyperglycaemia reduces coronary flow reserve and increases platelet aggregability.18

**Clinical implications**

Early identification and treatment of patients with prediabetes has the potential to reduce related macrovascular and microvascular disease. The European Society of Cardiology and the European Association for the Study of Diabetes already advocated investigating glucose metabolism in patients without known diabetes but with established cardiovascular disease, by performing OGTT.19 In view of the rather high prevalence of prediabetes in patients admitted with ACS without previously diagnosed diabetes, we would recommend routine OGTT in such a critical patient subset.

**Limitations of the study**

Our findings are based on a single-centre study with a relatively small sample size of the cohort, therefore, our results should be taken with caution. Multicentre studies employing the same protocol and examining a larger number of patients are needed for firm conclusions to be drawn. Moreover, variation of the time of performance of OGTT might have affected categorisation of our cohort. A hyperadrenergic state exists in the early phase of ACS – added to hospital admission – that might have influenced glucose tolerance. Perhaps some of the patients would not test positive for impaired glucose tolerance outside of the setting of ACS; nevertheless, the susceptibility shows itself in the outcomes measured. Testing a subset of these patients 3 months later may be interesting to clarify this issue. Moreover, hospital stay was relatively long, and this might have exaggerated the difference in MACE. Yet, it is the protocol of our hospital that a patient stays for at least 2 days in the ward after discharge from the coronary care unit in order to start a rehabilitation programme. Additionally, long-term follow up is needed to explore the impact of prediabetes (diagnosed by OGTT) on the long-term clinical outcome.

**Conclusion**

Prediabetes is fairly common in patients presenting with ACS who are not previously known to have diabetes. Prediabetic patients had worse in-hospital clinical outcomes compared with patients without diabetes.

**References**

10 Gonen B, Rubenstein A, Rochman H, Tanega SP, Horwitz DL. Haemoglobin © 2014 Royal Australasian College of Physicians


Comprehensive dietary education in treated gout patients does not further improve serum urate

R. Holland1 and N. W. McGill2

1Rheumatology Department, Westmead Hospital and 2Department of Rheumatology, RPA Institute of Rheumatology and Orthopaedics, Royal Prince Alfred Hospital, Sydney NSW 2050, Australia

Key words
gout, diet, uric acid, therapy, education.

Correspondence
Richard Holland, Westmead Hospital, Rheumatology Department, Cnr Hawkesbury and Darcy Roads, Westmead, New South Wales 2145, Australia.
Email: hollandrichardj@gmail.com

Received 30 August 2014; accepted 27 November 2014.
do:10.1111/imj.12661

Abstract
Background/Aim: This study aims to investigate the influence of dietary education in patients with gout on a stable dose of urate-lowering therapy (ULT).

Methods: Males and females aged >18 years with a history of gout, receiving an appropriate and stable dose of ULT, were recruited from two tertiary hospitals and randomised into two groups. The control group received basic advice regarding the importance of compliance with therapy and the benefit of weight loss. The intervention group received comprehensive dietary advice based on the British Society of Rheumatology Guidelines. Both groups received education at baseline and 3 months. Serum urate was measured at baseline, 3 months and 6 months, and a questionnaire was completed at baseline and at 6 months. The primary outcome of the study was to compare the change in serum urate between groups.

Results: Thirty patients were recruited into the study. There was no difference in serum urate between the control and intervention group at 6 months (0.29 mmol/L vs 0.29 mmol/L at baseline and 0.27 mmol/L vs 0.30 mmol/L at 6 months). The intervention group showed a statistically significant improvement in knowledge (8/13 in control group at baseline to 9/13 at 6 months vs 8/13 in intervention group at baseline to 12/13 at 6 months, \( P < 0.05 \)) and self-reported dietary modification (1 in control vs 7 in intervention \( P < 0.05 \) at 6 months).

Conclusion: This randomised controlled trial shows that in patients on ULT, providing education on diet does not lead to any clinically significant difference in serum urate at 6 months.

Introduction

Recent epidemiological studies have indicated that the prevalence of gout is increasing, and in some populations has been shown to double over a 10-year period.1–3 The prevalence ranges from 1–5%, and this is much higher among men and also certain populations such as New Zealand Maoris and Aboriginal Taiwanese.1,4 Furthermore, there is an increasing body of evidence that gout is associated with an increased risk of coronary artery disease and an increased risk of death from cardiovascular disease and death from all causes.3–5 Patients with gout often have a number of comorbidities including hypertension, abdominal obesity, hyper-triglyceridaemia and hyperglycaemia. The prevalence of the metabolic syndrome is high, and increases as serum urate increases.3–10

There is a significant burden of disease in patients with gout and acute flares of gout result in pain, dependency on family members and work disability. Untreated gout results in an increasing number of affected joints with escalating treatment required to control flares, as well as joint destruction and loss of function resulting from severe tophaceous gout.11 Despite this, the control of gout remains poor, and patients are often not aware of the optimal management; there is also a lack of application of current guidelines among health professionals.12,13

Adherence to drug therapy is a barrier to treatment. The compliance with drug treatment among gout patients is poor, with compliance rates between 37–64%. This is particularly problematic among young patients and those with few comorbid conditions when there is less of a need to visit a primary care physician on a regular basis.14 In a recent study involving 700 000 people, the adherence to treatment for hypertension and hypothyroidism was 72% and 68%, respectively,
compared to only 37% in gout patients.\textsuperscript{15} Even if patients are compliant, urate lowering therapy is frequently under-dosed, with a substantial proportion of patients failing to achieve a serum urate of $< 0.36 \text{ mmol/L}$ when taking the recommended dose.\textsuperscript{16} This issue is most marked in those with chronic kidney disease, where there is conflicting or scarce evidence regarding the correct dosing of allopurinol in renal failure.\textsuperscript{17} Together, the poor compliance rates and frequent under-dosing result in suboptimal control of hyperuricaemia in a large proportion of patients.

Recent evidence has determined a number of dietary factors that potentially influence both acute flares of gout and the incident risk of gout.\textsuperscript{18–22} While these factors may contribute to the risk of gout on a population basis, the influence of diet in patients with established disease is unclear. There is currently a lack of evidence regarding the therapeutic benefit of dietary modification in patients with gout. While a strict low calorie, low purine diet has been shown to reduce serum urate in untreated patients;\textsuperscript{23} this is difficult, if not impossible, to apply in clinical practice. Can education improve compliance and treatment outcomes? Previous studies have indicated that the recall of recommendations in those patients with chronic diseases is poor, with the recall of ancillary measures such as diet, exercise and self-care activities ranging from 22\% to 84\%.\textsuperscript{24} As the number and complexity of recommendations increase, there is the potential for the key treatment component to be forgotten. This prospective, randomised controlled trial sought to determine the effect, if any, of dietary education among treated patients with gout.

### Methods

Patients were recruited from the outpatient departments of the Royal Prince Alfred and Concord Repatriation General Hospitals over an 18-month period. Males and females aged $>18$ years with a history of gout as per American College of Rheumatology criteria,\textsuperscript{25} who were on a stable dose of urate lowering therapy at target (serum urate $< 0.36 \text{ mmol/L}$), were included in the study. Patients were excluded from the study if they were unable to communicate in English (both verbal and written, to standardise information). Patients were randomised using block randomisation in blocks of 10 to ensure even group sizes, and blinded as to group. Informed consent was obtained prior to enrolment in the study, and the study was approved by the local hospital ethics committees.

Thirty patients were required for a minimal detectable difference of 0.05 mmol/L at the 5\% significance level. Baseline characteristics were recorded for both groups at enrolment (Table 1). Both groups were asked to complete a multiple choice questionnaire at baseline to assess their knowledge of gout. The questionnaire had a simple reading level as determined by the Flesch–Kincaid readability algorithm.\textsuperscript{26} The groups received education at baseline and 3 months. The control group received advice regarding the importance of compliance with drug therapy, the benefit of weight loss and exercise (to achieve an ideal bodyweight) and the benefit of reduced alcohol intake. They were also advised on the target serum urate concentration.\textsuperscript{27} In addition to the advice given to the control group, the intervention group received dietary advice in line with the British Society for Rheumatology guidelines for the management of gout\textsuperscript{28} and a recent publication detailing the most suitable diet for patients with gout.\textsuperscript{29} The advice recommended: (i) reducing red meat intake, and avoiding offal, shellfish and yeast extract; and (ii) including low fat dairy products, vegetables and cherries and the potential benefit of coffee and vitamin C. Blood was taken at baseline, 3 months and 6 months, and the questionnaire was repeated at 6 months. Patients were asked to recall the

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control ($n = 15$)</th>
<th>Intervention ($n = 14$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range) (years)</td>
<td>61 (38–77)</td>
<td>64 (44–80)</td>
<td>0.285</td>
</tr>
<tr>
<td>Sex M : F</td>
<td>15 : 0</td>
<td>12 : 2</td>
<td>0.150</td>
</tr>
<tr>
<td>Duration of gout, median (range) (years)</td>
<td>10 (1–49)</td>
<td>5 (1–40)</td>
<td>0.233</td>
</tr>
<tr>
<td>Flares last 6 months, median (range)</td>
<td>2 (0–5)</td>
<td>0 (0–4)</td>
<td>0.116</td>
</tr>
<tr>
<td>Allopurinol dose, mean (range) (mg)</td>
<td>525 (100–900)</td>
<td>415 (200–900)</td>
<td>0.081</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>3 (20)</td>
<td>2 (13)</td>
<td>0.630</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>10 (67)</td>
<td>7 (47)</td>
<td>0.277</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>5 (33)</td>
<td>5 (33)</td>
<td>1.000</td>
</tr>
<tr>
<td>Chronic liver disease, n (%)</td>
<td>2 (13)</td>
<td>1 (7)</td>
<td>0.550</td>
</tr>
<tr>
<td>Ischaemic heart disease, n (%)</td>
<td>3 (20)</td>
<td>3 (20)</td>
<td>1.000</td>
</tr>
<tr>
<td>Alcohol, median g/week (range) (g/week)</td>
<td>70 (0–690)</td>
<td>70 (0–700)</td>
<td>0.653</td>
</tr>
<tr>
<td>Body mass index, mean (range) (kg/m$^2$)</td>
<td>30 (24–37)</td>
<td>29 (23–35)</td>
<td>0.624</td>
</tr>
</tbody>
</table>
number of flares in the previous 6 months at study entry and completion.

The primary outcome was the change in serum urate at 3 months and 6 months. Secondary outcomes were the change in number of flares, dietary modification or attempted weight loss and change in knowledge as measured by the questionnaire. Patients were not advised of the answers to the questionnaire until study completion. The dose of urate lowering therapy was kept unchanged throughout the study.

Statistics were analysed using SPSS v 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) with $\chi^2$ Fisher’s exact test used for dichotomous outcomes and Mann–Whitney U-test for continuous outcomes. Results were considered statistically significant if $P$-value <0.05.

Results

A total of 120 patients was screened for the study. Eighty-nine were excluded; 48 declined to participate, 15 due to a language barrier, 18 due to an unstable allopurinol dose and eight for other reasons. One patient was excluded during the study due to the development of tumour lysis, and two dropped out. Twenty-eight patients completed the 6-month study. There was no significant difference in baseline variables between groups (Table 1). Pre-existing knowledge of gout was poor, with only 16 participants able to recall the target urate level correctly. Only 36 correct responses were recorded to the dietary questions (out of a possible 120; Fig. 1).

The mean serum urate (standard deviation, range) in the control group at baseline was 0.29 mmol/L (±0.06, 0.20–0.42) and in the intervention group 0.29 mmol/L (±0.08, 0.18–0.49). At 6 months, there was no significant difference between groups, with the mean in the control group 0.27 mmol/L (±0.07, 0.18–0.44) and in the intervention group 0.30 mmol/L (±0.08, 0.17–0.51), $P > 0.05$ (Fig. 2). On subgroup analysis, there were no baseline characteristics that predicted the change in urate at 6 months.

There was a significant difference between groups in the questionnaire with the control group answering correctly 8.9 questions out of 13 at baseline and 10.1/13 at 6 months versus 8/13 at baseline in the intervention group and 12/13 at 6 months, $P < 0.001$ (Fig. 3). There was also a significant difference between groups for diet modification (one patient in control group vs seven in the intervention group, $P = 0.009$) but not for weight loss (four in control vs five in intervention, $P = 0.742$). The mean alcohol consumption in the intervention group reduced from a median of 70g/week at baseline to 50g/week at 6 months. Of the 10 people who consumed alcohol in the intervention group, five significantly reduced their alcohol intake. No patients in the control group reduced their alcohol consumption. There was no difference in flares between groups at 6 months (mean 1 vs 2, $P > 0.05$).

Discussion

In this prospective, blinded, randomised controlled trial, dietary education improved patient knowledge and
behaviour, but did not lead to any significant improvement in serum urate. Although cross-sectional studies have demonstrated that the incident risk of gout changes as a result of several dietary factors, this does not appear to translate to a benefit in those on treatment. There are several possible reasons for this. Only half of the patients in the intervention group attempted to change their diet. As there was no dietary recall, the degree of change could not be ascertained. Although not powered to detect a difference, a subgroup analysis showed there was no difference in serum urate in those who reported changing their diet compared to those who did not. Compliance was not recorded during the study and could have been a source of bias. No patient had a pattern of fluctuating urate levels suggestive of non-compliance.

The patients were well controlled on study entry (mean urate 0.29 mmol/L), and thus it is conceivable that a plateau had been reached beyond which any further reductions in serum urate were unlikely. One patient was unable to tolerate any urate lowering therapy and was included in the study. Despite a concerted effort to make a significant change in diet, the patient was unable to improve serum urate over the 6-month period (0.49 mmol/L at baseline and 0.51 mmol/L at 6 months).

There are several reasons why dietary modification may not lead to a clinically relevant change in serum urate. One study has shown that in a small group of uncontrolled gout patients, severe calorie restriction was associated with a reduction in urate of 0.10 mmol/L over a 16-week period. Analysis of the data determined that the reduction was almost solely due to weight loss rather than reduction in purine intake, and only one patient achieved the target urate during the study. This suggests that significant and sustained weight loss may be a bigger contributing factor than specific dietary intake, and this is supported by a further study that showed an 11% reduction in urate among patients who lost an average of 8 kg. The study does not exclude benefit from targeted interventions such as weight loss or reduction in alcohol intake in those patients for whom it is a significant contributing factor.

Studies that have investigated the reduction in urate with diet have predominantly looked at large dietary changes over a short period of time. For example, a study looking at the effect of milk on urate showed a reduction of only 0.03 mmol/L 3 h after consuming 800 mL of milk. It is unclear whether consuming this quantity of milk consistently would lead to a permanent reduction in urate. Similarly, eating 280 g of cherries reduced urate by 0.031 mmol/L over a 5-h period. Both of these studies were in healthy volunteers, and the effect in gout patients may not be similar. A retrospective study
demonstrated that regular use of cherry juice concentrate led to a significant reduction in flares over a minimum period of 4 months. In those not on urate lowering therapy, there was no reduction in serum urate over the same period, suggesting the reduction in flares was not as a result of a change in serum urate. In addition, a randomised trial of vitamin C 500 mg daily as an adjunct to allopurinol demonstrated no reduction in urate with vitamin C.

The dietary education provided in this study entailed 30 min of face-to-face discussion on two occasions (baseline and 3 months) supplemented by succinct written information. It is unlikely that this level and intensity of dietary education would be achieved more than rarely in clinical practice. Thus, despite the limitations mentioned above, the lack of any measurable benefit on serum urate levels as a result of specific dietary advice (in comparison to simple advice to avoid or correct obesity and alcohol excess) argues against this approach as a useful therapeutic intervention. Unless and until future prospective studies of dietary intervention, continued for a clinically meaningful period of time, demonstrate a reduction in serum urate, the clinician and patient should direct their attention to proven methods of achieving the target serum urate concentration, namely using sufficient doses of readily available hypouricaemic drugs and maintaining good compliance.

**Conclusion**

This randomised controlled study demonstrates that dietary education in well-treated gout patients does not lead to any significant improvement in serum urate despite an improvement in knowledge. Further prospective studies are needed to determine whether diet has a role in the management of patients with established gout, both in reducing flares while commencing urate lowering therapy and in achieving and maintaining target serum urate.

**Acknowledgement**

The authors thank the Royal Prince Alfred and Concord General Repatriation Hospitals for their support.
References


Hyponatraemia at hospital admission is a predictor of overall mortality

L. Balling,1 F. Gustafsson,1 J. P. Goetze,2 M. Dalsgaard,3 H. Nielsen,4 S. Boesgaard,1 M. Bay,5 V. Kirk,6 O. W. Nielsen,4 L. Køber1 and K. Iversen3

1Departments of Cardiology, and 2Clinical Biochemistry, Rigshospitalet, University Hospital of Copenhagen, 4Department of Cardiology, Bispebjerg Hospital, Copenhagen, 6Department of Cardiology, Frederiksberg Hospital, Frederiksberg, 7Department of Oncology, Herlev Hospital, Herlev and 3Department of Cardiology and Endocrinology, Hillerød Hospital, Hillerød, Denmark

Key words
Hyponatraemia, all-cause mortality, electrolyte disturbance.

Abstract
Background: Hyponatraemia is a prognostic marker of increased mortality and morbidity in selected groups of hospitalised patients. The aim of the present study was to examine the prevalence and prognostic significance of hyponatraemia at hospital admission in an unselected population with a broad spectrum of medical and surgical diagnoses.

Methods: Consecutive patients >40 years of age admitted to a general district hospital in Greater Copenhagen between 1 April 1998 and 31 March 1999. Median follow-up time was 5.16 years (range 0–4372 days). Plasma sodium measurements were available in 2960 patients, and hyponatraemia defined as P-Na+ < 137 mmol/L at hospital admission was present in 1105 (37.3 %) patients.

Results: One-year mortality was higher for hyponatraemic patients than for normonatraemic patients: 27.5 % versus 17.7 %. Moreover, hyponatraemia was an independent predictor of short and long-term all-cause mortality after 1 year and after the entire observation period respectively: hazard ratio (HR) 1.6 (95 % confidence interval (CI) 1.4–1.9, \( P < 0.0001 \)) and HR 1.4 (95 % CI 1.3–1.6, \( P < 0.0001 \)). Patients with hyponatraemia had longer hospitalisations than patients with normonatraemia: 7.6 (±0.38) days vs 5.6 (±0.21) days, \( P < 0.001 \). There was no interaction between hyponatraemia at admission and any admission diagnoses (\( P > 0.05 \) for all interaction analyses).

Conclusion: Hyponatraemia is associated with increased all-cause mortality and longer admission length independently of diagnosis and clinical variables.

Introduction

Hyponatraemia is the most common electrolyte disturbance in hospitalised and ambulatory patients.1,2 The presence of hyponatraemia is a prognostic marker for increased morbidity and mortality in patients with specific diagnoses, such as heart failure,1 myocardial infarction,4 liver cirrhosis,5 renal insufficiency,6 endocrine disease,7 stroke4 as well as in patients with bone fractures.9–14 Increased neurohormonal activity has been associated with the development of hyponatraemia.15,16

The pathology is multifactorial, and the complete mechanisms of development of hyponatraemia remain incompletely understood. Symptoms as a consequence of hyponatraemia vary from asymptomatic or subtle to severe neurologic symptoms with a need for prompt medical treatment. Mild hyponatraemia is often unnoticed by the physician, but is associated with an increased risk of fall and bone fractures as well as attention deficits in the elderly population.2,17 Hence, specific attention towards both mild and severe hyponatraemia remains important in the daily clinical practice.

The prognostic importance of hyponatraemia in a general population admitted to hospital has not been examined previously. Also, it is unclear whether the prognostic importance of hyponatraemia differs between medical and surgical diagnoses. The aim of the present study was to examine if baseline hyponatraemia...
measured at hospital admission predicts increased mortality and morbidity in an unselected population above 40 years of age admitted to a general hospital with a broad spectrum of medical and surgical conditions. A secondary aim was to investigate whether there was interaction between baseline hyponatraemia and admission diagnosis on overall mortality.

**Methods**

The Copenhagen Hospital Heart Failure Study (CHHF) included all patients above the age of 40 years admitted to a general city hospital in Copenhagen between 1 April 1998 and 31 March 1999 to either a medical (internal medicine and cardiology) or a surgical (gastro-intestinal or orthopaedic) department. The primary aim of CHHF was to investigate if N-Terminal pro-brain natriuretic peptide (NT-proBNP) could be used as a biomarker to predict a low left ventricular ejection fraction or clinical signs of HF in an unselected group of patients admitted to a general hospital. A thorough medical interview as well as a comprehensive medical examination, echocardiography and blood analyses were performed within the first 24 h after admission. A detailed description of the CHHF study has previously been published.\(^{16-20}\) Discharge diagnosis and events during hospitalisation were collected from patient files. Outcome information regarding death and re-hospitalisations was collected from the Danish National Patient Registry, which records all information regarding mortality and discharge diagnoses according to an individual civil registration number.\(^ {21}\) The validity of end points obtained from the Danish National Patient Registry has previously been obtained.\(^ {21}\) Patients were divided into one of eight possible admission diagnoses (i) cardiovascular, (ii) orthopaedic, (iii) gastrointestinal, (iv) haematological/ oncological, (v) pulmonary, (vi) neurologic, (vii) infectious and (viii) other diagnoses (endocrinological, nephrological, rheumatological and non-specific diagnoses, such as dehydration, social causes and drug abuse).

Complete follow up was possible for all except nine patients (0.6 %). Patients were lost to follow up because of emigration and were censored at the time of emigration.

**Blood sample analyses**

Blood samples were obtained within the first 24 h of hospital admission in the time period between 8 am and 10 am as part of the CHHF study. Sodium, potassium, C-reactive protein as well as creatinine levels were analysed according to the local standard method of the hospital laboratory. The glomerular filtration rate (eGFR) was estimated using the modification of diet in renal disease formula.\(^ {22}\) NT-proBNP was measured consecutively during the later 10 months of the study with an enzyme-linked immunosorbent assay (a two step sandwich assay, Roche, Basel, Switzerland).

**Ethics**

All patients gave informed consent prior to study inclusion. The study complied with the Helsinki Declaration and was approved by the local ethics committee of Copenhagen.

**Statistical analyses**

Patients were divided into two groups according to the plasma sodium level. Normonatraemia was defined as a plasma sodium concentration $\geq 137$ mmol/L and hyponatraemia as a plasma sodium concentration $< 137$ mmol/L. Mild hyponatraemia was defined as a plasma sodium concentration $< 137$ mmol/L and $\geq 130$ mmol/L and moderate to severe hyponatraemia as a plasma sodium $< 130$ mmol/L. The hyponatraemic groups were pooled into one group designated hyponatraemia for analyses, but additional analyses were performed for mild and moderate–severe hyponatraemia. Hypernatraemia was defined as a plasma sodium $\geq 146$ mmol/L and patients with hypernatraemia were pooled with the normonatraemic group for analyses. For baseline data, continuous variables are presented as means with standard deviation (SD), and categorical data are presented as frequencies and percentages as appropriate. Differences between baseline variables were tested using one-way analysis of variance for continuous variables and $\chi^2$ test for categorical variables. Time-to-event analyses were performed using the Kaplan–Meier method and illustrated as survival curves.

Univariate comparisons and multivariable Cox proportional hazard models with backward elimination were used to assess the impact of potential covariates by constructing multivariable models with inclusion of important demographic and clinical variables presented in Table 1. Hazard ratios (HR) were measured for all patients together and divided according to discharge diagnoses. The following models were constructed: model 1: hyponatraemia (unadjusted); model 2: hyponatraemia, age and gender; model 3: hyponatraemia, age, heart rate, use of alcohol, haemoglobin, use of diuretics at hospital admission, medical history of diabetes, pulmonary and liver disease; model 4: model 3 + NT-proBNP. The results from the Cox regression analyses are presented as HR.
with 95% confidence intervals (95% CI). A $P$-value $<0.05$ was considered significant.

Interaction between hyponatraemia and admission diagnosis on overall prognosis was tested in the final multivariable Cox proportional hazards model, including an interaction variable. By visual inspection, the assumption of proportional hazards was fulfilled.

Statistical calculations were performed using the statistical software program PASW version 20 (SPSS Inc, IL, USA).

**Results**

**Patient characteristics**

In the inclusion period a total of 3644 patients above 40 years of age was admitted to the hospital. Of these, 408 (11%) were excluded due to immediate discharge, death before inclusion or a lack of willingness or capability to give informed consent. Of the remaining 3236 patients, plasma sodium concentrations were available in 2960 patients (91.5%). These patients comprised the study population for the present analysis. Patients included in the analyses were slightly older (71.3 years vs 68.4 years) and had lower all-cause mortality (HR 0.89) than those not included (276 patients). There was no difference regarding gender between the two groups. The median follow-up time was 5.2 years (range 0–4372 days).

The mean plasma sodium concentration in the total population was 137 (±4.7) mmol/L. Of the 2960 patients, 1855 (62.6%) had a plasma sodium concentration $\geq 137$ mmol/L. Hyponatraemia, defined as a plasma sodium concentration $<137$ mmol/L, was considered significant.

<table>
<thead>
<tr>
<th>Table 1 Baseline patient characteristics at hospital admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age, mean (SD) (years)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
</tr>
<tr>
<td>Female ≤ 14 units/week</td>
</tr>
<tr>
<td>Female &gt; 14 units/week</td>
</tr>
<tr>
<td>Male ≤ 21 units/week</td>
</tr>
<tr>
<td>Male &gt; 21 units/week</td>
</tr>
<tr>
<td>Bilateral peripheral oedemas, n (%)</td>
</tr>
<tr>
<td>Vital signs</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD) (mmHg)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD) (mmHg)</td>
</tr>
<tr>
<td>Heart rate, mean (SD) (bpm)</td>
</tr>
<tr>
<td>Ejection fraction, mean (SD) (%)</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Liver disease, n (%)</td>
</tr>
<tr>
<td>Lung disease, n (%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor, n (%)</td>
</tr>
<tr>
<td>Clinical parameters</td>
</tr>
<tr>
<td>Sodium, mean (SD) (mmol/L)</td>
</tr>
<tr>
<td>Potassium, mean (SD)</td>
</tr>
<tr>
<td>Haemoglobin, mean (SD)</td>
</tr>
<tr>
<td>eGFR (SD)</td>
</tr>
<tr>
<td>C-reactive protein, mean (SD)</td>
</tr>
<tr>
<td>NT-proBNP, mean (SD)</td>
</tr>
</tbody>
</table>

bpm, beats per minute; eGFR, glomerular filtration rate; NT-proBNP, N-Terminal pro-brain natriuretic peptide; SD, standard deviation.
<137 mmol/L was present in 1105 (37.3%) of the patients. Among the hyponatraemic patients 899 (30.4%) patients had mild hyponatraemia (130 mmol/L ≤ plasma sodium <137 mmol/L) and 206 (7.0%) had moderate–severe hyponatraemia (plasma sodium <130 mmol).

Baseline variables (demographic characteristics, vital parameters, symptoms, medical history and clinical parameters) for patients with normo- or hyponatraemia at hospital admission can be seen in Table 1. Patients with hyponatraemia had a significantly higher degree of comorbidity with a significantly higher prevalence of liver disease (P = 0.001) and diabetes (P < 0.0001) than normonatraemic patients. Hyponatraemic patients were treated more frequently with diuretics and angiotensin-converting enzyme inhibitors than patients with normonatraemia. In addition, patients with hyponatraemia had a lower systolic blood pressure and a lower haemoglobin level than patients with normonatraemia. There was no difference in renal function estimated by eGFR between the two groups, but NT-proBNP and C-reactive protein levels were higher in the hyponatraemic group. There were no other clinically relevant differences between normo- and hyponatraemic patients.

**Association of hyponatraemia on outcome in all-comers**

After 1 year, 633 (21.4%) patients from the study population had died, and after the entire observation period, 2127 (71.9%) had died. Mortality in the hyponatraemic group was higher both after 1 year and after the entire observation period than for normonatraemic patients (27.5% vs 17.7% after 1 year and 79.3% vs 67.4% after the entire observation period, P < 0.001 for both).

In univariate analysis, hyponatraemia at hospital admission was found to be a predictor of mortality for all patients after 1 year (HR 1.6, 95% CI 1.4–1.9, P < 0.0001) and after the entire observation period (HR 1.4, 95% CI 1.3–1.6, P < 0.0001). For patients with moderate–severe hyponatraemia at hospital admission, the hazard ratio was similar after 1 year (HR 1.7, 95% CI 1.3–2.2, P < 0.0001) and after the entire observation period (HR 1.5, 95% CI 1.3–1.7, P < 0.0001). Patients with moderate–severe hyponatraemia had a higher risk of mortality when compared to patients with mild hyponatraemia (HR 1.2, 95% CI 1.0–1.4, P = 0.035). A Kaplan–Meier plot illustrating overall mortality according to plasma sodium concentrations for the entire observation period can be seen in Figure 1 (P < 0.0001).

In multivariate Cox regression analyses with stepwise adjustment for all clinical baseline parameters selected by backward elimination presented in Table 1, hyponatraemia remained a significant predictor of mortality for all patients after 1 year HR 1.5 (95% CI 1.2–1.9, P < 0.0001) as well as after the entire observation period: HR 1.2 (95% CI 1.1–1.3, P < 0.004).

Hazard ratios for the prognostic value of hyponatraemia for all patients as well as clinical baseline variables used in the Cox regression analysis can be seen in Table 2.

Patients with hyponatraemia had longer hospitalisations than patients with normonatraemia: 7.6 (0.38) days versus 5.6 (0.21) days, P < 0.001.

**Association of hyponatraemia on outcome in specific diagnoses**

In univariate analysis hyponatraemia was a very strong predictor of mortality after 1 year for all patients (HR 1.6, 95% CI 1.4–1.9, P < 0.0001), for patients with cardiovascular disease (HR 2.4, 95% CI 1.6–3.4, P < 0.0001) as well as for patients with orthopaedic, gastrointestinal and haematological/oncological diagnoses (P < 0.05 for all). In univariate analysis, hyponatraemia was also found to be a strong predictor of mortality for the entire study period for all patients (HR 1.4, 95% CI 1.3–1.6, P < 0.0001) as well as for patients with cardiovascular disease (HR 1.6, 95% CI 1.3–2.0, P < 0.0001), orthopaedic disease (HR 1.8, 95% CI 1.4–2.3, P < 0.0001) as well as for gastrointestinal, haematological/oncological, neurologic and for the category other diseases (P < 0.05 for all) (Table 3).

A forest plot illustrating overall mortality for patients with hyponatraemia for all disease categories can be seen in Figure 2. Mean and median sodium values for all disease categories as well as univariate hazard ratios for 1 year and for the entire observation period can be seen in Table 3.

© 2014 Royal Australasian College of Physicians
Hyponatraemia and overall mortality

Table 2  Prognostic importance of hyponatraemia for 1-year mortality and mortality for the entire observation period for all patients

<table>
<thead>
<tr>
<th>n = 2960</th>
<th>1-year mortality</th>
<th>Entire observation period mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Hazard ratio (HR, 95% CI)</td>
<td>(1.4–1.9)**</td>
<td>(1.3–1.6)**</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>(1.3–1.8)*</td>
<td>(1.2–1.5)**</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>(1.2–1.6)*</td>
<td>(1.1–1.4)**</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>(1.2–1.8)*</td>
<td>(1.1–1.3)*</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.0001.

Cox regression models with an indication of significant variables for 1-year mortality: Model 1: Unadjusted; Model 2: Adjusted for age and gender; Model 3: All variables in Table 1 were included in the model. Other significant variables in the model were: age**, heart rate*, use of alcohol**, haemoglobin**, use of diuretics at hospital admission*, medical history of diabetes, pulmonary* and liver disease**.

Model 4: All variables in Table 1 were included in the model. Other significant variables in the model were: Age**, heart rate*, use of alcohol**, haemoglobin**, use of diuretics at hospital admission*, medical history of diabetes, pulmonary and liver disease** + NT-proBNP**.

*P < 0.05, **P < 0.0001.

In multivariable Cox regression analysis, hyponatraemia was found to be a prognostic factor after 1 year in patients with cardiovascular disease (HR 2.1, 95% CI 1.2–3.4, P = 0.005) and haematological–oncological disease (HR 2.7, 95% CI 1.4–5.0, P = 0.002). In multivariable analysis, hyponatraemia was also found to carry prognostic information after the entire observation period in patients with cardiovascular disease (HR 1.3, 95% CI 1.0–1.7, P = 0.03), but not for any other admission diagnoses (P > 0.05 for all).

Association between admission diagnoses and hyponatraemia

When adjusted for relevant clinical variables, there was no interaction between hyponatraemia and admission diagnosis on overall mortality for the entire observation period (cardiovascular (P = 0.10), orthopaedic (P = 0.74), gastrointestinal (P = 0.49), haematological/oncological (P = 0.77), pulmonary disease (P = 0.68), neurologic disease (P = 0.47), other diagnoses (P = 0.77) or an infectious disease diagnosis at hospital admission (P = 0.06).

Discussion

In the present study, we found that hyponatraemia is common in patients hospitalised at a general hospital with a wide range of medical and surgical diagnoses. Furthermore, hyponatraemia is associated with increased comorbidity, increased admission length and increased short and long-term mortality in an unselected group of patients above 40 years of age admitted acutely to a general hospital. Hyponatraemia remained independently associated with mortality even when adjusted for known risk factors of increased mortality, such as age, gender, comorbid conditions, diuretics and NT-proBNP.

Hyponatraemia is the most common electrolyte disturbance encountered in hospitalised patients, as well as in ambulatory patients. In a recent study, hyponatraemia was reported to be a predictor of mortality in a general population of 14,697 patients included in the National Health and Nutrition Examination Survey independently of age, gender and comorbid conditions.24 The prevalence of hyponatraemia at hospital admission in the present study was 37.7%, which is higher than when compared to most previous studies in hospitalised patients that have found hyponatraemia to occur in up to 15–30% of patients depending on the definition of hyponatraemia and type of patients included.1,12,25–27 A previous report has found hyponatraemia to be present in up to 53% of geriatric patients which is higher than in our study. A likely explanation to the high prevalence of hyponatraemia in the present study may therefore be that patients were elderly with a mean age of 71.1 years. The high mean age in the study was also reflected as high mortality rates after both 1 year and the entire observation period for all patients in the study irrespective of hyponatraemia.

The present analysis shows that a single measurement of a low sodium concentration identifies patients with increased risk of short and long-term mortality. Furthermore, patients with hyponatraemia at hospital admission had longer hospital admissions and more comorbid conditions than patients with normonatraemia. It remains unresolved if hyponatraemia is merely a marker of advanced disease and increased risk of death or if hyponatraemia is in fact a mediator with deleterious effects on outcome. Hyponatraemia thus represents a significant clinical challenge in the daily treatment of patients and is associated great cost because of the magnitude. The presence of hyponatraemia at hospital
admission may indicate patients who are in need of closer monitoring during admission and follow-up post-discharge.

We found no interaction between hyponatraemia and a wide range of admission diagnoses. It is likely that confounding factors regarding hyponatraemia may very well exist. To our knowledge, no studies have examined the association between hyponatraemia and admission diagnosis. Our study thus extends the previous literature with the present finding. The findings suggest that hyponatraemia represents an unspecific response to severe illness rather than a disease-specific complication although, such an entity obviously exists.13,30

Several mechanisms may lead to hyponatraemia, such as use of polypharmacy (e.g. diuretics and laxatives), presence of multiple comorbidities, advanced age and hydration status.1,31 As hyponatraemia was found to be an independent predictor of survival, there may be a potential effect of treatment of hyponatraemia. Vasopressin antagonists may have a role in the treatment of hyponatraemic disorders associated with volume overload, such as heart failure, cirrhosis and syndrome of inappropriate secretion of anti-diuretic hormone.

Future prospective studies are warranted to investigate the prognostic significance of hyponatraemia in hospitalised patients and to investigate if there is a beneficial effect on morbidity and mortality of a correction of hyponatraemia. Intervention studies would be required to clarify the prognostic role of a normalisation of

<table>
<thead>
<tr>
<th>Admission diagnosis</th>
<th>n</th>
<th>Mean Na+ (SD)</th>
<th>Number of patients with hyponatraemia</th>
<th>HR 1 year (95% CI)</th>
<th>HR entire observation period (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2960</td>
<td>137.0 (4.7)</td>
<td>1105 (37.3)</td>
<td>1.6 (1.4–1.9)**</td>
<td>1.4 (1.3–1.6)**</td>
</tr>
<tr>
<td>Heart disease</td>
<td>685</td>
<td>137.7 (4.1)</td>
<td>202 (29.5)</td>
<td>2.4 (1.6–3.4)**</td>
<td>1.6 (1.3–2.0)**</td>
</tr>
<tr>
<td>Orthopaedic disease</td>
<td>413</td>
<td>137.4 (4.2)</td>
<td>129 (31.2)</td>
<td>1.7 (1.0–2.7)*</td>
<td>1.8 (1.4–2.3)**</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>375</td>
<td>136.7 (4.7)</td>
<td>142 (37.9)</td>
<td>1.7 (1.1–2.6)*</td>
<td>1.4 (1.1–1.8)*</td>
</tr>
<tr>
<td>Haematological/oncological disease</td>
<td>157</td>
<td>136.5 (4.3)</td>
<td>68 (43.3)</td>
<td>2.0 (1.3–3.2)*</td>
<td>1.5 (1.1–2.1)*</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>205</td>
<td>137.3 (3.8)</td>
<td>68 (33.2)</td>
<td>1.2 (0.7–2.1)</td>
<td>1.2 (0.9–1.7)</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>374</td>
<td>137.4 (4.7)</td>
<td>122 (32.6)</td>
<td>1.0 (0.7–1.6)</td>
<td>1.4 (1.1–1.9)*</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>387</td>
<td>135.6 (5.5)</td>
<td>207 (53.5)</td>
<td>1.2 (0.8–1.8)</td>
<td>1.0 (0.8–1.2)</td>
</tr>
<tr>
<td>Other diseases</td>
<td>363</td>
<td>136.8 (3.8)</td>
<td>94 (39.8)</td>
<td>1.5 (0.9–2.4)</td>
<td>1.5 (1.1–1.8)*</td>
</tr>
</tbody>
</table>

A P-value < 0.05 was considered significant. *P < 0.05, **P < 0.0001.
hyponatraemia in hospitalised patients and to determine if the association between hyponatraemia and outcome is a causal one.

**Limitations**

The retrospective nature of the present analysis implies several limitations. The study represents a large unselected prospective cohort consecutively admitted to a general hospital with a wide range of both medical and surgical conditions minimising the risk of selection bias. The size of the cohort and the unselected patient population as well as the long follow-up period are strengths of the study. The different disease categories represent a heterogeneous group of patients with a limited number of patients within each disease category. Glucose levels were not available in the present analysis, and the lack of glucose levels could indeed result in an overestimation of the high prevalence of hyponatraemia found in this study when compared with previous studies. A repeated measurement of sodium was not performed and hence the effects of continuous measurement of hyponatraemia could not be evaluated.

We adjusted our multivariable models for multiple potential confounders, but it is possible that residual bias remain. Only all-cause mortality was registered, and thus we have no end-point information on cause of death or re-hospitalisations. The mortality rates found in the present study in an elderly population, although high, are comparable to results found in a previous study with an older population.

**Conclusion**

Hyponatraemia at hospital admission is frequently encountered in patients with a wide range of medical and surgical diagnoses. Hyponatraemia is an independent predictor of all-cause mortality and admission length independently of diagnosis and important clinical variables associated with increased risk of death.

**Acknowledgements**

The authors thank the Copenhagen Hospital Heart Failure study organisers for access to the database and for assistance in writing of the paper.

---

**References**

19 Kirk V, Bay M, Parner J, Krogsgaard K, Herzog TM, Boesgaard S et al. N-terminal proBNP and mortality in hospitalised patients with heart failure and preserved vs. reduced systolic...
function: data from the prospective Copenhagen Hospital Heart Failure Study (CHHF). *Eur J Heart Fail* 2004; 6: 335–41.


Clinical outcome of drug-eluting versus bare-metal stents in patients with calcified coronary lesions: a meta-analysis

B.-C. Zhang,* C. Wang,* W.-H. Li and D.-Y. Li

Department of Cardiology, The Affiliated Hospital of Xuzhou Medical College, Xuzhou, Jiangsu, China

Abstract

Background: The relative safety and efficacy of drug-eluting stents (DES) versus bare-metal stents (BMS) in patients with calcified coronary lesions is still debated.

Aims: To evaluate clinical outcome of DES versus BMS in patients with calcified coronary lesions using a meta-analysis of the current literature.

Methods: We performed a systematic literature search using Medline, Embase, Cochrane and several other databases. Randomised controlled trials, prospective and retrospective cohort studies with a mean follow-up period >6 months were included. Primary efficacy was target lesions revascularisation (TLR) and primary end-point for safety was stent thrombosis. Secondary end-points were cardiac death and recurrent myocardial infarction (MI).

Results: Five trials were included in the meta-analysis, including 2440 patients (1230 in the DES group, 1210 in the BMS group). TLR was significantly lower in patients treated with DES as compared with patients treated with BMS (8.5% vs 16.0%; odds ratio (OR) = 0.50; 95% confidence interval (CI) 0.38–0.65; \( P < 0.00001 \)). There were no significant differences in the incidence of stent thrombosis (0.9% vs 0.3%; OR = 2.01; 95% CI 0.34–11.88; \( P = 0.44 \)), cardiac death (3.3% vs 4.2%; OR = 0.81; 95% CI 0.50–1.30; \( P = 0.38 \)) and recurrent MI (5.0% vs 5.2%; OR = 0.99; 95% CI 0.66–1.49; \( P = 0.97 \)) between the two groups. Subgroup analysis by the sample size and follow-up duration showed that the associations were similar between DES versus BMS.

Conclusions: DES significantly reduces TLR rates as compared with BMS in patients with calcified coronary lesions, with non-significant differences in terms of stent thrombosis, cardiac death and MI.

Introduction

Coronary lesion morphological characteristics affect immediate and late clinical outcomes after coronary stenting. Among them, heavily calcified lesion is one of the predominant risk factors and is linked with a high rate of restenosis and target lesion revascularisation (TLR). To improve therapeutic efficacy, high speed rotational coronary atherectomy is often required to modify calcified lesions to facilitate percutaneous coronary intervention (PCI).

Although drug-eluting stents (DES) have substantially reduced restenosis rates compared with bare-metal stents (BMS) in previous clinical trials, the relative efficacy and safety of DES and BMS in calcified coronary arteries remain unclear. To shed further light on this issue, we performed a meta-analysis of the current literature to assess the clinical outcomes of DES versus BMS use in patients with calcified coronary lesions.

Methods

Search criteria

The published research was scanned by formal searches of electronic databases (PubMed, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials) up to July 2014. Search terms included ‘calcified lesions’, ‘coronary’, ‘intervention’ and ‘stenting’. Citations were screened and evaluated using the established inclusion/exclusion criteria at the abstract level by two operators.

*These authors contributed equally to this work.

Funding: None.

Conflict of interest: None.

© 2014 Royal Australasian College of Physicians
Eligibility criteria
Inclusion criteria were: (i) involving calcified coronary lesions; (ii) direct comparison of DES versus BMS; (iii) reporting clinical outcomes; and (iv) all studies had to report results at a follow-up duration of ≥6 months after the index procedure. Exclusion criteria were defined as: (i) unpublished studies; (ii) abstract only; (iii) angioplasty without stenting; and (iv) studies not reporting relevant clinical outcomes.

Definitions and end-points
The primary outcome of interest was TLR and stent thrombosis. TLR was defined as either PCI or surgical revascularisation for a lesion anywhere within the stent. Other clinical outcomes of interest were of stent thrombosis, cardiac death and myocardial infarction. We accepted the individual protocol definitions of clinical events and did not attempt to recategorise them retrospectively.

Data extraction
Two independent investigators (WH Li and DY Li) reviewed each report to determine its eligibility and then extracted and tabulated all of the relevant data. Disagreement was resolved by consensus between the two authors. The following information was obtained from each article: first author, year of publication, country of origin, total numbers of subjects, follow-up duration, hypertension, diabetes, study design and clinical end-points from included trials.

Statistical analysis
All analyses were performed using Review Manager 5.0 software (available from The Cochrane Collaboration at http://www.cochrane.org). The Mantel-Haenszel method for fixed effects and the DerSimonian-Laird method for random effects were used to estimate pooled odds ratios (OR). We tested heterogeneity of the included studies with Q statistics and extent of inconsistency between results with I² statistics. In the absence of heterogeneity between studies, the Mantel-Haenszel and DerSimonian-Laird methods produce very similar results. We report fixed effects estimates, because fixed effects are more robust in meta-analysis calculations when there are small numbers of events. Possibility of publication bias was assessed by funnel plot analysis. Sensitivity analysis was also done by omitting one study at a time to examine influence of one study on the overall summary estimate. Data are presented as OR with 95% confidence intervals (CI); P < 0.05 were considered statistically significant.

Results

Description of studies
The flow diagram of the study analysis is shown in Figure 1. Of 520 potentially relevant articles initially screened, five trials met inclusion criteria and were included in the final meta-analysis consisting of a total of 2440 patients (1230 in the DES group, 1210 in the BMS group). One study was a randomised controlled trial (RCT) (247 participants), two studies had a prospective design (1598 participants) and two studies had a retrospective design (595 participants). Paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) were solely used in two studies respectively. The other three studies used PES combination with SES. The clinical characteristics of patients included in the meta-analysis are reported in Tables 1 and 2. All studies were published in English. The subject population was derived from three countries.

Analysis of main outcomes

Efficacy end-points
TLR Five interval trials with 2440 patients were included. The meta-analysis showed a significant decreased TLR in patients treated with DES (8.5%, 104/1230) as compared with patients receiving BMS (16.0%, 194/1210) (OR = 0.50; 95% CI 0.38–0.65; P < 0.00001) (Fig. 2). Heterogeneity was not significant (P = 0.17, I² = 38%). On sensitivity analysis, the results remained unchanged by excluding any individual trial.

Safety end-points
Stent thrombosis Three studies including 842 patients were included (550 treated by DES; 292 by BMS). One study reported the stent thrombosis rates in both groups were zero. There was no significant difference between two groups on fixed effect meta-analysis (OR = 2.01; 95% CI 0.34–11.88; P = 0.44). There was no heterogeneity across trials (P = 0.37, I² = 0%) (Fig. 3). Influence analysis
demonstrated that no single study significantly altered the summary OR.

Recurrent myocardial infarction (MI) A total of 1924 patients was included in four studies reporting MI rates. The MI rates in both groups were observed to be zero in one study.\(^9\) There was no significant difference in the rate of MI with DES as compared with BMS: 5.0% (42/839) in the DES group and 5.2% (56/1085) in the BMS group (OR = 0.99; 95% CI 0.66–1.49; \(P = 0.97\)). The statistical heterogeneity was not obvious (\(P = 0.79, I^2 = 0\%\)) (Fig. 4). Sensitivity analysis indicated that the results of the meta-analysis was reliable and stable.

Cardiac death Data for cardiac death were available from four studies including 1924 patients in whom 74 events

Table 1 Main characteristics of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study (year) (reference number)</th>
<th>Design, country of origin</th>
<th>Maximal length of follow up (months)</th>
<th>Stent comparators (n)</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Diabetes (%)</th>
<th>Hypertension (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moussa et al. (2005)(^8)</td>
<td>RCT, USA</td>
<td>12</td>
<td>PES 121 BMS 126</td>
<td>63.0 ± 11.9</td>
<td>73.6</td>
<td>69.8</td>
<td>21.5</td>
</tr>
<tr>
<td>Seo et al. (2007)(^9)</td>
<td>RS, Japan</td>
<td>9</td>
<td>SES 41 BMS</td>
<td>72 ± 9</td>
<td>71</td>
<td>63</td>
<td>26</td>
</tr>
<tr>
<td>Khattab et al. (2007)(^10)</td>
<td>PS, Germany</td>
<td>9</td>
<td>DES 27 BMS 34</td>
<td>70 ± 8</td>
<td>63</td>
<td>88</td>
<td>26</td>
</tr>
<tr>
<td>Rathore et al. (2010)(^11)</td>
<td>RS, Japan</td>
<td>9</td>
<td>DES 391 BMS 125</td>
<td>70.82 ± 8.84</td>
<td>64.7</td>
<td>66.4</td>
<td>43.5</td>
</tr>
<tr>
<td>Bangalore et al. (2011)(^12)</td>
<td>PS, USA</td>
<td>12</td>
<td>DES 653 BMS 884</td>
<td>67</td>
<td>66</td>
<td>60.1</td>
<td>36.1</td>
</tr>
</tbody>
</table>

BMS, bare-metal stent(s); DES, drug-eluting stent(s); PES, paclitaxel-eluting stent(s); PS, prospective study; RCT, randomised controlled studies; RS, retrospective study; SES, sirolimus-eluting stent(s).
were recorded. There was no significant difference between DES and BMS use (OR = 0.81; 95% CI 0.50–1.30; \( P = 0.38 \)). No evidence of statistical heterogeneity was identified (\( P = 0.61, I^2 = 0\% \)) (Fig. 5). On sensitivity analyses, the results remained unchanged by omitting one study at a time.

Subgroup analyses

Furthermore, a series of subgroup meta-analysis based on the sample size and different follow-up duration was conducted. Subgroup analysis showed that there was no difference in the rate of stent thrombosis, cardiac death and MI between the DES and BMS groups. DES significantly reduces TLR rates as compared with BMS in calcified coronary lesions (Table 3).

Table 2 End-points data of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DES</th>
<th>BMS</th>
<th>Odds Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis (n)</td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>9 months TLR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khattab AA et al 2007</td>
<td>2</td>
<td>27</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>Rathore S et al 2010</td>
<td>28</td>
<td>391</td>
<td>24</td>
<td>125</td>
</tr>
<tr>
<td>Seo A et al 2007</td>
<td>3</td>
<td>38</td>
<td>8</td>
<td>41</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>33</td>
<td>44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: \( \chi^2 = 0.90, df = 2 (P = 0.64); I^2 = 0\% \)
| Test for overall effect: Z = 4.69 (P < 0.00001) |

| 12 months TLR | | | | | |
| Banglore S et al 2011 | 65 | 653 | 135 | 884 | 61.5% | 0.61 [0.45, 0.84] |
| Moussa I et al 2005 | 6 | 121 | 15 | 126 | 8.3% | 0.39 [0.14, 1.03] |
| Subtotal (95% CI) | | | | | | 0.59 [0.43, 0.79] |
| Total events | 71 | 150 | | | |
| Heterogeneity: \( \chi^2 = 0.77, df = 1 (P = 0.38); I^2 = 0\% \)
| Test for overall effect: Z = 3.49 (P = 0.0005) |

| Total (95% CI) | | | | | |
| | 1230 | 1210 | 100.0% | 0.50 [0.38, 0.65] |
| Total events | 104 | 194 | | | |
| Heterogeneity: \( \chi^2 = 6.43, df = 4 (P = 0.17); I^2 = 38\% \)
| Test for overall effect: Z = 5.26 (P < 0.00001) |

**Figure 2** Odds ratios (OR) and 95% confidence intervals (CI) of target lesions revascularisation (TLR) associated with drug-eluting stents (DES) versus bare-metal stents (BMS).

Publication bias diagnostics

Funnel plots were performed for all outcomes to determine whether the literature showed a publication bias.
Figure 3  Odds ratio (OR) and 95% confidence intervals (CI) of stent thrombosis associated with drug-eluting stent(s) (DES) versus bare-metal stent (BMS).

Figure 4  Odds ratio (OR) and 95% confidence interval (CI) of myocardial infarction (MI) associated with drug-eluting stent(s) (DES) versus bare-metal stent(s) (BMS).

© 2014 Royal Australasian College of Physicians
The funnel plots were symmetrical by visual inspection indicating no evidence of publication bias was observed (Fig. 6a–d).

**Discussion**

DES are widely used in the coronary artery lesions and have been shown to reduce restenosis and TLR rates. However, there is a growing debate about whether the long-term safety of DES might be associated with stent thrombosis and MI. Delayed endothelial healing, drug-induced hypersensitivity reaction and incomplete stent apposition may account for the mechanisms of thrombosis-related events after DES implantation.

Atherosclerotic calcified lesions is often found in advanced lesions, which respond to a failed balloon angioplasty, and incomplete stent expansion. Currently, rotational atherectomy followed by stent implantation is the main therapeutic approach for calcified coronary lesions. However, whether DES improves the long-term safety and efficacy in calcified coronary lesions is still controversial. This is predominantly due to the limited number of patients, lack of data from RCT and a short follow-up period.

The present meta-analysis tries to overcome the statistical limitations of the individual trials and demonstrates

---

### Table 3: Subgroup analyses of efficacy and safety outcomes based on sample size and follow-up duration

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
<th>( I^2 (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size &gt;500</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>0.54</td>
<td>0.41–0.72</td>
<td>&lt;0.001</td>
<td>72</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0.96</td>
<td>0.10–9.30</td>
<td>0.97</td>
<td>NA</td>
</tr>
<tr>
<td>MI</td>
<td>0.98</td>
<td>0.63–1.52</td>
<td>0.93</td>
<td>NA</td>
</tr>
<tr>
<td>Death</td>
<td>0.78</td>
<td>0.47–1.29</td>
<td>0.33</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Sample size &lt;500</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>0.30</td>
<td>0.15–0.62</td>
<td>0.001</td>
<td>0</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0.29</td>
<td>0.25–1.13</td>
<td>0.28</td>
<td>NA</td>
</tr>
<tr>
<td>MI</td>
<td>1.08</td>
<td>0.32–3.61</td>
<td>0.90</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>1.10</td>
<td>0.27–4.50</td>
<td>0.89</td>
<td>0</td>
</tr>
<tr>
<td><strong>Follow-up 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>0.12</td>
<td>0.05–0.38</td>
<td>0.005</td>
<td>0</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.01</td>
<td>0.67–1.53</td>
<td>0.97</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>0.84</td>
<td>0.52–1.37</td>
<td>0.49</td>
<td>29</td>
</tr>
<tr>
<td>Death</td>
<td>0.29</td>
<td>0.18–0.49</td>
<td>&lt;0.0001</td>
<td>0</td>
</tr>
<tr>
<td><strong>Follow-up 9 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>0.11</td>
<td>0.06–0.27</td>
<td>0.13</td>
<td>0</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0.41</td>
<td>0.02–10.37</td>
<td>0.59</td>
<td>NA</td>
</tr>
<tr>
<td>MI</td>
<td>0.38</td>
<td>0.04–3.72</td>
<td>0.40</td>
<td>0</td>
</tr>
</tbody>
</table>

CI, confidence interval; MI, myocardial infarction; NA, not applicable; OR, odds ratio; TLR, target lesion revascularisation.
that DES implantation significantly reduces TLR in patients with calcified lesions compared with BMS. The total TLR rate of 8.5% in calcified coronary lesions treated with DES indicates an excellent clinical result, which is in line with other reports. Furuichi et al. and García de Lara et al.\textsuperscript{16,17} reported the TLR rates between 6.2% and 9.5% in heavily calcified lesions using rotational atherectomy followed by DES implantation. Rathore et al.\textsuperscript{18} published the cohort study demonstrated that among 391 Rota-DES patients, the TLR rate was 10.6% in a 6–9 months follow-up period.

Although DES are more effective in reducing TLR rate than BMS, the concerns raised by DES may increase the risk of thrombosis-related events.\textsuperscript{19} In our study, the incidence of definite stent thrombosis was 0.91% and 0.34% for patients receiving DES and BMS respectively at overall-term follow-up, which was consistent with most of the prior meta-analyses comparing DES with BMS in ST-segment elevation myocardial infarction patients.\textsuperscript{20,21}

To the best of our knowledge, this study is the first attempt to evaluate the efficacy and safety of DES versus BMS in patients with calcified coronary lesions. In this study, the subgroup analysis and sensitive analysis also support our conclusions that DES is more effective in reducing TLR rate in calcified coronary lesions; the risk of stent thrombosis, MI and cardiac death is not increased as compared with BMS.

Several limitations should be acknowledged in our study. First, most studies included in our meta-analysis were observational studies from different cohorts or

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{funnel-plots}
\caption{
Funnel plots for assessment of publication bias. (a) Target lesion revascularisation (TLR); (b) stent thrombosis; (c) myocardial infarction (MI); (d) cardiac death.
}
\end{figure}

\textsuperscript{©} 2014 Royal Australasian College of Physicians
consecutive patients due to the limited number of studies involved. Second, our meta-analysis were fully based on the published data; we did not contact the authors for any individual data. Third, not all the studies reported each of the outcomes of interest in our study, therefore selective reporting bias could not be excluded. Last, there is a wide range of follow-up duration among the included studies; this may have influenced the overall heterogeneity.

Conclusions

DES significantly reduces TLR rates as compared with BMS in patients with calcified coronary lesions, which is not associated with an increased risk of stent thrombosis, MI and cardiac death.

Acknowledgements

This work was supported by China Postdoctoral Science Foundation Research Funds 2013MS540468, The Natural Science Foundation of Jiangsu Province BK20141137 and Jiangsu Planned Projects for Postdoctoral Research Funds 1302169C to BC Zhang.

References


**BRIEF COMMUNICATIONS**

**Heatwave hyponatraemia: a case series at a single Victorian tertiary centre during January 2014**

S. A. Yong, D. A. Reid and A. E. Tobin

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

**Key words**

hyponatraemia, extreme heat, public health, aged.

**Correspondence**

Sarah A. Yong, Department of Critical Care, St Vincent’s Hospital Melbourne, 41 Victoria Parade, Fitzroy, Melbourne, Vic. 3065, Australia.

Email: drsarahyong@gmail.com

Received 29 July 2014; accepted 27 August 2014.

**Abstract**

Heatwaves are a major public health threat for Australians. Hyponatraemia is common, with an increased incidence previously described during heatwaves. We report a series of 10 patients admitted with moderate to profound hyponatraemia, the majority with a history of excess water consumption, during the January 2014 heatwave.

The south-eastern Australian heatwave from 13 to 18 January 2014 ranks as one of the most significant multi-day heatwaves, breaking a number of records for extended periods of heat.\(^1\) This period posed a significant public health problem, prompting the Department of Health Victoria to issue warnings and advice, such as ‘drinking plenty of water’, on Heat Health Alert days as an attempt to reduce heat-related illnesses.\(^2\)

Hyponatraemia is the most common biochemical disturbance encountered in clinical practice, with an increased frequency of presentations reported during heatwaves.\(^3\) We report a series of 10 patients admitted to a single institution with moderate to profound hyponatraemia over the month of January 2014.

During January 2014, 10 patients (seven females and three males) aged between 59 and 86 years (median 83.5 years) were admitted to St Vincent’s Hospital, Melbourne with hypoosmolar hyponatraemia. Of these, half were admitted to intensive care with profound hyponatraemia (initial Na < 125 mmol/L), four of whom had associated seizures. Eight were born outside of Australia; however, seven listed English as their preferred language. Notably, seven patients overall and all five of those admitted to intensive care gave a history of being instructed to drink an abundance of water from public health warnings in the media or their families. The most striking example was one man who drank 6 L of water per day and presented with initial sodium of 106 mmol/L.

Six patients were on medical therapy (four of whom had a history of excessive water intake) that increases risk of developing hyponatraemia, including three on thiazide diuretics, one on loop diuretics, one on spironolactone, three on angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and two on antipsychotics. Comorbidities among those hospitalised with hyponatraemia included cardiac failure (\(n = 2\)), hypertension (\(n = 6\)), cognitive impairment (\(n = 1\)) and alcohol excess (\(n = 2\)). Five had a previous history of hyponatraemia.
Based on current hyponatraemia guidelines, hypo-
natraemia was profound (<125 mmol/L) in all but one
patient. The initial presenting feature included seizures (n = 4), vomiting (n = 4), coma (n = 2, one of whom required
intubation), confusion (n = 3) and cardiorespiratory
distress (n = 2: rapid atrial fibrillation and myocardial
infarction with pulmonary oedema).

Therapy included fluid restriction in seven patients,
administration of hypertonic saline (n = 3 – all in inten-
sive care) and normal saline in nine. Associated drug
therapy was withheld in half the group. One patient with
myocardial infarction and pulmonary oedema was
administered diuretic therapy. One patient with a history
of chronic hyponatraemia was prescribed salt tablets as
part of her ongoing management. No patient developed
the complication of osmotic demyelination syndrome in
relation to management of their hyponatraemia.

An analysis of hospital admissions from January 2006
to January 2014 where hyponatraemia was a principal
diagnosis (E 87.1 was the first or second principal diag-
nostic code) was undertaken using the hospital patient
administrative system to determine associations with
temperature. Institutional admissions for hyponatraemia
were related to heatwaves as measured by excess heat
factor. Excess heat factor is a quantitative measure of
intensity, load, duration and spatial distribution of a
heatwave event, and represents the combined effect of
excess heat (a high mean temperature over a 3-day
period compared with historical reference) and heat
stress (a high mean temperature over 3 days compared to
the previous 30 days). A positive value for the excess
heat factor means a heatwave is in progress, and
increases in monthly admissions were plotted against
excess heat factor there was a positive association with
increasing values of excess heat factor (Fig. 2).

To our knowledge, this is the first case series in English
of hyponatraemia during a heatwave. Ambrosi et al.
report a series of three elderly women medicated with
thiazides and/or selective serotonin reuptake inhibitors,
who were hospitalised with severe hyponatraemia
during the August 2003 heatwave in France, after being
incited to drink in excess of 2 L of water per day by family
or media.

Hyponatraemia, defined as Na < 135 mmol/L, is the
most common electrolyte disturbance encountered in
clinical practice. It is associated with increased mortality,
although it remains unclear whether it is a causal asso-
ciation with death or whether hyponatraemia is a surro-
gate for severity of underlying disease. Hyponatraemia
also carries significant morbidity including increased
length of stay and discharge to a facility, with severity of
hyponatraemia prognosticating outcomes.

Presentation of hyponatraemia is varied and includes
headache, nausea, malaise and confusion, to severe symp-
toms of vomiting, seizures, cardiorespiratory distress and
coma resulting from cerebral oedema and raised intracr-
nial pressure. Management is guided by the acuity, sever-
ity of symptoms and underlying cause of hyponatraemia,
and in this case series appeared in accordance with
current practice guidelines. Cerebral osmotic demyelina-
tion is the most feared and potentially fatal complica-
tion of hyponatraemia therapy; however, its incidence
is low and did not occur in any of our patients. The
causes of hyponatraemia are broad and include certain
comorbidities, medications and postoperative states.

Globally and locally, heatwaves pose a significant public
health threat. Australian heatwaves are predicted to
more than double in the next 40 years, with a projected
increase in heat-related deaths. In Australia, those at risk include the elderly, the socially disadvantaged and those who live alone or with underlying comorbidities.\textsuperscript{10}

Major heatwaves are Australia’s deadliest natural hazards,\textsuperscript{10} with an increase in hospital emergency presentations, general medical admissions and deaths.\textsuperscript{9} We found the incidence of hyponatraemia at our institution spiked in coincidence with heatwaves, a finding that has been previously described during the European heatwave of 2003.\textsuperscript{3}

While the local health burden of heatwaves has been previously recognised, with subsequent formulation of the Victorian Heatwave Plan,\textsuperscript{2} the detrimental effects of the public health advice disseminated during heatwaves (specifically, to drink an abundance of water) is less appreciated. The Heatwave Plan for Victoria 2011’s primary public health messages include ‘Drinking plenty of water, even if you do not feel thirsty (if your doctor normally limits your fluids, check how much to drink during hot weather)’,\textsuperscript{2} which was disseminated via the media. We noted 70% of patients in this series had a history of drinking large volumes of water in the face of the heatwave, which is likely to have contributed to their presentation of hyponatraemia. Tempering general public health advice so that it is of benefit to the wider community, targets groups such as the elderly or socially disadvantaged and minimises risks to the individual is a challenge.

This case series highlights that hyponatraemia is an underrecognised medical presentation that occurs with greater incidence during heatwaves, as well as a potential consequence of public health messages encouraging liberal consumption of water during heatwaves. Medical practitioners play a pivotal role in delivering careful advice to individuals with health conditions at risk of heatwave-related complications, particularly in interpreting general health advice regarding fluid intake.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Monthly hyponatraemia admissions and excess heat factor. Quadratic prediction with 95\% confidence intervals of monthly admissions for hyponatraemia versus excess heat factor from January 2006 to January 2014. The values for excess heat factor have been divided by 10 for the purposes of scaling. ( ), 95\% CI; ( ), fitted values.}
\end{figure}

\begin{thebibliography}{9}
\bibitem{6} Ambrosi P, Villani P, Bouvenot G. \textit{Hyponatremia in elderly patients}
\end{thebibliography}

Treatment of refractory stomal variceal haemorrhage with embolisation and sclerosis

Z. Valaydon and P. Desmond
Department of Gastroenterology, St Vincent’s Hospital, Melbourne, Victoria, Australia

Key words
ectopic varices, stomal varices, variceal haemorrhage, sclerotherapy, transjugular intrahepatic portosystemic shunt.

Abstract
Stomal variceal bleeding is a rare but life-threatening complication of cirrhosis. As it is an uncommon condition, there is little evidence on the optimum treatment. We report a case of parastomal variceal bleeding in a cirrhotic and haemodynamically unstable patient. The bleeding had failed to respond to local therapy and was not amenable to transjugular intrahepatic portosystemic shunting. The varix was successfully treated under radiological guidance embolisation in conjunction with Fibrovein (STD Pharmaceuticals, UK) sclerosis. We propose that Fibrovein sclerosis through angiography should be considered as an initial treatment option in patients with parastomal variceal bleeding who are not candidates for transjugular intrahepatic portosystemic shunting.

A 69-year-old man with well-compensated, Child–Pugh A alcoholic cirrhosis underwent a Hartman’s procedure in a country hospital for a sigmoid stricture that was presumed to be malignant but was found to be a complicated diverticulum on the resection histopathology. Intraoperatively, the liver was noted to be nodular and cirrhotic and the splenic vasculature was abnormal suggestive of varices. He was not known to be cirrhotic preoperatively.

There was significant intraoperative bleeding and postoperatively, he developed intra-abdominal sepsis and ascites. A therapeutic paracentesis was performed and broad-spectrum intravenous antibiotics were instituted. The patient was discharged a week later on oral antibiotics.

Eight weeks postoperatively, he represented to the hospital with decompensated cirrhosis in the context of ongoing sepsis. He had reaccumulated gross ascites with bacterial peritonitis and was profoundly encephalopathic and coagulopathic (international normalised ratio (INR) 1.8). He was in septic shock as manifested by hypotension and anuric renal failure (creatinine 113 μmol/L, urea 15.6 mmol/L). His inflammatory markers were raised with a C-reactive protein 170 mg/L and a white cell count of 13.6 x 10^9/L. His bilirubin was only mildly elevated at 24 U/L, and his model for end-stage liver disease (MELD) score was 21.

He was transferred to St Vincent’s Hospital and admitted to the intensive care unit (ICU). He was treated with inotropes, broad-spectrum antibiotics and haemofiltration. He underwent a therapeutic paracentesis and was started on lactulose. His renal function improved,
and his inflammatory markers trended down and he was discharged from the ICU 12 days later.

On discharge from ICU, he was still coagulopathic (INR 1.8) and encephalopathic. He had a metabolic flap, was confused to time, place and person, and his speech was incoherent. His MELD score had improved to 13 mostly because of the improvement in renal function (creatinine 85 μmol/L).

He then developed frank parastomal haemorrhage. At that point, he was 12 weeks post-Hartman’s. There was a bleeding point at the site of the stoma associated with a significant drop in haemoglobin from 100 g/dL to 79 g/dL and haemodynamic instability with a systolic blood pressure drop to 90 mmHg and compensatory tachycardia (heart rate 110–120 bpm). A Doppler ultrasound of the parastomal vessels confirmed the presence of a mesenteric varix. The blood flow was hepatofugal, consistent with portal hypertension. A diagnosis of parastomal variceal bleeding was made.

The initial management included direct manual compression of the bleeding point, which stopped the haemorrhage temporarily. For haemodynamic resuscitation, packed red cells were transfused and fresh frozen plasma was administered to reverse the coagulopathy.

The patient had a second episode of brisk haemorrhage less than 48 h later. Again, this was associated with a significant drop in haemoglobin and haemodynamic instability. Manual compression was applied; the bleeding point was injected with adrenaline and sutured. This was immediately effective, but three further episodes of haemorrhage occurred. An octreotide infusion was commenced in an attempt to reduce portal pressures, but a further episode of bleeding occurred despite these measures.

Angiography was performed and a mesenteric vein was identified leading into the stoma and the varix (Fig. 1). Multiple adjacent collateral vessels were identified, but the flow in those vessels was antergrade. Multiple coils were inserted angiographically into the mesenteric vein supplying the varix and Fibrovein (STD Pharmaceuticals, UK) sclerosant was instilled into the varix.

There were no post-embolisation complications. It is now 12 months post-procedure, and there have been no further episodes of peristomal bleeding.

Stomal varices are ectopic mesenteric varices associated with ileostomies, colostomies and ileal conduits in the setting of portal hypertension. Although they are relatively rare, they can cause life-threatening bleeds and are associated with significant morbidity.

There is a paucity of data regarding the optimal management of stomal variceal haemorrhage. There are no randomised controlled trials of the different therapeutic modalities. Although there are multiple case reports and case series, the anatomical and clinical variations in each case make the establishment of a standard of care difficult.

We reviewed the current literature on the incidence, pathogenesis, diagnosis and management of stomal variceal haemorrhage.

Stomal variceal haemorrhage was first described by Resnick et al. in 1968 and has been most commonly observed in patients with primary sclerosing cholangitis who undergo a colonic resection and stoma formation for coexisting ulcerative colitis. Stomal varices arise in about 50% of patients with a stoma and concurrent portal hypertension, and the associated risk of bleeding is about 27%. Other pathologies requiring stoma formation include rectal and urinary tract carcinoma. The majority of stomal bleeds arise in ileostomies and a very small percentage bleed from ileal conduits.

Stomal varices are usually due to portal hypertension but can also be caused by local pathology, such as post-surgical adhesions or scarring or anatomical

Figure 1 Parastomal varix (A) pre-embolisation and (B) after embolisation with coils and sclerosis.
decompensation after TIPS. The high MELD score and hepatofugal flow are predictors of variceal haemorrhage, with a rate of 3–4% post-TIPS placement. The estimated mortality rate associated with stomal variceal haemorrhage is 3–4%. The point of bleeding is usually superficial and can be identified in simple inspection. Endoscopy through the stoma is not required unless the site of bleeding is deep within the stoma. Doppler ultrasound is useful to identify portal venous supply and the direction of blood flow. Typically in varices due to portal hypertension, the blood flow is hepatofugal (towards the stoma) as opposed to hepatopedal (towards the liver).

The initial immediate treatment of a bleeding stomal varix consists of direct pressure to the bleeding point, injection of vasocostricting agents, cauterity with silver nitrate and suturing. The use of beta-blockers, vasopressin and octreotide infusions has also been reported. These measures are effective, and haemostasis can be achieved rapidly at the bedside. However, they are only temporising measures, and the risk of rebleeding is high unless a more definitive treatment is offered.

The use of transjugular intrahepatic portosystemic shunt (TIPS) in the management of ectopic varices including rectal and duodenal varices is well documented. In the current literature, including American Association for the Study of Liver Diseases guidelines, TIPS is the preferred technique in secondary prevention of stomal variceal bleeding. It has the advantage of decompressing portal hypertension compared with the methods described further. However, the largest case series published on the use of TIPS in ectopic varices report a relatively high rate of rebleeding (37%) despite a portal gradient of less than 12 mmHg post-TIPS placement, and it is suggested that variceal embolisation be performed at the time of TIPS placement.

TIPS is also deemed to be a safe procedure in Child–Pugh A patients, but a high mortality rate has been reported in Child–Pugh B and C patients. TIPS is also associated with a 30% risk of hepatic encephalopathy. A high MELD score and hepatofugal flow are predictors of decompensation after TIPS. Bleeding stomal varices can be embolised either transhepatically or percutaneously. It is usually performed under ultrasound using coils or glue. A retrograde injection of sclerosing agent obliterates the draining veins of the varix and thromboses are formed inside the varix.

Embolisation is associated with risks of bowel infarction and portal vein thrombosis, which can have a mortality rate of up to 50% in some case series. Increased rates of bleeding and hepatic injury have been reported with direct percutaneous embolisation, and retrograde embolisation has been associated with renal failure, pulmonary embolisation and skin ulceration around the stoma.

There is also a relatively high risk of rebleeding with embolisation due to the formation of collateral vessels or additional varices around the stoma because the underlying portal hypertension remains untreated. However, embolisation is less invasive than TIPS and does not pose a risk of hepatic decompensation. Therefore, it is a therapeutic option in patients in whom TIPS is contraindicated, such as encephalopathy, portal vein thrombosis or diffuse metastatic disease.

Injection sclerotherapy consists of submucosal injection of sclerosants such as sodium tetradecyl sulfate, ethanol, polidocanol, pheonol and almond oil, and has been described in case reports for the treatment of massive stomal haemorrhage associated with portal hypertension. These case reports date back to the mid-1980s–1990s.

Sclerotherapy may be associated with ulceration, structuring and retraction of the stoma. Furthermore, it does not reduce portal pressures and the risk of rebleeding is high. Reversal or revision of the stoma is a definitive treatment but is not often feasible because of the high surgical risk in cirrhotic patients. It requires a laparotomy, which is associated with a 50% mortality risk in a Child–Pugh C cirrhotic. Furthermore, new venous collaterals may also develop at the newly formed stomal site.

Other surgical options include mucocutaneous disconnection, which involves an incision of the mucocutaneous junction of the stoma and division of portosystemic circulation. However, the number of cases performed is small, consisting of only seven patients, four of whom had recurrent haemorrhage. Portosystemic shunt surgery can also be effective in secondary prevention of stomal variceal bleeding but is associated with up to a 15% mortality rate. Exploratory laparotomy has also been reported in the literature but was negative in each case and associated with a high mortality rate postoperatively.

Liver transplantation is the ideal treatment for a patient with stomal bleeding and underlying cirrhosis. However, only approximately 5% of patients tend to be suitable surgical candidates.
The formation of an ileo pouch-anal anastomosis obviates the need for a stoma and bypasses the problem of stomal varices entirely. The Mayo Clinic published a case series with no rates of rebleeding, but there were long-term complications in approximately 55% of patients.19

The management of ectopic varices remains a therapeutic challenge in decompensated cirrhosis. The majority of the data comes from case reports and case series from which guidelines cannot be developed.

We described a case of parastomal variceal bleeding in a patient with previously unrecognised cirrhosis post-Hartmann procedure. Conservative, local treatment failed to achieve durable haemostasis. Other therapeutic options including TIPS and stomal revision were contraindicated as the patient was decompensated and floridly encephalopathic. He was not a transplant candidate. Coil embolisation and sclerosis of the varix with Fibrovein sclerosant was successful in achieving long-term haemostasis with no immediate complications.

We propose that embolisation in conjunction with Fibrovein sclerosis through angiography should be considered as an initial treatment option in patients’ parastomal variceal bleeding.

References


Delayed onset of benign pleural effusion following concurrent chemoradiotherapy for inoperable non-small-cell lung cancer

R. Kumar,1 G. Patel,1 G. Kichenadasse,1,2 S. Sukumaran,1,2 A. Roy,1,2 B. Koczwara,1,2 J. J Bowden,3 J. Leung,4 T. Woo4 and C. S Karapetis1,2

Departments of1 Medical Oncology and 1 Respiratory Medicine, Flinders Medical Centre, 2 Flinders Centre for Innovation in Cancer, Flinders University and 4 Adelaide Radiotherapy Centre, Flinders Private Hospital, Adelaide, South Australia, Australia

Key words non-small-cell lung cancer, benign pleural effusion, concurrent chemoradiotherapy, stage III inoperable, case series.

Abstract
Chronic benign pleural effusion (BPE) is a rare complication of concurrent chemoradiotherapy (CRT) for inoperable stage IIIA non-small-cell lung cancer (NSCLC). This report presents three cases of BPE, the workup to differentiate this benign condition from recurrence of cancer and recommends a pleural biopsy as part of the diagnostic process. These inflammatory exudates often remain indolent, and may not require drainage or surgical intervention. In the absence of clinical, radiological and pathological evidence of recurrent disease, we recommend clinicians manage these patients expectantly, using regular clinical assessment and imaging.

Stage III non-small-cell lung cancer (NSCLC) represents 45% of all NSCLC diagnoses.1 Where curative surgical resection is not possible, the optimal treatment is concurrent chemoradiotherapy (CRT) with curative intent in selected patients.2 However, the median survival of these patients remains poor at 17 months.3–5

Pleural effusion occurring after CRT is most likely due to recurrent disease and carries a poorer prognosis.6 However, benign pleural effusions (BPE) are a recognised complication of thoracic radiotherapy. Cases of BPE have been described in literature following primary CRT for esophageal cancer, breast cancer and Hodgkin lymphoma. However, there are few reports with regards to stage III NSCLC.6–8 This highlights the importance of a thorough evaluation of a pleural effusion following CRT for NSCLC in order to make an accurate distinction between BPE from malignant pleural effusion (MPE), as there are important implications for patient management and prognosis. We present a case series from our institution of BPE following CRT for stage III NSCLC, and suggest a diagnostic algorithm.

Seventy-nine patients with stage III NSCLC were treated with CRT at Flinders Medical Centre from May 2000 to June 2010. Of these, three cases developed BPE. As surveillance imaging is not routinely performed, we are unable to comment on the incidence of pleural effusion in the remaining 76 patients.

Case 1 was a 69-year-old man with a 50 pack-year smoking history, diagnosed with left-sided squamous cell carcinoma, stage cT3N2M0 (American Joint Committee on Cancer, 7th edition). He was treated with 60Gy in 30 fractions conformal three-dimensional radiotherapy and concurrent cisplatin (50 mg/m2 i.v. D1,8,22,29) and vinorelbine (50 mg/m2 p.o. D1,8,22,29).

At 4.4 months follow up, a left-sided pleural effusion was discovered on chest X-ray (CXR; Fig. 1), with elevation of the left hemi-diaphragm and hilar opacification. Computed tomography (CT) identified left perihilar radiation fibrosis, without recurrent disease (Fig. 1). A subsequent 18fluorodeoxyglucose positron emission tomography (18FDG-PET) scan did not show any FDG avid disease.

The fluid was drained to reveal an exudate with reactive mesothelial and inflammatory cells, without any malignant cells. Bronchoscopy did not show...
endobronchial disease, with random biopsies showing reactive changes.

At 25.1 months follow up, the patient remains asymptomatic, without recurrent disease. The pleural effusion has remained radiologically stable, not requiring drainage.

Case 2 was a 72-year-old man with a 15 pack-year smoking history, diagnosed with a right-sided adenocarcinoma, stage cT2N2M0 (American Joint Committee on Cancer, 7th edition). He was treated with 60Gy in 30 fractions 3D conformal radiotherapy with concurrent cisplatin (50 mg/m² i.v. D1, 8, 29, 36) and etoposide (50 mg/m² i.v. D1-5, 29–33).

At 18.4 months, he presented with cough and dyspnoea. His CXR demonstrated a right-sided pleural effusion, right lower lobe collapse and right perihilar opacification (Fig. 1). CT scan confirmed the presence pleural effusion, with right-sided post-radiotherapy changes of pleural thickening and perihilar fibrosis (Fig. 1).

Bronchoscopy did not reveal recurrent disease. Random biopsies showed reactive changes. A pleural tap showed an exudate with reactive mesothelial and inflammatory cells, without any malignant cells.

After 40.2 months of surveillance, his pleural effusion has remained radiologically stable. He died from recurrent NSCLC. His pleural effusion remained stable following recurrence.

Case 3 was a 77-year-old man with a 20 pack-year smoking history, diagnosed with a right-sided squamous cell carcinoma stage cT2N2M0 (American Joint Committee on Cancer, 7th edition). He was treated with 60Gy in 30 fractions conformal radiotherapy with concurrent cisplatin (50 mg/m² i.v. D1,8,29,36) and etoposide (50 mg/m² i.v. D1-5, 29–33).

At 37.7 months post-treatment, he presented with dyspnoea. A CXR demonstrated a large right pleural effusion and right hilar opacification (Fig. 1). CT scan confirmed the presence pleural effusion, with right-sided post-radiotherapy changes of pleural thickening and perihilar fibrosis (Fig. 1).

Bronchoscopy did not reveal recurrent disease. Random biopsies showed reactive changes. A pleural tap showed an exudate with reactive mesothelial and inflammatory cells, with no malignant cells. Pleural biopsy showed fibrous pleuritis with surface mesothelial cell proliferation representing reactive process with benign mesothelial entrapment.

After 32.6 months, significant dyspnoea led to repeated pleural drainage. A surgical pleurodesis was performed; however, he had ongoing dyspnoea from restrictive and obstructive lung disease. He had regular surveillance CT scans and clinical follow up. He died from acute

Figure 1 The imaging for cases 1, 2 and 3 at the time of diagnosis of the pleural effusion is shown here. CXRs are shown in row A, and computerised tomography (CT) scans are shown in row B. All CXRs show opacification of the perihilar region within the radiation field and ipsilateral volume loss with the associated pleural effusion. The representative CT slices demonstrate a unilateral pleural effusion, radiation-induced pulmonary fibrosis, the absence of both pleural-based disease and recurrent disease.
respiratory failure secondary to a lower respiratory tract infection and without recurrent disease at the time of death, 75.4 months after his initial diagnosis.

Pleural effusion occurring after radical treatment for NSCLC is commonly assumed to be due to recurrent cancer and is associated with a poor prognosis with a median survival of 4 months.6 It is therefore important to distinguish between an MPE and a BPE.

The mechanism of BPE is likely to be due to chronic inflammation following CRT, as evidenced by the lymphocyte-rich exudates, fibrous pleuritis on biopsy, without evidence of malignancy. As each of the effusions described in this case series was localised to the treated lung, it is likely that this is related to the radiotherapy, as has been previously described in breast cancer, Hodgkin lymphoma and oesophageal cancer,6–8 where pleural inflammation (pleuritis) was the hypothesised mechanism, based on oedematous changes, fibrotic thickening and adhesions. Fukuda et al. showed a positive correlation with the size of the radiation field and the development of a pleural effusion. Limiting the dose of radiotherapy to the pleura may be a potential strategy to reduce the risk of BPE. Corticosteroids and non-steroid anti-inflammatory drugs may play a role in management.

A thorough workup is recommended to exclude MPE before a diagnosis of BPE is considered. Contrast-enhanced CT scan findings suggestive of MPE include circumferential pleural thickening, nodular pleural thickening, parietal pleural thickening greater than 1 cm or mediastinal pleural involvement.10,11 Chest magnetic resonance imaging may be considered for complex pleural effusion.12 FDG-PET scan is useful after a non-diagnostic pleural tap or biopsy.13 This may also be used to help target the best site to biopsy and to exclude disease recurrence elsewhere.

A tissue diagnosis remains the gold standard for excluding MPE. Bronchoscopy has a low yield without evidence of parenchymal or airway disease.14,15 Biochemical analysis of pleural fluid can assist, using Lights’ criteria to distinguish between an exudate and a transudate.16 An exudative effusion has a higher chance of being malignant; however, 3–10% of MPE can be transudates.17 A positive pleural fluid cytology provides a definitive diagnosis of an MPE.18–20 Its diagnostic yield can be increased with repeated thoracocenteses.20 Where MPE is suspected after negative pleural cytology, a pleural biopsy may be indicated. However, this leads to a diagnosis of MPE in only 7% of patients.13 If the suspicion of MPE remains high, thoracoscopic visualisation of the pleural surface and biopsy can be considered.13 BPE can occur within months to years after the completion of CRT. As its development has therapeutic and prognostic implications, reasonable efforts should be made to distinguish this from MPE. We recommend initial assessment with contrast enhanced CT scan and pleural cytology. In patients where the clinical suspicion of recurrent disease remains high, a pleural biopsy can be considered. Once BPE has been established, an expectant approach with routine clinical and radiological follow up appears to be reasonable.

References
11 Yilmaz U, Polat G, Sahin N, Soy O, Gulay U. CT in differential diagnosis of

PERSONAL VIEWPOINT

No payments, copayments and faux payments: are medical practitioners adequately equipped to manage Medicare claiming and compliance?

M. A. Faux, J. L. Wardle and J. Adams
Faculty of Health, University of Technology, Sydney, New South Wales, Australia

Key words
Medicare, public health, medical education, copayment, claiming and compliance.

Correspondence
Margaret A. Faux, PO Box 330, Randwick, NSW 2031, Australia.
Email: margaret.a.faux@student.uts.edu.au

Received 24 July 2014; accepted 27 November 2014.
doi:10.1111/imj.12665

Abstract
The complexity of Medicare claiming means it is often beyond the comprehension of many, including medical practitioners who are required to interpret and apply Medicare every day. A single Medicare service can be the subject of 30 different payment rates, multiple claiming methods and a myriad of rules, with severe penalties for non-compliance, yet the administrative infrastructure and specialised human resourcing of Medicare may have decreased over time. As a result, medical practitioners experience difficulties accessing reliable information and support concerning their claiming and compliance obligations. Some commentators overlook the complexity of Medicare and suggest that deliberate misuse of the system by medical practitioners is a significant contributor to rising healthcare costs, although there is currently no empirical evidence to support this view. Quantifying the precise amount of leakage caused by inappropriate claiming has proven an impossible task, although current estimates are $1–3 billion annually. The current government’s proposed copayment plan may cause increases in non-compliance and incorrect Medicare claiming, and a causal link has been demonstrated between medical practitioner access to Medicare education and significant costs savings. Medicare claiming is a component of almost every medical interaction in Australia, yet most education in this area currently occurs on an ad hoc basis. Research examining medical practitioner experiences and understanding regarding Medicare claiming and compliance is urgently required to adapt Medicare responsibly to our rapidly changing healthcare environment.
In 1969, the Nimmo Report highlighted how ‘the operation of the health insurance scheme [was] unnecessarily complex and beyond the comprehension of many’, and the report became a catalyst for the 1975 introduction of Medibank, Australia’s first national health insurance scheme. Medibank introduced subsidies for healthcare services on an unprecedented scale; however, complexities in the health insurance scheme appear to remain.

In its first year, the cost of Medibank (of which medical services were only one component) was $1.647 billion. By 2009–2010, the cost of the medical services component alone, reimburshed under Medicare (Medibank’s successor), had risen to $21.2 billion. The decade 2000–2010 recorded an average medical services expenditure increase of 3.9% per annum, which, if continued, will see medical service costs rising to approximately $31 billion by 2020. Given these circumstances, it is not surprising that Medicare costs and the sustainability of the tax payer-funded health insurance scheme have often been the focus of attempts to contain rising healthcare costs.

Deliberate misuse of the system by errant medical practitioners has been cited as contributing significantly to Medicare’s financial pressures, although quantifying the precise monetary value attributable to inappropriate claiming has proven an impossible task. In 2004, minimum estimates were 10% and current estimates, which are based solely on extrapolation and expert opinion, are between 5% and 15%, representing approximately $1–$3 billion annually.

Despite this, there has been little research exploring possible alternative explanations for erroneous claims beyond rorting, including institutionalised inefficiencies within Medicare itself. Nor has there been any empirical examination of medical practitioners’ understanding of the Medicare scheme and its correct application at the point of service, or possible difficulties in adequately navigating what has become – despite the Nimmo report’s findings 45 years ago – a highly complex and often incomprehensible scheme.

This article summarises a selection of available literature on the topic of medical practitioners’ understanding of Medicare and examines the complexity of day-to-day Medicare claiming. Without further examination of this important topic, proposed changes to Medicare (including the introduction of copayments), may compound the compliance difficulties facing medical practitioners. Such empirical work is essential to adapt Medicare responsibly – or any institutionalised payment system – to the modern delivery of healthcare services.

**Historical development and system complexity**

The enabling legislation for Medibank (and subsequently Medicare) is the Health Insurance Act 1973 (Cwth) and associated regulations, articulated in the Medicare Benefits Schedule (MBS). In the 40 years since the Health Insurance Act was introduced, health financing has become more convoluted and now involves a web of legal statutes and agreements, regulations, policies and rules that impact the daily MBS claiming activity of medical practitioners who are heavily dependent on subsidised Medicare payments for their livelihoods (Table 1). This dependence has been the subject of deliberations by the High Court, which has confirmed the reliance of Australian medical practitioners on Medicare to ensure viability.

Australia’s national health insurance scheme has often been subject to political tinkering, including the previous introduction of copayments by two governments, reforms that were subsequently repealed. The Medicare scheme has become increasingly complex and now reimburses approximately 6000 professional services compared with the original 1000 reimbursed by Medibank. The hard copy of the MBS has more than doubled in size since the first edition and comprises 900 A4 pages of service descriptions, complex cross-referencing and rules.

In addition to MBS use by medical practitioners in private practice, cost sharing arrangements between States and the Commonwealth have enabled public hospitals to access MBS benefits to supplement Commonwealth grant funding. In practical terms, this is implemented by requiring salaried medical practitioners working in public hospitals to claim MBS benefits for private inpatients and referred outpatients, secured by way of individual Right of Private Practice (RoPP) agreements between medical practitioners and hospitals. MBS reimbursements collected under these arrangements may be retained by the medical practitioner, the hospital or shared in various proportions. RoPP arrangements differ in every State and Territory, as do the arrangements for unsalaried medical practitioners, who may also claim MBS reimbursement for private patients and referred outpatients in public hospitals.

Reimbursement for medical services is also provided by other payers such as private health insurers, the Department of Veterans Affairs, workers compensation and compulsory third party insurance organisations, all of which add further complexities to a system where a single service can now be the subject of 30 different...

---

**Funding:** None.

Conflict of interest: M. A. Faux is the founder and Principal of an Australian medical billing company.

© 2015 Royal Australasian College of Physicians
No payments, copayments and faux payments

**Table 1** Minimum legal literacy required by medical practitioners to claim correctly for medical services provided on a daily basis

<table>
<thead>
<tr>
<th>Private practice</th>
<th>Public hospital practice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IP</td>
</tr>
<tr>
<td>Health Insurance Act 1973</td>
<td>X</td>
</tr>
<tr>
<td>General Medical Services Table</td>
<td>X</td>
</tr>
<tr>
<td>Diagnostic Imaging Services Table</td>
<td>X</td>
</tr>
<tr>
<td>Pathology Services Table</td>
<td>X</td>
</tr>
<tr>
<td>Health Insurance Regulations 1975</td>
<td>X</td>
</tr>
<tr>
<td>Medicare Benefits Schedule (MBS)</td>
<td>X</td>
</tr>
<tr>
<td>Veterans Entitlement Act 1986</td>
<td>X</td>
</tr>
<tr>
<td>Military Rehabilitation and Compensation Act 2004</td>
<td>X</td>
</tr>
<tr>
<td>National Health Reform Agreement</td>
<td>X</td>
</tr>
<tr>
<td>Right of Private Practice agreements</td>
<td>X</td>
</tr>
<tr>
<td>Employment/contractor agreements</td>
<td>X</td>
</tr>
<tr>
<td>Private Health Insurance Act 2007</td>
<td>X</td>
</tr>
<tr>
<td>Workers compensation and third party insurance schemes in each state and territory§</td>
<td>X</td>
</tr>
</tbody>
</table>

The MBS is a departmental interpretation of the first five statutes referred to in this table. It is updated regularly and is available as an online reference.

Veterans’ claims are administered by Medicare and use MBS item numbers.

Current defence personnel claims are administered by Garrison Health Services, a business line within Medibank Health Solutions.

There are 34 registered private health funds‡.

Workers compensation and third party schemes derive medical services from the MBS.

†Non-admitted patients in public emergency departments are categorised differently from other public non-admitted patients (called outpatients) and can never have MBS charges raised against them.‡http://www.phio.org.au/downloads/file/PublicationItems/SOHFR2013.pdf. The 34 registered private health funds have unique schemes, arrangements and fees for the same medical services. See Table 2. §All States except Victoria and Western Australia have now adopted the new national law http://www.safeworkaustralia.gov.au/sites/swa/model-whs-laws/pages/jurisdictional-progress-whs-laws. Victoria and Western Australia continue to operate under their respective Occupational Health and Safety schemes. Each State and Territory has unique third-party insurance arrangements and legislative frameworks. IP, inpatient; MBS, Medicare Benefits Schedule; OP, outpatient.

payment rates, multiple claiming methods and a myriad of rules (Table 2), with strict penalties for medical practitioners who claim incorrectly.

**Medicare’s administrative infrastructure**

Despite greater complexity and substantial growth of the MBS since 1975, no corresponding rise in departmental infrastructure and expertise to manage this growth, or support the increased number of providers using the scheme is evident. Rather, even when accounting for efficiencies afforded by new and emerging technologies, there appears to have been a decrease in the administrative infrastructure and specialised human resourcing of Medicare.

Prior to the launch of Medibank in 1975, a nationwide administration system, unprecedented in size and scale, was implemented. A dedicated and highly skilled team was required, and the Health Insurance Commission (HIC) was established for this purpose. In what was described as a critically important decision by Medibank’s founders, the HIC was created as a separate commission with HIC staff employed outside of the Public Service Act, ensuring promotional opportunities lay exclusively within the Commission and essential expertise would not be lost with every round of promotions. However,
<table>
<thead>
<tr>
<th>Insurer</th>
<th>Fee</th>
<th>Comments</th>
<th>Claiming method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare schedule fee</td>
<td>150.90</td>
<td>The Australian Constitution s51 (xxiiiA) provides that doctors are free to set their own fees. Any fee can therefore be charged depending on the claiming method used and the context in which the service is provided. The schedule fee is the total patient rebate available for a private inpatient service. Medicare reimburses 75% of the schedule fee and the patients' private health fund, the additional 25%. If a gap cover scheme is selected by the doctor, different fees apply.</td>
<td>Claim usually sent to patient to pay and then claim rebates. Three statutory claiming options are available.</td>
</tr>
<tr>
<td>Medicare outpatient rebate</td>
<td>128.30</td>
<td>Medicare reimburses 85% of the schedule fee for outpatients and 75% for inpatients if the claim is bulk billed. When bulk billing, raising additional charges or copayments is illegal.</td>
<td>Electronic or manual claim usually sent directly to the department. The patient is required to sign the assignment of benefit in the approved form.</td>
</tr>
<tr>
<td>Medicare inpatient rebate</td>
<td>113.20</td>
<td>To claim item 110 as a telehealth service, it must be claimed together with item 112. Additional incentives are also payable but not simultaneously with the claim submission. There are complex requirements for obtaining the patients signature if bulk billing as the patient is not physically present. Gaps can be charged for telehealth services.</td>
<td></td>
</tr>
<tr>
<td>Medicare telehealth rebate</td>
<td>192.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Department of Veterans Affairs inpatient</td>
<td>208.15</td>
<td>Specific requirements concerning the charging of ex-servicemen and women are contained in the Veterans Entitlements Act 1986 which prevents Veterans being charged if the medical practitioner has accepted the Veterans card.</td>
<td></td>
</tr>
<tr>
<td>Australian Defence Force</td>
<td>203.75</td>
<td>Garrison Health Services is a new business line within Medibank Health Solutions now administering current serving member claims. Specific requirements exist concerning the charging of Defence personnel.</td>
<td>Manual claim sent to Garrison Health Services.</td>
</tr>
<tr>
<td>HCF</td>
<td>193.65</td>
<td>Inpatient gap cover arrangements where the patient enters an agreement with their private health fund to assign their Medicare benefit to the fund. The patient is not required to sign the assignment of benefit form. No additional fee can lawfully be charged to the patient when using gap cover schemes unless a known gap scheme operates. HCF does not operate a known gap scheme.</td>
<td>ECLIPSE 'scheme' (additional requirements to the 'agreement' above) sent manually or electronically to the health fund</td>
</tr>
<tr>
<td>St Lukes Health</td>
<td>193.65</td>
<td>St Lukes Health operates a known gap scheme where an additional amount up to 10% of the St Lukes Schedule can be charged to the patient. Written informed financial consent (IFC) is a legal requirement under all known gap arrangements.</td>
<td></td>
</tr>
<tr>
<td>Latrobe Health</td>
<td>188.63</td>
<td>Latrobe Health provides known gap cover under an MPPA.</td>
<td></td>
</tr>
<tr>
<td>HBF</td>
<td>195.20</td>
<td>HBF operates a known gap scheme where the patient can be charged up to 10% above the HBF schedule. IFC required.</td>
<td></td>
</tr>
<tr>
<td>GMHBA</td>
<td>181.10</td>
<td>GMHBA operates a known gap scheme where an additional amount can be charged to the patient. This amount is unspecified. IFC required. Can charge an additional amount of $500 per episode under BUPAs known gap scheme which were expanded from Victoria and South Australia to all states on 1 July 2014. Restrictions to some practitioners apply. IFC required.</td>
<td></td>
</tr>
<tr>
<td>BUPA NSW, QLD and ACT</td>
<td>181.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUPA VIC</td>
<td>212.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUPA SA</td>
<td>209.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUPA TAS</td>
<td>181.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUPA WA</td>
<td>181.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUPA NT</td>
<td>181.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHSANL NSW and QLD</td>
<td>178.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHSANL VIC</td>
<td>184.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHSANL SA, TAS and NT</td>
<td>183.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHSANL WA</td>
<td>162.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHSANL ACT</td>
<td>179.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medibank Private and Australian Health Management (AHM)</td>
<td>195.20</td>
<td>Medibank Private and AHM operate a known gap scheme where an additional $500 amount per claim (as opposed to per MBS item) can be charged to the patient. IFC required. Specific rules for certain specialties.</td>
<td></td>
</tr>
<tr>
<td>NIB</td>
<td>173.45</td>
<td>NIB does not operate a known gap scheme.</td>
<td></td>
</tr>
<tr>
<td>AMA recommended fee</td>
<td>300.00</td>
<td>The AMA fee is also the fee payable for workers compensation and third party claims not otherwise listed in this table.</td>
<td>Claim usually sent to the patient or to the insurer.</td>
</tr>
<tr>
<td>Victorian Workcover</td>
<td>244.93</td>
<td>This is also the applicable rate for third party Transport Accident Commission claims in Victoria.</td>
<td></td>
</tr>
<tr>
<td>Workcover SA</td>
<td>232.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workcover WA consulting rooms</td>
<td>266.20</td>
<td>Includes the issue of a certificate if required.</td>
<td></td>
</tr>
<tr>
<td>Workcover WA hospital on home</td>
<td>318.80</td>
<td>Includes the issue of a certificate if required.</td>
<td></td>
</tr>
</tbody>
</table>

*Item 110 was chosen as it is a commonly claimed physician item for both inpatient and outpatient services. General practitioner (GP) items operate differently. The most commonly claimed GP services is item 23, which can only be claimed on an outpatient basis. The equivalent IP inpatient attendance is item 24 to which this entire table applies. However, item 24 is subject to additional complex rules as GPs are paid different amounts if they are an inpatient or not. A sliding fee scale applies. If a GP is not a referred service, they are paid at 100% of the schedule fee, but this does not apply to item 110, which is a specialist service.* 

© 2015 Royal Australasian College of Physicians
legislative reforms in 2005 dissolved the HIC as a separate commission and the original crucial safeguards, specifically designed to retain departmental Medicare expertise, were undone, dismantling the barriers designed to prevent Medicare staff from moving to other public service departments.

Reviews into Medicare claiming

By 2011, MBS claiming had become so complex it came under the scrutiny of a Senate Committee inquiry. During the inquiry, medical practitioners openly expressed their frustrations and difficulties accessing reliable information and support from Medicare regarding billing and compliance. This conflicted with institutional submissions from Medicare, which suggested that ample resources and reliable support were available.

Submissions to the inquiry from medical defence organisation (MDO) representatives suggested that processes should be in place to enable medical practitioners to obtain clarity about the use of the MBS, drawing a comparison between the advice and written rulings available from the Australian Taxation Office and the lack of similar information and advice from Medicare, suggesting that as a result medical practitioners often unknowingly fell into non-compliance.

One personal submission from a medical practitioner (who had previously been investigated by the Professional Services Review (PSR)) was highlighted by the Committee to illustrate practitioner frustrations with the response of Medicare to requests for further information around claiming:

... ‘[Medicare said] we cannot give you an answer ... We suggest you contact the AMA and the college of GPs.’ I contacted the AMA and the College of GPs ... and they said: ‘We are not here to interpret the Medicare schedule. That should be done by Medicare.’ Medicare will not do it. The PSR will not do it. The AMA will not do it. The College of GPs will not do it. And we get fined.12

The MDO of this medical practitioner may also have provided limited assistance, as standard practice for MDOs is to refer members to Medicare to seek advice concerning MBS claiming in the first instance, and indemnity cover under the policies of some MDOs excludes fees charged, which are subsequently required to be repaid to Medicare, irrespective of whether the medical practitioner personally retained the fees in question.

The Senate Committee concluded that, although it was the responsibility of medical practitioners to make clinical judgments, as much advice and information as possible should be available to them in relation to MBS itemisation, but fell short of clarifying or identifying who should provide such advice and information.12

A notable case

PSR decisions, unlike Medical Board decisions, are not publicly available and therefore offer little further guidance to medical practitioners concerning how to claim Medicare benefits correctly. Very occasionally, when incorrect Medicare claiming amounts to criminal activity, reported cases are found on the public record, and it is in this context where the complexity of Medicare has proven a challenge for members of the legal profession.

In 2006, a case of Medicare fraud was appealed in the NSW Court of Criminal Appeal, where the meaning of three ubiquitous words in the scheme – ‘in respect of’ – was considered. A medical practitioner, who had been found guilty by a jury of 96 counts of fraud, maintained that the fees in question were not fees ‘in respect of’ the relevant MBS service. One of the three appeal court judges (Justice Adams) agreed.

The conduct for which the medical practitioner was found guilty was in bulk billing and also charging another amount to her patients on the same day. The medical practitioner had, in effect, charged her patients a copayment, which was then and remains illegal.

Justice Adams commented that requiring the medical practitioner to have known in advance the legal meaning of ‘in respect of’ amounted to requiring her to interpret a point of law and apply it to the facts which, as a medical practitioner, she had neither the skills nor qualifications to do so. Justice Adams pointed out that interpretation of the MBS will always be debatable, and medical practitioners should not be rendered liable to criminal prosecution for making a ‘not unreasonable’ interpretation of it.

Yet while even senior members of the Australian judiciary may not agree on issues of MBS interpretation, medical practitioners must make claiming decisions every day and remain personally responsible for every MBS service claimed. This is cited as a responsibility that can never be delegated or abrogated as there is very limited scope for third parties to be held accountable for MBS claiming. As a result, hospital administrators, front desk staff and other third parties who may direct or facilitate

‘The Crown case contended that charging a co-payment whilst bulk billing contravened s20A of the Health Insurance Act which provides for the assignment of Medicare benefits to practitioners (known as bulk billing) ‘in full payment of the medical expenses incurred in respect of (emphasis added) the professional service’.
medical practitioner’s MBS claims will not themselves be held to account should that claiming be incorrect.

**Government initiatives**

Some commentators overlook the increasing complexity of Medicare, maintaining that incorrect claiming is due to widespread and wilful misuse of Medicare by medical practitioners. The government’s response to such claims has been to increase pressure on medical practitioners through expanding audit and compliance initiatives, but despite these initiatives, a recent report tabled in parliament indicated that Medicare compliance activity since 2008 has been largely unsuccessful. Additionally, since its establishment, the PSR has consistently cited MBS claiming confusion by medical practitioners in its annual reports, referring to it as an ongoing problem. Other government initiatives, such as the current copayment proposal (which would legalise concurrently charging a copayment, initially proposed at $7, later amended to $5, while also bulk billing for the same service), necessitate amendments to the Health Insurance Act. However, for the medical practitioners who will be required to interpret and apply any such changed arrangements, new layers of complexity may further obfuscate an area of law, which in many respects is already unclear.

**Medical practitioner support**

While most attention focuses on overclaiming, some medical practitioners have been caught in cost-shifting battles between State and Commonwealth provision of health services, and are pressured to increase their Medicare claiming. A Queensland Audit Office report revealed that RoPP schemes operating in Queensland public hospitals had cost the Queensland government at least $800 million despite being designed to be cost neutral. This was held to be due to underclaiming of Medicare benefits by medical practitioners for privately insured patients, as it was a requirement that hospital salaried medical practitioners generate MBS claims for these patients (which had not occurred, affecting a net revenue loss to the State). The Queensland report provided a rare empirical investigation of medical practitioner support and knowledge for proper MBS claiming, with a questionnaire of medical practitioners (n = 86) indicating 79% of respondents believed induction concerning which professional services were billable to Medicare or the private health funds was inadequate, 65% believed ongoing support in relation to MBS claiming was inadequate, and 62% were uncertain about what services could be billed under the MBS. The possible link between system complexity and erroneous claiming patterns has been raised previously. In 2007, the then Human Services Minister announced that by changing medical practitioner claiming and prescribing behaviour through an education and compliance programme, $250 million in Medicare programme savings had been achieved in the previous year. This suggests that a significant cost reduction can be achieved without requiring Australians to pay the impost of a copayment. However, despite the importance of Medicare in almost every medical interaction in Australia, most claiming and compliance education currently occurs on an ad hoc basis, and there is no Australian Medical Council requirement for medical courses to provide such education to medical students.

**Conclusion**

Despite mounting pressure on medical practitioners to claim from Medicare correctly, no formal, systematic research has explored the factors associated with Medicare compliance, the level of Medicare knowledge among claimants or the education needs of claimants. As such, the contemporary debate on Medicare claims compliance remains dominated by anecdotal and polemical commentary. This differs from other jurisdictions (such as the USA) where medical practitioner claiming and compliance has been more comprehensively studied.

The sustainability of Medicare is a stated objective of the current government that has recently proposed copayments as a solution to rising Medicare expenditure. However, in the absence of a detailed understanding of the utility and infrastructure of the Medicare system and its application in practice, copayments may do nothing more than increase the administrative complexity of Medicare, and further the potential impact of both wilful and inadvertent non-compliance.

It is reasonable for doctors and patients to expect that the government will base policy initiatives on a firm research base and give due consideration to possible internal inefficiencies before charging consumers more for the same services. However, the dearth of research in this area presents challenges for policy-makers in developing appropriate system reform.

If we are to modernise Medicare responsibly in a rapidly changing healthcare environment, research in the crucial area of medical practitioner experiences, perceptions and understanding of Medicare claiming, is urgently required.
References


15 Section 20A of the Health Insurance Act 1973 currently provides that when a doctor bulk bills he/she must accept the Medicare benefit in full payment for the service provided and is prohibited from charging a co-payment. [cited 2014 Oct 30]. Available from URL: http://www.health.gov.au/internet/main/publishing.nsf/content/mbsservices/mbsservices


© 2015 Royal Australasian College of Physicians

No payments, copayments and faux payments
Non-enhancing subcortical white matter lesions in central nervous system Listeriosis

*Listeria monocytogenes* infection is a devastating disease, especially in high-risk groups, consisting of infants, pregnant women and immunosuppressed individuals.\(^1\) Listeria is one of the most important organisms transmitted by the foodborne route.\(^2\)

A 66-year-old, previously independent Caucasian man, was referred to the neurology service for acute onset left-sided hemiplegia and drowsiness 2 days after total colectomy. Four days earlier, he was admitted for a severe exacerbation of ulcerative colitis. There was no clinical response to the initial treatment with mesalazine, azathioprine, prednisone and a single dose of infliximab.

On clinical examination, he was conscious and drowsy with dense left-sided hemiplegia. Blood tests showed...
leucopenia of $1.9 \times 10^9/L$ (neutrophils $1.18 \times 10^9/L$) and anaemia with haemoglobin of 72 g/L. C-reactive protein was 129 mg/L. Computed tomography brain showed a hypodensity in the right fronto-parietal and subinsular region. Magnetic resonance imaging (MRI) brain revealed a diffuse high signal abnormality in the white matter of the right subinsular region, right parietal and posterior frontal lobe without perilesional oedema, with restricted diffusion, which were not typical of ischaemia, and did not demonstrate contrast enhancement (Fig. 1). Lumbar puncture showed clear cerebrospinal fluid (CSF) with $37 \times 10^6/L$ white cells (polymorphs 4%, lymphocytes 96%), elevated protein (1000 mg/L) and low glucose (3.2 mmol/L; blood glucose 11 mmol/L). CSF Herpes Simplex virus 1 and 2, Cytomegalovirus, JC virus and Epstein Barr virus were negative. Blood and CSF culture grew *Listeria monocytogenes* sensitive to ampicillin. Antibiotic therapy with ampicillin at 2 g 4 hourly was initiated and planned for a period of 4 weeks. Two sets of blood cultures sent after 1 week of ampicillin showed no growth. The patient’s sensorium improved with treatment. However, the dense left hemiplegia persisted. Unfortunately, the patient passed away 4 weeks later due to complications from aspiration pneumonia. On autopsy, cerebral tissue from the right fronto-parietal lobe showed *L. monocytogenes* on gram staining and culture.

Our patient was immunosuppressed and prone to developing *L. monocytogenes* meningoencephalitis and *Listeria* septicaemia. With *Listeria* septicaemia, cerebral parenchymal involvement can occur from cerebral invasion via endothelial cells of capillaries, and meningeal involvement can occur via epithelial cells of the choroid plexus. While cerebral abscesses, *Listeria* rhombencephalitis and *Listeria* encephalitis are well described in the literature, the imaging appearance of our patient’s cerebral lesions was unique. The lesions involved the subcortical U fibres and white matter diffusely and did not enhance with contrast. There was minor perilesional oedema. There was no enhancement with contrast which is well described with *Listeria* abscesses and encephalitis, and there was no cortical involvement.3,5

The MRI findings of *Listeria* encephalitis in our patient were similar to progressive multifocal leucoencephalopathy with diffuse white matter lesions that do not enhance with contrast.6 Another possibility is that our patient’s lesion was an atypical subcortical early cerebritis stage of *Listeria* abscess formation. We acknowledge that the lack of enhancement of our patient’s lesions could also have been due to chronic immunosuppression and ongoing steroid use. This case adds that involvement of only white matter with diffuse non-enhancing lesions is possible in central nervous system Listeriosis. Central nervous system Listeriosis should be considered in such patients with an appropriate clinical history, investigated and treated accordingly.

Received 18 June 2014; accepted 24 July 2014.
doi:10.1111/imj.12654

A. Salonga-Reyes,1 M. S Badve,2,3 S. Bhuta,3,4
S. Broadley2,3 and A. Jones3,5

Departments of 1 Medicine, 2 Neurology, 4 Medical Imaging and
3 Infectious Diseases, Gold Coast University Hospital and 3 School of
Medicine, Griffith University, Gold Coast, Queensland, Australia

References


Effective treatment of Kaposi sarcoma with everolimus in a patient with membranous glomerulonephritis

A 78-year-old female patient with hypertension, atrial fibrillation, drug-induced diabetes mellitus and chronic kidney disease stage 3 was diagnosed with heavy nephrotic syndrome. A renal biopsy proved membranous nephropathy, serum antibodies against phospholipase A2 receptor (anti-PLA2R antibodies) were negative (Fig. 1A). The secondary causes of nephrotic syndrome were excluded. Tests for autoantibodies, viral infection (hepatitis B virus, hepatitis C virus, human immunodeficiency virus), serum protein electrophoresis and immunofixation for monoclonal protein were normal. Carcinoma antigens, except for Ca 125 antigen (132.3 U/mL, N: 0–35 U/mL), were negative. Transvaginal ultrasound revealed normal images of the uterus and ovaries and the presence of fluid in the Pouch of Douglas. We recognised that increased Ca 125 antigen corresponded to nephrotic syndrome.

Due to persistent severe nephrotic syndrome with impaired renal function (serum albumin 17 g/L N: 35–52, total protein 42 g/L N: 66–83, daily proteinuria 7 g, serum creatinine 174 μmol/L, N: 62–115), the patient received steroids with the starting dose of 40 mg/day with cyclosporine of 125 mg/day (trough level 129.7 ng/mL), replaced after 2 months by tacrolimus 2 mg/day (trough 4.5 ng/mL). Partial remission of nephrotic syndrome was obtained (serum albumin 31 g/L, total protein 52 g/L, daily proteinuria 1.4 g).

During the fifth month of the treatment, several lifted purple nodules appeared on the patient’s calves and shins. The lesions gradually spread to the thighs, the trunk and the left forearm (Fig. 1B). During the histopathologic examination of skin samples Kaposi sarcoma (KS) was identified (Fig. 1C,D). One month later, additional 5 mm maculopapular KS lesion developed in the right eye (Fig. 1E). The presence of serum anti-human herpesvirus-8 (HHV-8) IgG antibodies confirmed the history of infection.
Taking into account KS treatment patterns in organ transplant recipients, we decided to reduce the intensity of immunosuppression. Tacrolimus dose was reduced to 1.5 mg/day (trough level < 2 ng/dL) and steroids dose to 25 mg every second day. Additionally, everolimus was introduced at a dose of 0.75 mg/day (trough level 1.3 ng/mL).

Two months later, the remission was sustained. Skin lesions became pale and flat and partly vanished (Fig. 1F).

KS is a rare neoplasm that develops in the course of HHV-8 infection. Iatrogenic (immunosuppression-induced) KS occurs mainly in organ transplant recipients (up to 5%). Treatment is focused on the immunosuppression withdrawal or reduction, and mammalian target of rapamycin (mTor) inhibitor introduction. We decided to provide such a treatment for our patient. However, the severity and resistance to immunosuppression of nephrotic syndrome led us to maintain the tacrolimus treatment. Still, the dose of tacrolimus was reduced.

Literature reports of KS in glomerulonephritis are rare. Only a few of them describe KS in the course of membranous nephropathy. There was only one reported case of mTor inhibitor application as an antineoplastic treatment of KS accompanying membranous nephropathy.

The described severe nephrotic syndrome in negative anti-PLA2R membranous nephropathy poorly responding to immunosuppression may accompany or precede the occurrence of KS. There is also a possibility that the occurrence of KS was determined by type of immunosuppression and its intensity. We believe that the most important observation is that everolimus therapy of KS has proven to be effective despite the fact that tacrolimus treatment was continued.

References


Drug safety in Aboriginal Australians: three cases of angiotensin-converting enzyme inhibitor angioedema

Angiotensin-converting enzyme (ACE) inhibitor-associated angioedema is a known adverse effect of ACE inhibitors, with an estimated incidence of 0.1–0.7%. The racial profile of a patient is a recognised risk factor. African Americans have a fivefold higher risk than the general population. The relative risk in indigenous Australians is unknown.

We report three cases of ACE inhibitor-associated angioedema in South Australian Aboriginals, all of whom had airway compromise. These are the first reports of ACE inhibitor-associated angioedema in the indigenous Australian population and occurred between January 2011 and April 2013. Cases were identified from a retrospective audit of adverse drug reaction reports by the Royal Adelaide Hospital (RAH) Drug Information Service.

The RAH Drug Information Service reviews clinical cases where an adverse drug reaction is considered to have occurred and writes a formal report which is provided to the treating clinician, filed in the case notes and forwarded to the Therapeutic Goods Administration. In the period January 2011 to April 2013, there was a total of 187 adverse drug reaction (ADR) reports, 9 (4.8%) where racial status was identified as Aboriginal or Torres Strait Islander (Table 1). The number of angioedema separations (International Classification of Diseases 10 T78.3) from the RAH, by racial status and intensive care unit attendance over this period is outlined in Table 2.
Case 1 was a 49-year-old Aboriginal man who, in February 2013, developed angioedema after his first dose of perindopril (2 mg). He experienced swelling of the tongue, lips and stridor. He was retrieved from a rural centre via air ambulance to the RAH and was intubated in the intensive care unit (ICU) for 24 h. He made a full recovery.

Case 2 was a 63-year-old Aboriginal woman who had been on perindopril (2.5 mg) for 1 year. It was noted that she had three prior episodes of tongue swelling over the previous 6 months. Her fourth episode was more severe with markedly swollen tongue, dyspnoea and oxygen desaturation. She required ICU admission for observation and received adrenaline and hydrocortisone.

Case 3 was a 40-year-old Aboriginal woman who had been receiving perindopril (8 mg) for 1 year. She presented in February 2013 in the middle of the night with swelling of her soft palate and difficulty managing airway secretions. She was intubated in ICU and received a bradykinin receptor antagonist (icatibant). Symptoms resolved in hours.

All these cases had been assigned a Naranjo ADR probability score of 7, suggesting a probable relationship with ACE inhibitor use. While it is not possible to be certain about the causal role of the ACE inhibitor, there were no other identified likely causes such as hereditary angioedema. Patients’ symptoms resolved in hospital, but we are unable to comment on longer term outcome, or future episodes, or the effects of re-challenge as there was no clinical follow-up given the retrospective identification of the cases. A previous study has suggested the attributable risk for angioedema in those exposed to an ACE inhibitor is about 80% (95% confidence interval 51–92).

Our cases were all from South Australia, with no temporal or geographic cluster identifiable. In the 2011 census, Aboriginal and Torres Strait Islanders comprised 1.9% of the South Australian population with 30,431 individuals. This is the second lowest absolute Aboriginal and Torres Strait Islander population of all the Australian states. We have no information regarding cases from other hospitals, or other states or territories, although this would be worth exploring. We have done this previously with statin-associated myositis in Indigenous Australians, which lead to this audit of the RAH Drug Information ADR database.

In conclusion, these cases describe ACE inhibitor associated in Aboriginal Australians. They are notable in that all three required ICU admission, and two required intubation. This compares with current data that suggest that the rate of airway compromise in ACE inhibitor-associated angioedema is approximately 10%. It is very important that prescribers are aware of the potential for this adverse effect given the potential severity, frequency of use of ACE inhibitor and the often remote locations of Indigenous Australians. Further studies to investigate the relative risk in Indigenous compared with non-indigenous Australian populations are required. Pharmacovigilance is important for Indigenous Australian populations.

H. Mahajan, T. Thynne, G. M. Gabb and E. W. Poh

1Medicine, University of Adelaide, 2Pharmacology, Flinders University, 3General Medicine, and 4Drug Information Service, Pharmacy, Royal Adelaide Hospital, Adelaide, South Australia, Australia

Table 1 Royal Adelaide Hospital drug information service ADR reports January 2011 to April 2013, by ATSI and non-ATSI racial status

<table>
<thead>
<tr>
<th>ADR reports</th>
<th>ATSI</th>
<th>Non-ATSI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor angioedema</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>ACE inhibitor angioedema with airway obstruction</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

†Of the remaining six reports, two were of statin-associated myositis, two were reactions to anti-infective agents, and two were hyponatraemia with psychotropic or anticonvulsant medication. ACE, angiotensin-converting enzyme; ADR, adverse drug reaction; ATSI, Aboriginal and Torres Strait Islander.

Table 2 Angioedema (ICD 10 T78.3) separations from Royal Adelaide Hospital January 2011 to April 2013, by ATSI and non-ATSI racial status

<table>
<thead>
<tr>
<th></th>
<th>ATSI</th>
<th>Non-ATSI</th>
<th>Not stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3†</td>
<td>66‡</td>
<td>3</td>
</tr>
<tr>
<td>Time in ICU</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

†All ACE inhibitor associated. ‡Prescribing information not available. ACE, angiotensin-converting enzyme; ATSI, Aboriginal and Torres Strait Islander; ICD, International Classification of Diseases; ICU, intensive care unit.
General correspondence

Vancomycin vintage: my favourite DRESS

We read with interest the recent report of three cases of vancomycin-associated drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome by Young et al. from Westmead Hospital. They note that since DRESS was first described in 1996, 19 cases of DRESS syndrome secondary to vancomycin have been reported, nine cases since 2012.1 We commend the authors for highlighting this condition, but would like to provide an important historical context.

Although the label is new, vancomycin-associated DRESS syndrome was recognised over 50 years ago when vancomycin was introduced for the treatment of penicillinase producing Staphylococcus aureus. In 1962, Geraci reported rash in 4–5% of 85 patients receiving vancomycin; fever and eosinophilia were also noted.2 Early preparations of vancomycin, often called ‘Mississippi mud’, contained many impurities that were considered to have contributed to the frequency of adverse effects. Subsequently, the toxicity associated with vancomycin therapy diminished along with improved purification procedures.3

Vancomycin was soon replaced by penicillinase-stable penicillins, but was reintroduced in the 1980s after the emergence of methicillin-resistant Staphylococcus aureus (MRSA). In 1983 Farber & Moellering reported skin rash in three of 98 patients,4 while Sorrell & Collignon (at Westmead Hospital in 1985) reported skin rash in 4 of 54 patients, two who had fever.4 In a 1990 report of 16 severe cases of severe vancomycin-associated cutaneous reactions, six patients had fever and two had eosinophilia.5

In 1997 we reported delayed cutaneous reactions in ten (5.7%) of 174 patients who received iv vancomycin courses, eight also had fever (one with rigors), six had associated eosinophilia, and one developed acute renal failure. Two patients were treated with systemic corticosteroids. We found no correlation between vancomycin levels and development of reactions.6 The mean trough vancomycin concentration was 10.5 ± 5.9 mg/L (data not included in our original publication). Young et al. speculate that the recent ‘increase’ in reports may be due to increased vancomycin use following the ‘emergence of MRSA’ and ‘more continuous infusions leading to higher trough levels and total dosages’.7 We have concerns about these suggestions since the number of published case reports is not an accurate measure of incidence, MRSA infection rates have in fact reduced in recent years with the roll out of hospital hand hygiene culture-change programmes and other initiatives,8 and continuous infusions do not of themselves predict higher drug exposures. Although more intensive vancomycin dosing schedules (including continuous infusions) are being used to achieve vancomycin trough levels of 15–20 mg/L, and vancomycin trough levels >15 mg/L are an independent predictor of nephrotoxicity,9 any relationship with other vancomycin-associated adverse effects, including DRESS, have not been examined systematically in recent studies.

Received 18 September 2014; accepted 9 October 2014.

doi:10.1111/imj.12660

T. M. Korman,1 J. D. Turnidge2 and M. L. Grayson3
1Monash Infectious Diseases, Monash Health, Monash University, 2Department of Infectious Diseases, Austin Health, The University of Melbourne, Melbourne, Victoria and 3Australian Commission on Safety and Quality in Health Care, Sydney, New South Wales, Australia

References

Letters to the Editor

References


Author reply

We thank Korman et al. for their incisive comments regarding the case series we described of vancomycin-associated drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome presenting to our hospital, particularly the historical aspects regarding vancomycin. They correctly point out that many of the salient features of the syndrome were recognised clinically many decades ago before it had been established that this was an immune mediated phenomenon that can occur in response to a variety of drugs. It is possible that many of the cases that Korman et al. list as having a reaction to vancomycin (with either an associated isolated cutaneous reaction and/or fever or eosinophilia) may not strictly meet the criteria for DRESS syndrome, and there may have been other mechanisms leading to their clinical presentation.

We concur that the number of reports of DRESS associated with vancomycin use cannot be used as an accurate measure of incidence, but may simply reflect better recognition and reporting of the condition. Anecdotally, in our hospital network, we have seen a further three cases of vancomycin-associated DRESS syndrome in the past 12 months, making it the most common drug associated with DRESS syndrome in our network this year. This may reflect different prevalence rates of methicillin-resistant Staphylococcus aureus (MRSA) in our hospital and community population in Western Sydney and/or in the use of vancomycin, compared to other parts of Australia.

The precise immune mechanism(s) behind vancomycin-associated DRESS syndrome remains obscure. Large prospective studies with specimens collected for human leucocyte antigen typing and in vitro immunological studies, in patients receiving vancomycin for MRSA and who go on to develop DRESS syndrome, may be able to answer some of these intriguing questions. However, such studies are logistically difficult to perform because of the very low rates of DRESS syndrome. Studies to define optimal treatment (e.g. corticosteroids vs observation) of patients with DRESS syndrome have been hampered for the same reason.

Received 5 December 2014; accepted 11 December 2014.

doi:10.1111/imj.12670

S. Swaminathan,1 H. Dunckley,2 S. Ojaimi,3 M.-W. Lin,3 D. A. Fulcher,2 S. Young,4 J. Kok1 and M. W. Douglas5
1Immunology, ICPMR, 2Department of Immunopathology, 3Immunology Department, 4Centre for Research Excellence in Critical Infections and 5Storr Liver Unit, WML Westmead Hospital, Sydney, New South Wales, Australia
Access to ‘investigational’ cancer drugs: perspective of a trainee

The thoughtful article by Lewis et al.\(^1\) would have drawn the attention of oncology trainees who face the dilemma of discussing cancer drugs not yet subsidised by the Pharmaceutical Benefit Scheme (PBS) and remain ‘investigational’. These drugs are expensive, accessible only through enrolment into clinical trials open for recruitment or patient access schemes offered by pharmaceutical companies. They can be categorised into two distinctive groups, as Lewis et al.\(^1\) eluded to: one, the truly investigational drugs for which the evidence supporting their use was based only on early-phase clinical trials, and the other, the drugs that had been investigated in phase III randomised controlled trials, defining their roles over the current standard of care and may have already gained regulatory approval by the Therapeutics Good Administration (TGA). Nivolumab is one drug that falls to the first group which mandates the ethical considerations discussed by Lewis et al.\(^1\) when their compassionate access is first being initiated and later being sought by patients. However, for the second group of drugs, availability of patient access schemes becomes crucial, being the only means to access the drugs for most patients. As an oncology trainee, the lack of access to treatments with a high level of supportive evidence can be frustrating.

The nanoparticle albumin-bound paclitaxel Abraxane (Specialised Therapeutics Australia, STA) exemplified such need for patient access schemes. Based on the pivotal phase III MPACT trial that demonstrated a significant improvement in the overall survival (OS) over the standard of care (hazard ratio 0.72; \(P < 0.001\)) in the treatment of metastatic pancreatic cancer,\(^2\) Abraxane gained TGA approval in March 2014 but would become PBS-subsidised after 1 November 2014, an 8-month delay. STA has been providing Abraxane on a cost-sharing scheme to patients who would fulfil the inclusion criteria of the MPACT trial, and after the announcement of confirmed PBS listing in September 2014, STA began supplying Abraxane to patients who met the established PBS criteria to access it free of charge.

Trastuzumab emtansine is another example of cancer drugs that has gained TGA approval, but its subsidy is being met only by the cost-sharing scheme. This is again a drug investigated in a phase III clinical trial to have demonstrated a superior OS benefit over the standard of care in the treatment of metastatic breast cancer.\(^3\) If no patient access scheme existed, this drug would be financially out of reach for the majority of patients eligible for it.

From a personal perspective, the potential loss of opportunity to treat patients with an effective, regulatory-approved cancer drug is at the time being prevented by the presence of compassionate access schemes. While decisions regarding compassionate supply of cancer drugs need to be carefully made, compassionate access schemes have nevertheless an important role in facilitating access to important cancer drugs. The dilemma in the setting where compassionate access to cancer drugs is available then becomes one of whether to discuss it or not, and whether it is justifiable not to discuss it.

Received 21 October 2014; accepted 27 November 2014.

doi:10.1111/imj.12666

J. C. Kuo
Department of Medical Oncology, The Canberra Hospital, Canberra, Australian Capital Territory, Australia

References


Corrigendum


The following error was published on page 109.

D. Turner,¹ S. McGuiness¹ and K. Leder¹,²

The text was incorrect and should have read as:

D. Turner,¹ S.L. McGuinness¹ and K. Leder¹,²

The authors regret any inconvenience caused by this error.
195 Hyponatraemia at hospital admission is a predictor of overall mortality
L. Balling, F. Gustafsson, J. P. Garcia, M. Dalaygaard, H. Nielsen, S. Breugard, M. Bay, V. Kirk, O. W. Nielsen, L. Keber and E. Jørner

203 Clinical outcome of drug-eluting versus bare-metal stents in patients with calcified coronary lesions: a meta-analysis
B. C. Zhang, C. Wang, W.-H. Li and D.-Y. Li

Brief Communications

211 Delayed onset of benign pleural effusion

214 Treatment of refractory stomal variceal haemorrhage with embolisation and sclerosis
Z. Valaydon and P. Demond

218 Delayed onset of benign pleural effusion following concurrent chemotherapy for inoperable non-small-cell lung cancer

Personal Viewpoint

221 No payments, copayments and faux payments: are medical practitioners adequately equipped to manage Medicare claiming and compliance?
M. A. Fung, J. L. Wodile and J. Adams

228 Non-enhancing subcortical white matter lesions in central nervous system Listeriosis
A. Jones

231 Drug safety in Aboriginal Australians: three cases of angiotensin-converting enzyme inhibitor angioedema
H. Malkanjan, T. Thynne, G. M. Gabb and E. W. Poh

233 Vancomycin vintage: my favourite DRESS
T. M. Korman, J. D. Turnidge and M. L. Grayson

235 Access to 'investigational' cancer drugs: perspective of a trainee
J. C. Koo

236 Corrigendum

Advances in ankylosing spondylitis and axial spondyloarthritis
Deep brain stimulation for Parkinson disease
Breast cancer therapy: markers of aortic stiffness
Enteric fever in the Pacific
Axial isolated distal deep venous thrombosis
Dose tailoring of anti TNF-a therapy