Probiotics in luminal gastroenterology

Obesity and sodium picosulphate bowel preparation

SPAST mutations in hereditary spastic paraplegia

“Code Stroke” rapid access protocol for thrombolysis

HMG-CoA reductase inhibitors and falls in older people

Leukaemia cutis in chronic lymphocytic leukaemia and varicella zoster virus
Let your partners in research energize your career.

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

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

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

Part of Wiley Job Network

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

**abstracting and indexing**

**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 9256 5485). For enquiries regarding ScholarOne Manuscripts (formerly known as ManuscriptCentral) submissions please email ManuscriptCentral@racp.edu.au (e.g. IMJ-0000-2012).
General enquiries should be directed to Virginia Savickis, the Editorial Office, *Internal Medicine Journal*, using imj@racp.edu.au
Comments on published papers are welcomed. Authors are offered right of reply (no more than 500 words) at the discretion of the Editor. Given the current pressures on editorial space, however, invited comments are restricted to one reply.

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

Copyright © 2012 Royal Australasian College of Physicians.

For submission instructions, subscription and all other information visit www.blackwellpublishing.com/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 standardize and improve our efforts around the world to reduce our carbon footprint. Follow our progress at www.wiley.com/go/citizenship

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

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

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

http://authorservices.wiley.com
Editorial
1285 Is there a role for coercive treatment in the management of addiction in Australia?
M. Lloyd-Jones

Clinical Perspectives
1287 Probiotics in luminal gastroenterology: the current state of play
J. M. Andrews and M. Tan

Original Articles
1292 Evaluation of an Australian chest pain assessment unit
A. Sonigra, J. Lawlor and L. Roberts

1297 Cisplatin plus etoposide versus other platin-based regimens for patients with extensive small-cell lung cancer: a systematic review and meta-analysis of randomised, controlled trials
L. Jiang, K.-H. Yang, Q.-L. Guan, D.-H. Mi and J. Wang

1310 Prevalence of food allergy in Taiwan: a questionnaire-based survey

1316 Does a ‘code stroke’ rapid access protocol decrease door-to-needle time for thrombolysis?
Y. J. Tai, L. Weir, P. Hand, S. Davis and B. Yan

1324 Obesity does not affect sodium picosulphate bowel preparation

1329 Relationships between HMG-CoA reductase inhibitors (statin) use and strength, balance and falls in older people
W. Haerer, K. Delbaere, H. Bartlett, S. R. Lord and J. Rowland

1335 Awareness regarding venous thromboembolism among internal medicine practitioners in Mexico: a national cross-sectional study
A. Majluf-Cruz, G. Castro Martinez, M. A. Herrera Cornejo, G. Liceaga-Cravioto, F. Espinosa-Larrahaga and J. Garcia-Chavez

1342 SPAST mutations in Australian patients with hereditary spastic paraplegia
H. Vandebona, N. P. Kerr, C. Liang and C. M. Sue

Brief Communications
1347 Changes in serum phosphate during treatment of diabetic ketoacidosis: predictive significance of severity of acidosis on presentation
T. Shen and S. Braude

1351 Ironic case of hepatic dysfunction following the global withdrawal of sitaxentan
G. W. Don, F. Joseph, D. S. Celermajer and T. J. Corte

1355 Leukaemia cutis in chronic lymphocytic leukaemia following varicella zoster virus reactivation
G. Haygood, E. Mooney, H. V. Dinh, D. Gin, C. McLean and S. B. Ting

1358 Successful treatment of macrophage activation syndrome complicating adult Still disease with anakinra
N. K. Loh, M. Lucas, S. Fernandez and D. Prentice
Letters to the Editor

Clinical-scientific notes

1363 Rapid recovery of renal function after pulse steroid therapy in a human immunodeficiency virus-infected patient with glomerulonephritis
D. Gracey, R. Garsia, W. Britton and P. McKenzie

1365 Drug reaction with eosinophilia and systemic symptoms associated with H1N1 vaccination
N. Hewitt, M. Levinson and G. Stephenson

1367 The i-patient or the eyeball patient?

General correspondence

1368 FDG-PET for investigation of patients with fever of unknown origin
J. C. Lee and A. M. Redmond

1368 Reply
Y. J. Kim, S. I. Kim, K.-W. Hong and M. W. Kang

1369 A plea for the use of systematic review methodology when writing guidelines and timely publication of guidelines
T. G. Phan, A. Thrift, D. Cadilhac and V. Srikanth

1371 Reply
L. Wright, K. M. Hill, J. Bernhardt, R. Lindley on behalf of the National Stroke Foundation Stroke

1372 Chest ultrasound in practice: a review of utility in the clinical setting
J. Bowra

1373 Reply
M. Hew and S. Heinze

Volume 42 contents
WILEY ONLINE LIBRARY
Access this journal and thousands of other essential resources.

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

Sign up for content alerts and RSS feeds, access full-text, learn more about the journal, find related content, export citations, and click through to references.
Did you know you can access *Internal Medicine Journal* online through the Royal Australasian College of Physicians’ website?

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

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

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

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

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

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

Access your College journal online

[![Wiley-Blackwell](image)](image)
EDITORIAL

Is there a role for coercive treatment in the management of addiction in Australia?

In October 2010, the Victorian Parliament passed the Severe Substance Dependence Treatment Act no. 43 of 2010, which replaced the Alcoholics and Drug-Dependent Persons Act 1968.1 The objectives of this Act are: ‘to provide for the detention and treatment of persons with a severe substance dependence where this is necessary to save the person’s life or prevent serious damage to the person’s health’ and ‘to enhance the capacity of those persons to make decisions about their substance use and personal health, welfare and safety’.

It is stipulated that ‘detention and treatment is a consideration of last resort’ and ‘that any limitations on the human rights and any interference with the dignity and self-respect of a person who is the subject of any actions authorised under this Act are kept to the minimum necessary to achieve the objectives specified’.

This legislation allows for the detention and treatment of individuals suffering from severe substance dependence who fulfil the criteria laid out in the Act for a period of 14 days.

The idea of providing treatment rather than punitive custodial sentences for those convicted of drug-related offences has been in practice for a number of years in many different countries. In these situations, police may divert offenders into treatment, or a court may mandate treatment in addition to, or instead of, a prison sentence.

One of the difficulties facing us when we address the role of coercion in treatment is that much of the work done on evaluating the effectiveness of coercive treatments come from legally coerced treatment where engagement in treatment programs is as a result of an individual being charged with, or convicted of, an offence that relates to their substance use and as an alternative to imprisonment.2,3 The public health imperative since the rise of HIV/AIDS, and perhaps of hepatitis C, gives support to the concept of providing treatment rather than imprisonment as a means of limiting the spread of blood-borne virus infections.

Coercive treatment has been hitherto provided largely through the judicial system, with imprisonment as the incentive for entry into treatment. The individual having the choice whether they engage in treatment or suffer the legal penalty as determined by the court. Such court diversion programs have been in place for many years in some countries, including Australia. A range of new court-sentencing options have emerged, such as Court Diversion (for minor possession), Magistrates Early Referral into Treatment (a mid-range intervention response) and Drug Court (intensive intervention).2,3 Such programs may work in two ways: first, the police may take an individual to a treatment centre rather than to court in order to avoid a court appearance altogether. Alternatively, where a court has determined that an individual is guilty of an offence, he/she may be bound into treatment as an alternative to a punitive sentence, or the court may make attendance at treatment as a condition of bail.

One such post-sentencing program, the NSW Compulsory Drug Treatment Program, has been operating in NSW since 1999. In an evaluation of this program, performed after it had been running for 4 years, it was concluded that the majority of the offenders participating in the program perceived their involvement to be voluntary and that there was evidence that the offenders genuinely wanted to change their behaviour as evidenced by their desire to remain in the program.2 Interestingly, our experience in treating patients under the Victorian Severe Substance Dependence Treatment Act has not been dissimilar, in that most of the individuals treated were willing to remain in treatment for the duration of the Act and to continue in treatment post-discharge. Indeed, some were extremely grateful for the opportunity to access treatment.

The decision to deprive an individual of their freedom in order to provide necessary treatment must not be taken lightly.4 Psychiatrists have long been tasked with making the decision to provide involuntary treatment under the Mental Health Act in cases where the individual is deemed to be at risk to themselves or others, and unable to make appropriate decisions about their healthcare. However, the role of such coercive treatment in the management of addiction is less accepted, and there is no guidance from the literature as to how long such a period of treatment should continue.

Other concerns relate to the very idea of forcing treatment on resistant individuals who are perceived to be electing to make unwise choices about their lifestyle.4 Justifiable concerns about where such policies will end are understandable if one considers alcohol and drug...
addiction to be lifestyle choices rather than diseases with medical, neurobiological, behavioural and social consequences. Recent functional imaging studies have demonstrated impairment in response inhibition and abnormal salience attribution contributing to the overwhelming and often apparently incredible determination to continue using substances despite what might appear to be obvious life-threatening consequences. This concept of impaired autonomy is further explored by Caplan in which parallels with treating burns victims and other severely injured individuals in the early stages of their injury are made and support the idea that coercive measures do not, of necessity, lead to an infringement of autonomy but that they may be necessary in order to allow for the provision of good medical care.

Examples from around the world are not necessarily reassuring. There are countries, an example being Singapore, where those caught engaging in illicit drug use are locked up and forced to engage in therapeutic communities/drug treatment for significant lengths of time.

We need to consider the evidence of effectiveness of interventions before we decide to force treatment onto individuals. Certainly, we need to be sure that our interventions are not harmful and are applied with respect to evidence of effectiveness as far as this is possible. Some might advocate that the burden of proof of effectiveness needs to be rigorous. A consensus view on coercive drug treatment for the World Health Organisation concluded that ‘such treatment was legally and ethically justified only if the rights of the individuals were protected by due process’.

There is a paucity of literature to guide us in determining whether coercive treatment is effective.

There are more than 770 drug courts throughout the United States, some in operation for over 30 years. The rearrest rate following successful completion of the court-mandated programs provides some evidence for the benefit of such treatment. Farabee and colleagues in their review of 11 empirical studies of compulsory treatment noted that while the criminal justice system was able to act as an effective referral source and was able to enhance compliance in treatment programs the outcomes of treatment were variable.

In their extensive literature review of coercive treatment, Sullivan et al. identified a variety of situations in which coercion could be implemented as a means of initiating treatment or to ‘leverage’ therapy both to psychotherapeutic interventions as well as pharmacologically.

In a study of participants from five outpatient programs in Ohio, legally coerced participants were more likely than noncoerced participants to report abstaining from substances in the month prior to their follow-up interview and also demonstrated a lower addiction severity score. While there was no difference in the assessed readiness to change at admission into treatment, the numbers lost to follow-up were high, leading to some doubt about the reproducibility of these findings.

Some of the hesitation to adopt similar principles as those that apply to the Mental Health Act may lie with the historical reluctance to utilise this Act when dealing with individuals who were substance-affected. However, the recognition of the status of addiction as a disease and the emerging understanding of the neurobiology of addiction helps to provide further guidance to the debate. The planned fifth edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders will likely categorise substance abuse and dependence as ‘Substance Use and Addictive Disorders’ both destigmatising and recognising the spectrum of this disease. The idea that all individuals who are ‘caught up’ in their addiction whether intoxicated or in withdrawal are somehow able to make a valid, competent decision about whether they wish to receive treatment or not is recognised as being unreasonable. Severely dependent (addicted) individuals deemed to be at imminent risk of severe harm or death can be reasonably considered as being in need of treatment to allow them to regain capacity ‘to make decisions about their substance use, personal health, welfare and safety’.

This recognises that addiction is a disease with potent neurobiological consequences such that addicted individuals may be unable to exercise appropriate decision making because of the cognitive impairment resulting from the effects of their substance use on their brain function.

Nonetheless, we must beware of becoming complacent and accepting the role of social controls without further evidence as to the effectiveness of such interventions. This particular area of legal coercion and medical treatment will remain a work in progress for some time to come.
References

1 Severe substance dependence treatment act 2010 No. 43 of 2010.

CLINICAL PERSPECTIVES

Probiotics in luminal gastroenterology: the current state of play

J. M. Andrews1,2 and M. Tan3

1Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, 2School of Medicine, University of Adelaide and 3Royal Adelaide Hospital, Adelaide, South Australia, Australia

Key words
probiotics, luminal gastroenterology, diarrhoea, inflammatory bowel disease, constipation.

Correspondence
Jane M. Andrews, Department of Gastroenterology and Hepatology, Q7, North Wing, RAH, North Terrace, Adelaide, SA 5000, Australia.
Email: jane.andrews@health.sa.gov.au

Received 25 February 2012; accepted 16 August 2012.
doi:10.1111/imj.12015

Abstract
In recent years, there has been a growing interest in the use of probiotics in various areas of gastrointestinal (GI) health. Probiotics are defined as live microorganisms that provide beneficial health effects on the host when administered in adequate amounts. Various probiotics have been shown to suppress bacterial growth, modulate the immune system and improve intestinal barrier function. However, despite several studies with promising results, most trials are small and many have substantial methodological limitations. However, with better targeting and appropriate randomised controlled trials, this area may soon yield important therapeutic strategies to optimise GI health. Here, we review the current knowledge of probiotics of relevance to luminal GI health.

Introduction
The study of gut ecology and how probiotics may exert an effect on the intestinal tract has attracted increasing recent interest. A probiotic is defined as live microorganisms that provide beneficial health effects on the host when administered in adequate amounts.1 For over a century, various cultures
around the world have purposely incorporated the use of probiotics into their diet for putative health promotion and preventive purposes. Since then, many products that claim to contain live organisms have appeared widely in health-food stores, pharmacies and supermarkets. Microorganisms used in commercially available probiotics include *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus* and *Streptococcus thermophiles* in VSL#3, *Escherichia coli* Nissle 1917 and yeasts like *Saccharomyces boulardii* (Streptococcus boulardii).2

There are four general mechanisms proposed for the benefits of probiotics: to inhibit the growth of enteric pathogens,3 promote the integrity of intestinal barrier function,4 modulate host immune system by inducing protective cytokines and suppressing pro-inflammatory cytokines5 and modulate pain perception by inducing expression of analgesic receptors in intestinal epithelial cells, such as micro-opioid and cannabinoid receptors.6 However, whether these mechanisms are at play in individual settings when some probiotics yield positive clinical effects used is largely uncertain. This is due to the reasonably small number of rigorous clinical studies, such as randomised controlled trials (RCT), and a significant lack of mechanistic examination of any demonstrated benefits.

This clinical perspective will review the existing data on probiotics that pertain to issues of luminal gastroenterology. When considering the data and mechanisms, it should be noted that any effects with individual probiotics are likely to be species/strain, dose and disease specific, as one would expect with standard pharmaceuticals.

The widespread marketing of probiotics as a general principle and the lack of strict licensing of indications have hampered rigorous evaluation of this field. This has led perhaps to some benefits being underappreciated by mainstream medicine with the relevant data being lost in advertorial hype.

**Diarrhoeal illnesses**

There are two main areas where probiotics are well researched and thought to be efficacious: acute infectious diarrhoea caused by rotavirus and antibiotic-associated diarrhoea (AAD). The logic in using probiotics for treatment of infectious diarrhoea is based on the ability of probiotics to modify the composition of colonic microflora and combat enteric pathogens.7 Studies have shown an overall reduction in duration of diarrhoeal illnesses while patients are on probiotics, and no serious adverse events have been reported. An analysis of placebo-controlled studies of infants and children with acute diarrhoea has shown that probiotic use was associated with significant reduction of diarrhoea duration by about 20 h.8 *Lactobacillus GG* (LGG) is the most widely investigated strain and has been suggested to be particularly effective in rotaviral diarrhoea.9 Despite studies showing good results in reducing the duration of acute diarrhoea, there are limited data to justify whether the routine use of probiotics is beneficial, given that most episodes of acute diarrhoea are self-limiting. Moreover, there are, as yet, inadequate data to demonstrate whether probiotics can reduce serious complications from acute diarrhoeal illnesses.10

Twenty-five per cent of patients who commenced on antibiotics can develop AAD, with *Clostridium difficile* being the most commonly identified single infectious agent. The onset of diarrhoea can vary from 1 day to 6 weeks after the initiation of antibiotics. Examples of oral antibiotics that commonly cause AAD are broad-spectrum penicillins, cephalosporins and clindamycin.11 Several studies have been reviewed; most reaching similar conclusions suggesting that probiotics decrease the occurrence of diarrhoea in patients on antibiotics. A meta-analysis conducted by Pham et al.12 discovered that probiotics were better than placebo in treating AAD. However, it is unclear whether probiotics can be used for all AAD cases, as type, timing and optimum doses of probiotics with respect to antibiotic therapy are unknown.

Over the years, the frequency and severity of *C. difficile*-associated diarrhoea (CDAD) have been increasing. The key mechanisms behind treatment of CDAD with probiotics are thought to be by alteration of intestinal microflora and suppression of pathogenic colonisation through acid or toxin production in certain probiotic preparations.13 Data on using probiotics for *C. difficile* infections are not clearly established, despite small series or case reports showing beneficial results. However, larger studies are needed to confirm the clinical role of probiotics in the treatment of CDAD. The Cochrane Group conducted a systematic review of four studies and concluded that there was no evidence for probiotics to be used alone in treatment of *C. difficile*. There were also limited data that recommended the use of probiotics as an adjunct for CDAD treatment.14

**Irritable bowel syndrome (IBS) and other functional bowel disorders**

IBS is a common functional gastrointestinal disorder characterised by unexplained abdominal pain and bloating associated with altered bowel habits, which can be difficult to treat. There are also different subgroups in IBS—diarrhoea predominant, constipation predominant and mixed/alternators. Perhaps because current efficacy of drug therapies like antispasmodics, antidepressants, laxatives and antidepressants for IBS is weak, a popular
alternative to alleviate IBS symptoms, especially among consumers, is probiotics. The rationale behind using probiotics is that IBS may be induced by a bacterial cause (post-infectious IBS) and that changes in colonic flora as well as immune dysfunction may be prevalent in IBS.  

Unfortunately, however, a meta-analysis of 16 studies found most RCT lacking in adequate reporting of adverse events and additionally did not have appropriate study designs, making it difficult to ascertain the efficacy (or lack thereof) of probiotics. Despite these limitations, some of the larger studies found B. infantis to be significantly more effective than placebo in treating patients with IBS, with significant reduction in abdominal pain, bloating and distension reported. In another systematic review, probiotics showed modest improvement in overall symptoms of IBS, but this was not of statistical significance. Again, many study limitations were identified: variation in strain, dosage and strengths of probiotics used, which led to the conclusion that further research focusing on the type and adequate dose of probiotics was required to establish whether or not subgroups of IBS patients may benefit from certain specific probiotics. This conclusion has again been recently emphasised by Clarke et al., who also noted that potential benefits of these therapies are unable to be ascertained given the poor approach taken to evaluating them to date.

A recent RCT has shown benefit for patients with functional constipation when consuming a diet of probiotic-enriched artichokes. This benefit was accompanied by an alteration in short-chain fatty acids in the stool. Moreover, subjects consuming E. coli Nissle in other clinical trials or as over-the-counter therapy often report some loosening of stools during therapy, suggesting that there may be benefits from probiotics for those with constipation, although larger well-designed studies appear to be needed before this can be validated.

Inflammatory bowel diseases (IBD)

Ulcerative colitis (UC) and Crohn disease (CD) are chronic inflammatory conditions that both have waxing and waning intensity and severity. In UC, the inflammatory response is confined to the mucosa and submucosa of the bowel; whereas in CD, while inflammation appears to start mucosally, transmural disease is seen. The rationale behind using probiotics in IBD is based on the hypothesis that intestinal bacteria may be implicated in the pathogenesis of IBD as IBD is not seen in germ-free animals and antibiotics can give limited, but clinically relevant improvement. The main aims for treatment are induction of remission and prevention of relapse.

Ulcerative colitis

The use of probiotics in prevention of relapse of UC is better documented and appears promising. However, a clear benefit has yet to be outlined for induction of remission. Kruis et al. found that E. coli Nissle 1917 was as effective as low-dose 5-aminosalicylic acid (5-ASA) in prevention of relapse, as did Henker et al., who tested this probiotic among children with UC. Another study combined VSL#3 with balsalazide in a study involving patients with mild to moderate active UC. It was found that patients on a combination of balsalazide and VSL#3 did slightly better than those on balsalazide or mesalazine alone. Those who were on the combination therapy had a higher rate of remission and experienced an improvement in well-being, bowel frequency, as well as endoscopic and histologic scores.

A few studies have examined probiotics to induce remission of active UC. One RCT in 77 patients with mild to moderately active UC showed VSL#3 to be more effective than placebo in improving UC disease activity index and remission rates. A recent paediatric study showed that a probiotic enema in addition to oral 5-ASA was more effective at achieving remission than oral 5-ASA alone. Of interest, this study also documented some favourable changes in mucosal cytokines in response to the probiotic enema. It is this work which deserves further examination, the only disappointment being that we are left unsure whether the probiotic enema is any better/worse than a 5-ASA enema would have been – as this is the appropriate comparator for clinical purposes – rather than placebo.

Pouchitis

Ileal pouch-anal Anastomosis (IPAA) is the favoured surgical treatment for chronic UC and familial adenomatous polyposis where possible; as it removes almost the entire colorectal mucosa, preserving intestinal continuity and sphincter function. However, a long-term complication of IPAA in 15–35% of patients is acute or chronic idiopathic inflammation in the ileal pouch: pouchitis. Different microflora have been identified in those who develop pouchitis, thus leading to the rationale behind clinical trials, which aim to modulate the microflora with probiotics.

Initially, Gionchetti et al. carried out a double-blind, randomised, placebo-controlled trial that involved 40 patients in remission with antibiotics who were assigned to VSL#3 or a placebo. After 9 months, 85% of those on VSL#3 remained in remission while all patients on placebo relapsed. A similar study carried out by Mimura et al. also confirmed that more patients with refractory or
recurrent pouchitis remained in remission while on daily VSL#3.\textsuperscript{28} However, a systematic review\textsuperscript{29} concluded that for treatment of acute pouchitis, LGG was not more effective than placebo; while VSL#3, for the treatment of chronic pouchitis, was found to be more effective than placebo, in maintaining remission but not more effective than no treatment. Therefore, taking all available data into account, the efficacy of VSL#3 for prevention is questionable.

**Crohn disease**

Mixed and somewhat disappointing results have been shown in studies with probiotics in CD patients. This is mainly due to the size of trials being too small and few being double-blind, randomised and controlled clinical trials. Schultz et al.,\textsuperscript{30} in a small placebo-controlled trial of 11 patients with CD, showed that LGG did not demonstrate any benefit in induction or maintenance of remission. LGG was also found to be ineffective in a study\textsuperscript{31} involving 75 children in remission randomised to receive either LGG or a placebo in addition to standard medical therapy with 2-year follow up. The end-point of the trial was to observe rates of clinical relapse. Thirty-one per cent in the LGG group relapsed as opposed to 17% of the placebo group and this occurred within a median time of 9.8 months in the LGG group and 11 months in the placebo group.

Other probiotics examined in CD include *E. coli* Nissle 1917 and *S. boulardii*. Malchow\textsuperscript{32} did not identify any significant differences between patients with active CD who were treated with steroids and *E. coli* Nissle or those who were on placebo during that period to induce remission. Use of *Saccharomyces* in one study, however, did show some positive results for maintenance of remission, with lower relapse rates in the group treated with mesalamine plus *S. boulardii* (6.25%) compared with those who were only on mesalamine (37.5%).

At some point, most CD patients require a surgical resection and often, recurrent inflammation at the anastomosis can occur within a year. Doherty *et al.*\textsuperscript{33} tested antibiotics and probiotics, particularly VSL#3, for prevention of postoperative recurrence of CD and found that probiotics failed to show any efficacy for postoperative prophylaxis. Likewise, Van Gossum *et al.*’s study (*n* = 70),\textsuperscript{34} using *Lactobacillus johnsonii* versus placebo immediately after ileoaceal resection for CD for 3 months, failed to show any difference in endoscopic recurrence or clinical relapse between the two groups. Therefore, in IBD to date, it appears that probiotics have some efficacy in the prevention of relapse of UC and possibly pouchitis with disappointing outcomes for CD. Interestingly, new data\textsuperscript{35} demonstrate a low proportion of *Faecalibacterium prausnitzii* on resected ileal Crohn’s mucosa to be associated with early endoscopic recurrence (6 months). Moreover, studies have revealed anti-inflammatory properties, *in vitro* and *in vivo*, of this bacterial candidate. Thus, using *F. prausnitzii* as a probiotic agent appears to be a promising future strategy in preventing postoperative endoscopic recurrence of CD. Nevertheless, more studies are needed to define and establish the ideal population of patients who may benefit from this particular probiotic species. It is hoped that this targeted approach where the use of probiotics linked to discoveries in microbial dysbiosis may yield greater therapeutic gains analogous to the recent gains seen with biologic/monoclonal therapies in malignant and inflammatory disorders as the involved pathways are defined in detail.

**Conclusion**

Despite several studies showing promising results in the use of probiotics on gastrointestinal health, most trials are small and some do not have appropriate study designs. Furthermore, there is the need to establish the strain, optimum dosage and whether one probiotic agent alone or in combination with other probiotics would be more efficacious in treating gastrointestinal diseases. Current data only support the use of probiotics in a few areas. Therefore, more detailed research is needed to define further the clinical role of probiotics among children and adults. With appropriate RCT and a combined clinical and basic science approach, it appears highly likely that this area will soon yield important therapeutic strategies to optimise gastrointestinal health—but we are not there yet.

**References**

4. Seth A, Yan F, Polk DB, Rao RK. Probiotics ameliorate the hydrogen peroxide-induced epithelial barrier disruption by a PKC- and MAP kinase-dependent mechanism. *Am J...


Evaluation of an Australian chest pain assessment unit

A. Sonigra, J. Lawlor and L. Roberts

The Townsville Hospital, Townsville, Queensland, Australia

Key words
chest pain, CPAU, assessment unit, acute coronary syndrome.

Correspondence
Lynden Roberts, Department of Rheumatology, The Townsville Hospital, PO Box 670, Townsville, Qld 4810, Australia. Email: lynden_roberts@health.qld.gov.au

Received 31 July 2011; accepted 5 March 2012.
doi:10.1111/j.1445-5994.2012.02799.x

Abstract

Background: In order to mitigate the risk of missing atypical or low probability presentations of acute coronary syndromes (ACS), many hospitals have designated resources specifically for the assessment of chest pain.

Aim: This study aims to evaluate the introduction of a chest pain assessment unit (CPAU) in a North Queensland hospital.

Methods: Information on admission status, diagnosis, procedures, length of stay and chest pain representation rates was obtained for patients presenting with chest pain to the emergency department (ED) at The Townsville Hospital in the 2.5 years prior to the introduction of a CPAU in March 2007 \( (n = 6665) \). This was compared with information on chest pain patients \( (n = 7885) \) presenting to the ED in the 2.5 years after it opened.

Results: The CPAU resulted in a reduction in the percentage of ‘missed’ cases of ACS. The rate of people who represented with chest pain at 3 months and who ultimately received an ACS diagnosis reduced from 1.9% to 1.4%. There was an increased rate of apparently appropriate angiograms from 6.7% to 9.4% of chest pain admissions. The admission rate of ED chest pain presentations was stable as was the median length of stay \( (1.14–1.16 \text{ days}) \). A relative decrease in the proportion of admitted patients diagnosed with ACS compared with those with unspecified chest pain was observed.

Conclusion: The implementation of a CPAU at The Townsville Hospital resulted in improved care of those presenting to the ED with chest pain. Further Australian CPAU evaluations are recommended.

Introduction

Coronary heart disease (CHD) is the leading cause of death for Australians and is a national priority for healthcare. CHD generally presents with chest pain, which itself is common, constituting approximately 5–10% of the total presentations to emergency departments (ED). Of those with chest pain, however, only 10–15% have an acute myocardial infarction confirmed. The majority of the remaining causes are benign and are generally not formally diagnosed, with investigative efforts aimed largely at excluding hazardous causes. Therefore, the challenge for an efficient health system is to optimise the diagnostic yield for chest pain investigations – even when CHD presents in an unusual way – and to reduce resource use when dealing with benign causes.

In order to mitigate the risk of missing atypical or low probability presentations of acute coronary syndromes (ACS) while reducing unnecessary chest pain admissions, many hospitals have designated resources specifically for the assessment of chest pain. Chest pain assessment units (CPAU) appeared in the early 1980s in the USA and are often administered in or by EDs. These units are typically staffed with additional medical and nursing support and contain equipment specific for the evaluation of cardiac illnesses. Although not always implemented for fiscal benefits, several studies have demonstrated the cost-savings of ED-based CPAU. These are usually the consequence of retaining patients in ED for an expedited period of assessment rather than incurring the costs associated with admission to hospital.

Evidence for the clinical performance of CPAU is harder to come by. A US review of studies comparing routine care with that received in CPAU found no clear evidence for the improvement of clinical outcomes by CPAU. A subsequent randomised controlled trial did identify fewer admissions to hospital following CPAU assessment. However, this trial did not find significant differences in the number of patients with ACS inappropriately discharged, readmitted to hospital or experiencing adverse events. While evidence for their superiority is...
scant, many studies promote them as a safe alternative to routine care. This is based on the results from both prospective trials and retrospective audits that show CPAU produce similar outcomes to routine care. Australian studies have examined the adherence with chest pain guidelines in CPAU, but none to date has compared the performance of a purpose specific CPAU with routine care. The present study aims to test the hypothesis that a new CPAU introduced into a North Queensland hospital improves the quality and safety of patient care.

Methods

The Townsville Hospital (TTH) is a 460-bed tertiary referral facility in North Queensland. On 1 May 2007, a CPAU was established at TTH to provide timely access for those patients with intermediate risk chest pain. Originally opened as a four-bed unit, the CPAU’s capacity was reduced to two beds in 2009. The TTH unit is co-located with the coronary care unit and administered by the cardiology department. A ratio of two patients to one cardiology nurse has been maintained. Admission criteria for the unit include all of the following: the presence of acute chest pain, the absence of electrocardiogram changes, a normal 8-h troponin result, intermediate risk features for ACS and the patient having the capacity to undertake exercise stress testing. Prior to the introduction of the CPAU, patients meeting the admission profile were similarly assessed but were admitted to the cardiology or general medical service or discharged at the discretion of ED physicians. Some patients with chest pain were also transferred from ED to Townsville’s only other health facility (Mater Private Hospital).

A retrospective audit was conducted for all patients 18 years and older presenting to TTH ED with chest pain from 22 September 2004 to 31 December 2009. Chest pain presentations were ascertained from the local ED clinical database ‘EDIS’, a system that is widely used in Australia (http://www.ozmedicine.com/wiki/doku.php?id=it:edis). By cross-referencing with the hospital’s discharge diagnosis database, information about the following outcomes was gathered: rates of admission to TTH from the ED, rates of discharge and transfer to a private facility from ED, length of stay (LOS), rates of ACS and the International Classification of Diseases-10 diagnosis of unspecified chest pain. Information on outcomes relating to rates of coronary angiography and revascularisation procedures and the number of patients representing with chest pain within three months of an initial presentation who were diagnosed with ACS was also collected. Data were grouped according to whether patients presented prior to the introduction of the CPAU (pre-CPAU) or after the unit became operational (post-CPAU). Categorical variables were compared with a chi-square test, and continuous variables were compared with the Mann Whitney U using SPSS version 19 (IBM Corporation, Somers, NY, USA). Ethics approval for this study was received from TTH Human Research Ethics Committee.

Results

In total, there were 14,847 presentations of chest pain to the TTH ED over the audit period. Of these, 297 were excluded from the study as they were under the age of 18. Patient characteristics comparing pre- and post-CPAU time periods did not reveal any significant differences in patient age, or male to female ratio (Table 1).

There was a 9% increase in the total number of chest pain presentations to ED in the post-CPAU time period. The percentage of these patients admitted (admission rate) to any hospital remained stable ($P = 0.071$). However, the admission rate to TTH increased by 3.8% ($P < 0.0001$) apparently due to a decline in transfers from ED to the private hospital ($P < 0.0001$).

Overall, there was a very small but statistically significant increase in median LOS for all presentations of chest pain following the introduction of the CPAU (Table 2). When examined by the diagnostic group, there were

<table>
<thead>
<tr>
<th>Table 1 Characteristics and admission status ED chest pain presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Patients presenting with chest pain – n [%]</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Males – n [%]</td>
</tr>
<tr>
<td>Females – n [%]</td>
</tr>
<tr>
<td>Age – median (IQR)</td>
</tr>
<tr>
<td>Total chest pain presentations admitted to any hospital – n [% of total chest pain presentations]</td>
</tr>
<tr>
<td>Total chest pain presentations admitted to TTH – n [% of total chest pain presentations]</td>
</tr>
<tr>
<td>Total chest pain presentations admitted to the private hospital – n [% of total chest pain presentations]</td>
</tr>
</tbody>
</table>

†Classical chi-square. ‡Mann Whitney U. §Statistically significant at $\alpha = 0.05$, two-tailed. ED, emergency department; CPAU, chest pain assessment unit; IQR, interquartile range; TTH, The Townsville Hospital.
nonsignificant increases in LOS for ACS diagnosis and decreases in LOS for unspecified chest pain diagnoses.

The discharge diagnosis of patients admitted to TTH differed across time periods (Fig. 1). The introduction of the CPAU appeared to be associated with a decrease in the diagnosis of ACS and an increase in the proportion of those discharged without an identifiable cause for their chest pain despite testing. Diagnoses classified as ‘other’ remained relatively stable over time.

The 3-month rates of representation with ACS are shown in Table 3 demonstrating a reduction from 1.9% before CPAU to 1.4% after CPAU ($P = 0.024$).

Differences were noted in the rates of invasive procedures following the introduction of the CPAU. Increases were noted in the rates per chest pain presentation for both angiograms and angioplasties; however, the number of coronary artery bypass grafts (CABGs) decreased during the post-CPAU period. The angiogram rate in patients who ultimately did not receive a diagnosis of ACS remained stable over time at 1.5% of presentations, suggesting that the increase in the use of this test in the CPAU period did not reflect inappropriate testing.

**Discussion**

This study found the introduction of a CPAU produced outcomes worthy of note. An important finding is that the CPAU appears to have contributed to a reduction in the number of ‘missed’ cases of ACS. This result occurs in a context where definitive support for the clinical success of CPAU has been scant internationally.

There was an increased rate of admission of chest pain presentations at TTH. However, overall admission rate to the combined public and private hospitals did not rise

---

**Table 2** Length of stay for patients presenting with chest pain

<table>
<thead>
<tr>
<th></th>
<th>Pre-CPAU [median days (range)]</th>
<th>Post-CPAU [median days (range)]</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>1.14 (99.46)</td>
<td>1.16 (74.51)</td>
<td>0.012‡</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>3.18 (66.50)</td>
<td>3.53 (67.45)</td>
<td>0.323</td>
</tr>
<tr>
<td>Unspecified chest pain</td>
<td>1.46 (22.62)</td>
<td>1.08 (43.00)</td>
<td>0.054</td>
</tr>
<tr>
<td>Other – discharge diagnosis not related to heart condition</td>
<td>1.93 (99.35)</td>
<td>2.11 (73.49)</td>
<td>0.044‡</td>
</tr>
<tr>
<td>Other – discharged from ED</td>
<td>0.26 (2.11)</td>
<td>0.27 (2.73)</td>
<td>0.988</td>
</tr>
</tbody>
</table>

†Statistically significant at $\alpha = 0.05$, two-tailed. ‡Mann Whitney U. CPAU, chest pain assessment unit; ED, emergency department.

**Table 3** Representations and investigations for chest pain patients

<table>
<thead>
<tr>
<th></th>
<th>Pre-CPAU [n (%)]</th>
<th>Post-CPAU [n (%)]</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed with ACS at 3-month representation with chest pain</td>
<td>126 (1.9)</td>
<td>100 (1.4)</td>
<td>0.024‡‡</td>
</tr>
<tr>
<td>Angiogram</td>
<td>446 (6.7)</td>
<td>722 (9.2)</td>
<td>0.000†‡</td>
</tr>
<tr>
<td>Angiogram – n (% of presentations without ACS diagnosis)</td>
<td>169 (1.5)</td>
<td>162 (1.4)</td>
<td>0.352</td>
</tr>
<tr>
<td>CABG</td>
<td>71 (1.1)</td>
<td>56 (0.7)</td>
<td>0.027‡‡</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>137 (2.1)</td>
<td>214 (2.7)</td>
<td>0.012‡‡</td>
</tr>
</tbody>
</table>

†Statistically significant at $\alpha = 0.05$, two-tailed. ‡Classical chi-square. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CPAU, chest pain assessment unit.

---

**Figure 1** Discharge diagnosis of patients admitted with chest pain. ■, acute coronary syndrome; ••, non-specific chest pain; □, other; ◯, chest pain for investigation.
significantly. Although there is no clear explanation for the reduced rate of transfer to the private hospital, it may have arisen if the CPAU provided a more appealing pathway for referral of privately insured patients than the public hospital provided prior to CPAU. This is plausible given the private hospital is a distance of 7 km from the public hospital ED. The private hospital cardiology staffing was stable over the period and would not be an explanation for the observed effect. That management within CPAU was based on evidence-based guidelines may also have reassured referring ED staff and altered their referral patterns.

In addition to the increased rate of admission at TTH, the percentage of patients who underwent angiograms also increased. One possible explanation would be that the CPAU created an over-servicing environment with a resultant increase in unnecessary angiograms. This is thought to be unlikely however as the rates of this procedure for those not receiving a diagnosis of ACS did not increase. Furthermore, the indications for angiography in this publicly funded institution are relatively rigid and objective, and there are minimal financial incentives for clinical decision-makers to perform angiograms. The increased angiography rate is therefore more likely to represent appropriate usage and therefore may represent a further benefit from the CPAU.

At face value, the decrease in CABGs performed across time periods appears significant. It must be noted however that for 18 months after the introduction of the CPAU, the cardiothoracic unit at TTH was closed. As a consequence, the vast majority of patients requiring a CABG was transferred to Brisbane for the procedure.

Overall, there was very little effect of the CPAU on LOS. Given that one of the reasons for a CPAU is to improve system efficiency, this finding may be of some concern. Most previously reported benefits have been for CPAU adjacent to a hospital ED that was under the clinical governance of ED staff. Prior to the TTH CPAU, an admitting team would need to evaluate the need for admission of a chest pain patient, which meant that the inpatient team was the final arbiter of the need for admission. With CPAU, the formalised structure and attendant clinical pathway made refusal of admissions by the inpatient team largely impossible. Having the CPAU governed by the cardiology inpatient service might have provided a reassuring alternative for ED staff to admit chest pain patients when the clinical risk was at the admission/discharge threshold. These structural elements of the TTH CPAU may have reduced its clinical efficiency.

The CPAU appears to have altered the diagnostic yield of an admission as relatively less patients were diagnosed with ACS and more were diagnosed with unspecified chest pain. Comparing the two study periods though, the CPAU seems to have achieved a higher diagnostic accuracy, because the rates of readmission for ACS that were presumably ‘missed’ initially were lower in the CPAU period.

Although a formal cost effectiveness analysis was not done, the improvements seen with CPAU are likely to have consumed additional resources. New medical, nursing, space and equipment resources were added to the hospital with the opening of the CPAU. The increased rates of angiography presumably reflects the optimised evidence-based processing that CPAU was built on, but can be considered as a cost of implementing the CPAU. Changes in LOS can impact substantially on costs, however, very little effect was observed in this study. Changes in diagnostic yield may also have an important impact on costs; however, the changes seen with CPAU are likely to have resulted in both increases and decreases in costs. A more formal cost analysis would be needed before conclusions can be drawn overall.

A weakness of the present study is its retrospective examination of hospital outcomes and non-randomised design. Consequently, assumptions of causality must be interpreted with caution. It is worth noting however that the information collected in the databases is collected prospectively as part of routine hospital reporting. The strengths of this study include the inclusive design whereby all presentations with chest pain were captured, and individual patient journeys through the system up to the point of discharge or procedure were captured. This also encompassed sufficiently long periods before and after CPAU to ensure effects were not due to temporary fluctuations. Finally, the geographical isolation of Townsville with only one ED for patients with chest pain to attend is a particular strength as migration in and out of particular patients to other facilities is minimised.

Conclusion

The implementation of a CPAU at TTH resulted in improved care of those presenting to the ED with chest pain evidenced by additional appropriate rates of angiography and revascularisation and fewer missed diagnoses of ACS at follow up. The proportion of patients diagnosed with unspecified chest pain increased. Very little impact on either overall admission rates or LOS was observed. Further Australian CPAU evaluations and formal cost effectiveness analyses are recommended.

Acknowledgements

The authors would like to thank Susan Donnelly and Rachael Payne for their assistance with data extraction and arrangement.
References


Cisplatin plus etoposide versus other platin-based regimens for patients with extensive small-cell lung cancer: a systematic review and meta-analysis of randomised, controlled trials

L. Jiang,1,2 K.-H. Yang,1 Q.-L. Guan,2 D.-H. Mi1,3 and J. Wang1

1Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, 2Department of Oncology Surgery, The Surgery, The First Hospital of Lanzhou University, and 3Oncology Treatment Center, The Second Hospital of Gansu Province, Lanzhou, China

Key words
extensive-stage small-cell lung cancer, irinotecan, cisplatin, platinum, meta-analysis.

Correspondence
Ke-hu Yang, Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, 199 Dong Gang Road, Chengguan District, Lanzhou, Gansu 730000, China. Email: yangkehuebm2006@126.com

Received 28 June 2011; accepted 15 March 2012.


Abstract

Aim: To determine whether the cisplatin plus etoposide (EP) combination was more efficacious and less toxic than other platinum-based regimens for patients with extensive-stage small-cell lung cancer.

Methods: We performed an extensive literature search (from their inception to July 2010). Two reviewers independently assessed search results and methodological quality of included studies. Pooled hazard ratios (HRs) and relative risks (RRs) were calculated according to a random-effects model.

Results: Twelve randomised, controlled trials involving seven different platinum-based chemotherapy regimens were included into this meta-analysis. The meta-analysis showed that compared with EP regimen, irinotecan plus cisplatin (IP) might decrease the risk of death (HR = 0.87, 95% confidence interval (CI) 0.78–0.97, P = 0.01) (five trials), unlike the sensitivity analysis (HR = 0.91, 95% CI 0.81–1.02, P = 0.12), progression-free survival (HR = 0.95, 95% CI 0.86–1.05, P = 0.28) and overall response rate (RR 1.08, 95% CI 0.93–1.24) that were not superior for IP. IP regimen produced more non-haematological toxicities and less haematological toxicities. One trial found that etoposide + cisplatin + epirubicin + cyclophosphamide and cisplatin + etoposide + ifosfamide regimen might prolong the overall survival respectively. Etoposide + cisplatin + epirubicin + cyclophosphamide regimen also might improve progression-free survival but with high rate of haematological toxicities. None of the other trials included in the study demonstrated a significant improvement in survival.

Conclusions: There is no strong evidence that any clinical advantage for extensive small-cell lung carcinoma patients requiring chemotherapy when comparing EP with other platin-based regimens, with exception of IP that might prolong overall survival. The decision to prescribe which chemotherapy should take into consideration both cost and treatment preference.

Introduction

Lung cancer is the most common cancer in the world, with 1.61 million new cases diagnosed every year.1 Small-cell lung carcinoma (SCLC) that constitutes about 15% of all lung cancer is an aggressive form that is strongly associated with cigarette smoking and has tendency for early metastasis. Approximately 67% of patients present with extensive disease.2 The prognosis of patients with extensive-stage SCLC is especially poor. The median survival time for untreated patients ranges from only 6 to 12 weeks, whereas patients treated with combination chemotherapy have a median survival of 10–12 months.7 Platinum therapy is considered one of the most efficacious agents.4 Etoposide and cisplatin (EP) used in combination is the most common treatment regimen for extensive-stage SCLC. This regimen, which has been the mainstay of treatment for patients with extensive-stage SCLC since the 1980s,3 is less toxic and more effective than single-agent treatment with oral etoposide.6 While the consensus is that chemotherapy prolongs survival in patients with extensive-stage SCLC, the exact magnitude of survival benefits and safety with EP compared with other platinum-based regimens is less clear. Therefore, we aimed to do a meta-analysis of randomised controlled trials (RCT) to determine whether EP is associated with better therapeutic effect and safety.
Methods

Literature search
A comprehensive search was performed to identify RCT in PubMed, EMBASE, the Cochrane Library, Science Citation Index, Web of Science, and Chinese biomedical literature database in any language (from their inception to July 2010), using the text and key words in combination both as Medical Subject Headings terms and text words. We hand-searched reference lists of every retrieved paper and reviewed previous meta-analyses and reviews for additional publications. We also searched conference proceedings including the American Society of Clinical Oncology and European Society for Medical Oncology. The first authors of all identified studies were contacted to determine whether they were aware of any relevant unpublished, published or in-progress studies. We also searched World Health Organisation International Clinical Trials Registry Platform, Clinical Trials, Current Controlled Trials and Chinese Clinical Trial Register to identify further potential relevant studies and ongoing trials. Any ongoing trial was considered for inclusion if data were provided by the authors.

Study selection
Two reviewers (Lei Jiang) and (Kehu Yang) independently assessed every retrieved study for inclusion. Inclusion criteria were: (i) all RCT that compared EP with other platin-based regimens in the treatment of patients with extensive-stage SCLC; (ii) histologically or cytologically confirmed SCLC; and (iii) extensive-stage disease (defined as tumour that extends beyond the ipsilateral lung and regional lymph nodes).7 Where more than one publication of a single trial exists, only the publication with the most complete data was included unless the relevant outcomes were only published in earlier versions. Corresponding authors were contacted to verify whether their studies were actually RCT.

Data extraction
The same two reviewers independently extracted data from the included studies using standard data extraction forms. The following data were extracted from each study: first author’s name, year of publication, location of study, mean age, sample size, periods of enrolment, median duration of follow-up (months), regimens compared, number of events in each group, performance status (PS), and study endpoints of overall survival (OS) and progression-free survival (PFS) in each arm. Disagreements in data extraction were discussed to reach consensus. All data were collected on an intention-to-treat (ITT) basis, where possible.

The following data were extracted, checked, estimated and recorded: hazard ratio (HR) of OS and its standard error (SE), confidence interval (CI) or P-value; HR of PFS and its SE; CI or P-value; number of deaths at interval time; number of patients available for follow-up at the time of evaluation of survival risk; response rate (RR); and adverse events. Toxicity was analysed by extracting the total number of grades 3 and/or 4 events. All data were centrally reanalysed and checked for discrepancy.

OS was defined as the time from randomisation to death from any cause or to the last follow-up that was used as a date of censoring. PFS was measured as the time from randomisation to the first observation of disease progression or death from any cause if there had been no progression. All analyses were by ITT.

Quality assessment
The methodological quality of the studies was assessed independently by two reviewers according to the criteria stated in The Cochrane Collaboration Handbook,8 without masking the trial names. Disagreements were resolved by discussion with a third reviewer. If the methodological criteria were not clear from the published article, the study authors were contacted for clarification. For each trial, the risk of bias was assessed and tabulated for each of the following items: generation of the allocation sequence, allocation concealment, blinding of participants, personnel or outcome assessors, incomplete outcome data addressed, selective outcome reporting, and other biases. Items were scored as ‘yes’ for low risk of bias, ‘unclear’ for either lack of information or uncertainty over the potential for bias, and ‘no’ for high risk of bias.

Statistical methods
Statistical analyses were performed with Revman Version 5 (Cochrane Collaboration). The primary outcomes were OS and PFS for which the HR is the most appropriate statistic. OS and PFS were calculated as HR with data from published studies. We pooled log HR for time-to-event outcomes using an inverse variance method. If not enough data were available, we estimated HRs indirectly using methods described by Parmar by using either other available summary statistics or by extracting data from published Kaplan–Meier curves.9,10 A pooled HR was obtained from the derived observed (O) minus expected (E) number of events and the variance for each trial using the fixed-effect model.11 The pooled HR represents the overall risk of an event on another platin-based regimen...
versus an EP regimen. HR less than 1.0 favours the test group and values greater than 1.0 favour EP regimens.

We estimated relative risks (RRs) and their 95% CI for dichotomous data (response rates, grade 3/4 toxicity) using the Mantel–Haenszel method. We repeated the primary analysis using a random-effects model (DerSimonian and Laird method) in a sensitivity analysis.\(^{12}\) Statistical heterogeneity among studies was evaluated by using the Q and I\(^2\) statistics.\(^{13}\) The ability to conduct subgroup analyses depended on whether the required information was recorded in the trial publications. The following items considered for possible subgroup analysis: dose and schedule of EP regimen, first-line chemotherapy, and second-line chemotherapy. This work was performed in accordance with the quality of reporting of meta-analysis guidelines of RCT.\(^{14}\)

## Results

### Literature search

We identified a total of 18 eligible trials that had used EP regimen versus other platin-based regimens for patients with extensive-stage SCLC. Of these, six were ongoing studies.\(^{15-20}\) Ultimately, the remaining 12 RCT met our inclusion criteria, the detailed steps of our literature search are shown in Figure 1.

### Study characteristics of included studies

The characteristics of included studies are shown in Table 1.

### Risk of bias in included studies

We assessed study quality according to the criteria set out in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0. The risk of bias for each study is set out in Table 2.

### Effects of interventions

**Irinotecan/cisplatin versus EP**

HRs for OS data were available for four trials, including 1539 patients.\(^{21,23-25}\) The overall HR of 0.87 suggested that irinotecan/cisplatin (IP) might be likely to prolong OS in patients with previously untreated extensive SCLC (HR = 0.87, 95% CI 0.78–0.97, \(P = 0.01\); Fig. 2). This 13% relative decrease in the risk of death was equivalent to an absolute benefit of 3.5% at 2 years increasing OS from 10% to 13.5%. Heterogeneity was seen among included studies (\(I^2 = 59\%\); \(P = 0.06\)). Population-related differences in pharmacogenomics may explain the divergent results of J9511 and S0124.\(^{24}\) Sensitivity analysis excluding Japanese trials\(^{21}\) reduces heterogeneity (\(I^2 = 0\%\),
<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Age (year)</th>
<th>Schedule</th>
<th>Dosage</th>
<th>Sample size</th>
<th>Follow-up median</th>
<th>Outcome</th>
<th>Performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang et al.</td>
<td>Japan</td>
<td>63</td>
<td>every 4 weeks (4 cycles)</td>
<td>I: 60 mg/m² IV (days 1, 8, 15) P: 60 mg/m² IV (day 1) E: 100 mg/m² IV (days 1, 2, 3)</td>
<td>77/77</td>
<td>IP 16.8 mo</td>
<td>P*: OS, S*: PFS, RR*, site of relapse toxicity</td>
<td>0-2 (IP: 92.2%, EP: 87%, 0 or 1)</td>
</tr>
<tr>
<td>Pan et al.</td>
<td>China</td>
<td>61</td>
<td>every 4 weeks (3.3 cycles)</td>
<td>I: 80 mg/m² IV (days 1, 8, 15) P: 80 mg/m² IV (day 1, 2, 3) E: 120 mg/m² IV (days 1, 2, 3)</td>
<td>30/31</td>
<td>Not mentioned</td>
<td>P*: RR*, S*: PD toxicity</td>
<td>0 or 1</td>
</tr>
<tr>
<td>Hanna et al.</td>
<td>USA Canada</td>
<td>IP: 63 EP: 63</td>
<td>every 3 weeks (4 cycles)</td>
<td>I: 65 mg/m² IV (days 1, 8, 15) P: 80 mg/m² IV (day 1, 2, 3) E: 120 mg/m² IV (days 1, 2, 3)</td>
<td>221/110</td>
<td>33 mo</td>
<td>P*: OS, S*: PFS, RR* toxicity</td>
<td>0 or 2 (IP: 92.3%, EP: 98.2%, 0 or 1)</td>
</tr>
<tr>
<td>Lara et al.</td>
<td>Japan</td>
<td>63</td>
<td>every 4 weeks (4 cycles)</td>
<td>I: 60 mg/m² IV (day 1) P: 80 mg/m² IV (days 1, 2, 3) E: 120 mg/m² IV (days 1, 2, 3)</td>
<td>22/11</td>
<td>23.4 mo</td>
<td>P*: OS, S*: RR* toxicity</td>
<td>0 or 1</td>
</tr>
<tr>
<td>Zatloukal et al.</td>
<td>12 countries</td>
<td>60</td>
<td>every 3 weeks (6-cycles)</td>
<td>I: 65 mg/m² IV (days 1, 8, 15) P: 80 mg/m² IV (day 1, 2, 3) E: 120 mg/m² IV (days 1, 2, 3)</td>
<td>202/203</td>
<td>IP 31.6 mo</td>
<td>P*: OS, RR* survival, TIP</td>
<td>0-3</td>
</tr>
<tr>
<td>Carboplatin + etoposide (CE) versus EP in the treatment of previously untreated extensive SCLC</td>
<td>Japan</td>
<td>74</td>
<td>every 3/4 weeks (6 cycles)</td>
<td>C: AUC of five IV (day 1) E: 80 mg/m² N (days 1, 2, 3) P: 80 mg/m² N (days 1, 2, 3)</td>
<td>110/109</td>
<td>Not mentioned</td>
<td>P*: OS, S*: Toxicity, PFS, RR* palliation scores</td>
<td>age ≥ 70 and PS 0-2, or age &lt; 70 and PS 3</td>
</tr>
<tr>
<td>Skarlos et al.</td>
<td>Hellenic</td>
<td>60</td>
<td>every 3 weeks (6-cycles)</td>
<td>C: AUC of five IV (day 1) E: 80 mg/m² N (days 1, 2, 3) P: 80 mg/m² N (days 1, 2, 3)</td>
<td>31/30</td>
<td>27</td>
<td>P*: survival, RR* S*: Toxicity</td>
<td>0-3</td>
</tr>
<tr>
<td>Carboplatin (GC) and gemcitabine versus EP in the treatment of previously untreated extensive SCLC</td>
<td>UK</td>
<td>62</td>
<td>every 3 weeks (6-cycles)</td>
<td>C: AUC of five IV (day 1) E: 120 mg/m² IV (days 1, 8, 15) P: 100 mg/m² IV (days 1, 2, 3)</td>
<td>69/69</td>
<td>Not mentioned</td>
<td>P*: OS, S*: Toxicity, PFS, RR* quality of life</td>
<td>≥2</td>
</tr>
<tr>
<td>Etoposide + cisplatin + 4′-epidoxorubicin + cyclophosphamide (PCDE) versus EP in treatment of previously untreated extensive SCLC</td>
<td>France</td>
<td>59</td>
<td>every 4 weeks (6-cycles)</td>
<td>E: 100 mg/m² IV (days 1, 2, 3) P: 100 mg/m² IV (day 1, 2) C*: 100 mg/m² IV (days 1, 2, 3)</td>
<td>117/109</td>
<td>24</td>
<td>P*: OS, S*: Toxicity, PFS, RR, QOL</td>
<td>0-2</td>
</tr>
<tr>
<td>Etoposide + cisplatin + paclitaxel (PET) versus EP in treatment of previously untreated extensive SCLC</td>
<td>USA</td>
<td>65</td>
<td>every 3 weeks (6-cycles)</td>
<td>E: 80 mg/m² N (days 1, 2, 3) P: 80 mg/m² N (days 1, 2, 3) D: 40 mg/m² N (day 1)</td>
<td>283/282</td>
<td>EP 23.4 mo</td>
<td>Survival, RR, toxicity</td>
<td>0-2</td>
</tr>
<tr>
<td>Topotecan + cisplatin (TC) versus EP in treatment of previously untreated extensive SCLC</td>
<td>USA</td>
<td>59</td>
<td>every 4 weeks (6-cycles)</td>
<td>E: 100 mg/m² IV (days 1, 2, 3) T: 175 mg/m² IV (day 1)</td>
<td>38/395</td>
<td>Not mentioned</td>
<td>P*: OS, S*: toxicity, PFS, RR, QOL, TIP</td>
<td>0-2</td>
</tr>
<tr>
<td>Cisplatin + etoposide + ifosfamide (SPI) versus EP in treatment of previously untreated extensive SCLC</td>
<td>USA</td>
<td>63</td>
<td>every 3 weeks (4 cycles)</td>
<td>E: 1200 mg/m² IV (days 1–4) P: 80 mg/m² IV (days 1–4) I*: 1200 mg/m² po (days 1–4)</td>
<td>87/84</td>
<td>26</td>
<td>Survival, TTR, PFS, Not mentioned</td>
<td></td>
</tr>
</tbody>
</table>

AUC, area under the curve; bid, twice daily; C*, cyclophosphamide; C, carboplatin; 0, 4′-epidoxorubicin; E, etoposide; EP, etoposide and cisplatin; G, gemcitabine; I*, ifosfamide; I, irinotecan; IV, intravenous; O1, overall survival; P*, primary; P, cisplatin; PD, progressive disease; PFS, progression-free survival; po, orally; QOL, quality of life; RR*, response rate; S*, secondary; SCLC, small-cell lung cancer; SD, stable disease; T*, topotecan; T, paclitaxel; TTR, time to tumour progression; TR, time to relapse.
Table 2: Risk of bias in included studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Allocation concealment</th>
<th>Random sequence generation</th>
<th>Blinding</th>
<th>Incomplete outcome data addressed</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noda et al. 22</td>
<td>Unclear (not stated)</td>
<td>Random number table (yes)</td>
<td>No</td>
<td>No loss to follow-up</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pan et al. 22</td>
<td>Double-blind</td>
<td>Unclear (not stated)</td>
<td>Yes</td>
<td>No loss to follow-up</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hanna et al. 24</td>
<td>Central allocation</td>
<td>Unclear (not stated)</td>
<td>Yes</td>
<td>No loss to follow-up</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zatloukal et al. 25</td>
<td>Central allocation</td>
<td>Unclear (not stated)</td>
<td>Yes</td>
<td>No loss to follow-up</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Okamoto et al. 26</td>
<td>Minimisation method (yes)</td>
<td>Central allocation</td>
<td>No</td>
<td>No loss to follow-up</td>
<td>Yes</td>
<td>Unclar</td>
</tr>
<tr>
<td>Skarlos et al. 27</td>
<td>Central allocation</td>
<td>Minimisation method (yes)</td>
<td>Yes</td>
<td>No loss to follow-up</td>
<td>Yes</td>
<td>Unclar</td>
</tr>
<tr>
<td>Pujol 2001 28</td>
<td>Block randomisation</td>
<td>Minimisation method (yes)</td>
<td>Yes</td>
<td>No loss to follow-up</td>
<td>Yes</td>
<td>Unclar</td>
</tr>
<tr>
<td>Niell et al. 30</td>
<td>Block randomisation</td>
<td>Central allocation</td>
<td>Yes</td>
<td>No loss to follow-up</td>
<td>Yes</td>
<td>Unclar</td>
</tr>
<tr>
<td>Eckardt et al. 31</td>
<td>Central allocation</td>
<td>Unclear (not stated)</td>
<td>Yes</td>
<td>No loss to follow-up</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>et al. 32</td>
<td>Block randomisation</td>
<td>Central allocation</td>
<td>Yes</td>
<td>No loss to follow-up</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Yes indicated low risk of bias; *No indicated high risk of bias.

EP, etoposide and cisplatin; IP, irinotecan/cisplatin.

P = 0.47); however, we did not detect a significant effect of IP regimens versus EP on OS (HR = 0.91, 95% CI 0.81–1.02, P = 0.12; Fig. 3). Data on PFS were available from four trials totalling 1539 patients.21,22,23,25 No significant difference between two treatment arms in PFS was observed (HR = 0.95, 95% CI 0.86–1.05, P = 0.28; Fig. 4). There was evidence of statistical heterogeneity between trials (I² = 73%; P = 0.01). However, a sensitivity analysis excluding a Japanese study21 not only reduces heterogeneity (I² = 42%, P = 0.18) but also gives similar fixed-effect estimates (HR = 0.99, 95% CI 0.89–1.10, P = 0.84; Fig. 5).

Data on response rate were available from all trials totalling 1591 patients, but Hanna N et al. reported only overall response rate.23 There was no significant difference between the two regimens in overall response rate (RR = 1.08, 95% CI 0.93–1.24), heterogeneity was seen among included studies (I² = 54%, P = 0.07). Exclusion of the Japanese study again reduces heterogeneity (I² = 19%, P = 0.30),21 as well as giving similar fixed-effect estimates (RR = 1.02, 95% CI 0.91–1.15, P = 0.72). A similar effect on complete response rate and partial response rate was observed in the four studies with an RR of 1.35 (95% CI 0.54–3.40, P = 0.52), 1.05 (95% CI 0.81–1.35, P = 0.72) respectively. The results were shown in Figure 6.

The meta-analysis of grade 3 or 4 treatment-related adverse events between the treatment arms are listed in Table 3. The results showed that compared with patients receiving EP, patients treated with IP experienced more grade 3/4 diarrhoea, grade 3/4 fatigue, grade 3/4 anorexia, whereas grade 3/4 neutropenia, grade 3/4 thrombocytopenia, grade 3/4 anaemia and grade 3/4 leukocytopenia were more common in patients receiving EP than IP. There was no significant difference between the two groups with regard to grade 3/4 infection and grade 3/4 fatigue. For the grade 3/4 neutropenia, although there is obvious statistical heterogeneity between the results of these trials (I² = 93%, P < 0.00001), the results for trials comparing IP versus EP are consistent, all favour IP arm alone.

**Carboplatin/etoposide versus EP**

There were two eligible trials. Skarlos et al. reported a study in which participants with small-cell lung cancer were randomised to EP with etoposide plus carboplatin and irradiation.23 This paper only provided extractable data on response rate. Okamoto et al. found no significant differences in OS (HR = 0.99, 95% CI 0.75–1.30, P = 0.92), PFS (HR = 0.99, 95% CI 0.75–1.30, P = 0.92), grade 3/4 leukocytopenia (RR 1.04, 95% CI 0.81–1.34, P = 0.74), grade 3/4 neutropenia (RR 1.05, 95% CI 0.97–1.14, P = 0.20), grade 3/4 anaemia (RR 1.17, 95% CI
Jiang et al.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight</th>
<th>Hazard ratio</th>
<th>Exp((O-E)/V), Fixed, 95% Cl</th>
<th>Hazard ratio</th>
<th>Exp((O-E)/V), Fixed, 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Irinotecan+cisplatin</td>
<td>Hanna et al.</td>
<td>8.5%</td>
<td>0.95 [0.75, 1.21]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lara et al.</td>
<td>18.1%</td>
<td>0.95 [0.81, 1.12]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noda et al.</td>
<td>4.5%</td>
<td>0.60 [0.43, 0.83]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zatloukal et al.</td>
<td>10.0%</td>
<td>0.81 [0.65, 1.01]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>41.1%</td>
<td>0.87 [0.78, 0.97]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 7.26, df = 3 (P = 0.06); I² = 59%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.51 (P = 0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.2 Carboplatin+etoposide</td>
<td>Okamoto et al.</td>
<td>6.4%</td>
<td>0.99 [0.75, 1.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>6.4%</td>
<td>0.99 [0.75, 1.30]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.10 (P = 0.92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.3 Carboplatin+gemcitabine</td>
<td>Lee et al.</td>
<td>4.1%</td>
<td>1.07 [0.76, 1.51]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>4.1%</td>
<td>1.07 [0.76, 1.51]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.41 (P = 0.68)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.4 Etoposide+cisplatin+4′-epidoxorubicin+cyclophosphamide</td>
<td>Pujol et al.</td>
<td>6.8%</td>
<td>0.69 [0.53, 0.90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>6.8%</td>
<td>0.69 [0.53, 0.90]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.71 (P = 0.007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.5 Etoposide+cisplatin+paclitaxel</td>
<td>Niell et al.</td>
<td>16.7%</td>
<td>0.92 [0.78, 1.09]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>16.7%</td>
<td>0.92 [0.78, 1.09]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.96 (P = 0.34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.6 Topotecan+cisplatin</td>
<td>Eckardt et al.</td>
<td>19.8%</td>
<td>1.05 [0.90, 1.23]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>19.8%</td>
<td>1.05 [0.90, 1.23]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.61 (P = 0.54)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.7 Cisplatin+etoposide+ifosfamide</td>
<td>Loehrer et al.</td>
<td>5.1%</td>
<td>0.73 [0.54, 0.99]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>5.1%</td>
<td>0.73 [0.54, 0.99]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.01 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.90 [0.84, 0.97]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 18.42, df = 9 (P = 0.03); I² = 51%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.83 (P = 0.005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 11.16, df = 6 (P = 0.08); I² = 46.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Meta-analysis of overall survival comparing platin-based regimen versus etoposide and cisplatin (EP). CI, confidence interval.
0.76–1.82, \( P = 0.47 \)), grade nausea/vomiting (RR 0.66, 95% CI 0.11–3.88, \( P = 0.65 \)) and grade 3/4 infection (RR 1.32, 95% CI 0.47–3.68, \( P = 0.59 \)), but grade 3/4 thrombocytopenia occurred more frequently in the carboplatin/etoposide arm than in the EP arm (RR 3.56, 95% CI 2.23–5.68, \( P < 0.00001 \)).

Data on response rate were available from all trials totalling 280 patients; the combined results showed that no significant difference was observed between two regimens in overall response rate (RR 1.10, 95% CI 0.81–1.48, \( P = 0.56 \)), complete response rate (RR 0.80, 95% CI 0.33–1.97, \( P = 0.63 \)) or partial response rate (RR 1.01, 95% CI 0.86–1.20, \( P = 0.86 \)).

**Carboplatin/gemcitabine versus EP**

One study compared carboplatin/gemcitabine (GC) with EP regimen in patients with previously untreated extensive SCLC; the result indicated that there was no difference in treatment effect on OS (HR = 1.07, 95% CI 0.76–1.48, \( P = 0.56 \)), complete response rate (RR 0.80, 95% CI 0.33–1.97, \( P = 0.63 \)) or partial response rate (RR 1.01, 95% CI 0.86–1.20, \( P = 0.86 \)).

**Etoposide + cisplatin + epirubicin + cyclophosphamide versus EP**

In only one study, etoposide + cisplatin + epirubicin + cyclophosphamide (PCDE) was compared with EP in previously untreated extensive SCLC. OS (HR = 1.09, 95% CI 0.69–1.76, \( P = 0.68 \)) or PFS (HR = 1.19, 95% CI 0.84–1.68, \( P = 0.323 \)). There was a significantly higher incidence of grades 3 and 4 haematological toxicity in patients on GC than in those on PE, but GC produced less non-haematological toxicities than PE arm.21

**Topotecan/cisplatin versus EP**

In one study comparing oral topotecan/cisplatin versus EP in chemotherapy-naive patients with extensive SCLC, OS (HR = 1.05, 95% CI 0.90–1.23, \( P = 0.54 \)) and overall response rate (RR = 0.91, 95% CI 0.83–1.01, \( P = 0.08 \)) were similar between groups. In the topotecan/cisplatin (TC) arm, the incidence of grade 3/4 leukopenia and neutropenia was lower, whereas the incidence of grade 3/4 thrombocytopenia and anaemia was higher than in the PE arm. The most common non-haematological toxicities occurring in both groups were nausea, vomiting and anorexia, but diarrhoea occurred more frequently in the TC group. Oral topotecan with cisplatin may provide greater patient convenience compared with
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight</th>
<th>Hazard ratio</th>
<th>Exp((O-E)/V), Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.2.1 Irinotecan+cisplatin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanna et al. (^{23})</td>
<td>31.5%</td>
<td>1.11</td>
<td>[0.93, 1.32]</td>
</tr>
<tr>
<td>Lara et al. (^{24})</td>
<td>40.0%</td>
<td>0.89</td>
<td>[0.76, 1.04]</td>
</tr>
<tr>
<td>Noda et al. (^{21})</td>
<td>9.1%</td>
<td>0.61</td>
<td>[0.44, 0.84]</td>
</tr>
<tr>
<td>Zatloukal et al. (^{25})</td>
<td>19.5%</td>
<td>1.03</td>
<td>[0.82, 1.29]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.95</td>
<td>[0.86, 1.05]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 11.12, df = 3 (P = 0.01); I² = 73%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.09 (P = 0.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2.2 Carboplatin+etoposide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okamoto et al. (^{26})</td>
<td>100.0%</td>
<td>0.89</td>
<td>[0.68, 1.17]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.89</td>
<td>[0.68, 1.17]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.84 (P = 0.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2.3 Carboplatin+gemcitabine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al. (^{28})</td>
<td>100.0%</td>
<td>1.19</td>
<td>[0.84, 1.68]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>1.19</td>
<td>[0.84, 1.68]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.99 (P = 0.32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2.4 Etoposide+cisplatin+4'-epidoxorubicin+cyclophosphamide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pujol et al. (^{29})</td>
<td>100.0%</td>
<td>0.58</td>
<td>[0.44, 0.77]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.58</td>
<td>[0.44, 0.77]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.89 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2.5 Etoposide+cisplatin+paclitaxel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niell et al. (^{30})</td>
<td>100.0%</td>
<td>0.92</td>
<td>[0.78, 1.09]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.92</td>
<td>[0.78, 1.09]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.92 (P = 0.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2.6 Topotecan+cisplatin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eckardt et al. (^{31})</td>
<td>100.0%</td>
<td>1.19</td>
<td>[1.03, 1.38]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>1.19</td>
<td>[1.03, 1.38]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.29 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for subgroup differences: Chi² = 22.98, df = 5 (P = 0.003); I² = 78.2%

**Figure 4** Meta-analysis of progression-free survival comparing platin-based regimens versus etoposide and cisplatin (EP).
1.11 [0.93, 1.32]  
0.89 [0.76, 1.04]  
1.03 [0.82, 1.29]  

Total events 
Heterogeneity: $\chi^2 = 3.45$, df = 2 ($P = 0.18$); $I^2 = 42\%$ 
Test for overall effect: $Z = 0.20$ ($P = 0.84$) 

34.6%  
44.0%  
21.4%  

100.0%  

Hanna et al.23 
Lara et al.24 
Zatloukal et al.25 

Subtotal (95% CI) 

Test for subgroup differences: Not applicable

Figure 5 Sensitivity analysis of progression-free survival comparing (IP) versus etoposide and cisplatin (EP).

Study or subgroup Weight 
Irinotecan+cisplatin 
Hanna et al.23 34.6% 
Lara et al.24 44.0% 
Zatloukal et al.25 21.4% 
Subtotal (95% CI) 100.0% 

Total events 
Heterogeneity: $\chi^2 = 3.45$, df = 2 ($P = 0.18$); $I^2 = 42\%$ 
Test for overall effect: $Z = 0.20$ ($P = 0.84$)

1.5.1 Irinotecan+cisplatin 

Hazard ratio 

Exp((O-E)/V), Fixed, 95% CI 

Study or subgroup Weight 
Irinotecan+cisplatin 

Hanna et al.23 34.6% 1.11 [0.93, 1.32] 
Lara et al.24 44.0% 0.89 [0.76, 1.04] 
Zatloukal et al.25 21.4% 1.03 [0.82, 1.29] 
Subtotal (95% CI) 100.0% 0.99 [0.89, 1.10] 

Test for subgroup differences: Not applicable

Figure 6 Meta-analysis of response rate comparing irinotecan/cisplatin (IP) versus etoposide and cisplatin (EP).

Study or subgroup Weight 
Irinotecan/cisplatin Etoposide/cisplatin 

Hanna et al.23 34.6% 1.01 [0.88, 1.17] 
Lara et al.24 44.0% 1.28 [1.07, 1.53] 
Pan et al.22 21.4% 1.09 [0.75, 1.59] 
Subtotal (95% CI) 100.0% 1.25 [0.94, 1.69] 

Test for overall effect: $Z = 0.64$ ($P = 0.52$)
intravenous EP regimen because of similar efficacy and tolerability.

**Cisplatin + etoposide + ifosfamide versus EP**

There was one study comparing cisplatin + etoposide + ifosfamide (EPI) with EP regimen in previously untreated extensive SCLC. The results indicated that EPI regimen is associated with an improved OS (HR = 0.73, 95% CI 0.54–0.99, \( P = 0.04 \)) and PFS (5.8 months vs 6.6 months, \( P = 0.039 \)). There was no significant difference in haematological toxicity with the exception of more grade 3/4 anaemia in the EPI arm, non-haematological toxicities were mild, and this did not reach statistical significance.\(^{12}\)

**Discussion**

We studied 12 randomised trials that compared EP versus other platin-based regimens for patients with extensive SCLC. We have quantified the size of the survival benefit and safety. Data from our analyses show that compared with EP regimen, IP- and EP-based (PCDE and EPI) regimens might prolong the OS, and PCDE regimen might also improve PFS for these patients. The IP regimen produced more non-haematological toxicities and less haematological toxicities, whereas more patients experienced toxicity in PCDE arm. There was insufficient evidence to determine whether PCDE and EPI regimen are superior to EP for the treatment of extensive SCLC given the small number of participants. The metaanalysis also showed that IP regimens could prolong OS \( (P = 0.01) \), but sensitivity analysis after the trial J9511 (Noda K 2002) was excluded, failed to show an advantage for the IP regimen \( (P = 0.12) \). Multiple potential explanations might exist for the divergence of results between the IP and EP regimens. It is possible that overestimation of treatment effect as a result of early termination of accrual in the J9511 trial, the smaller sample size of J9511 may have significantly overestimated the treatment effect, which diminishes when the number of events accrued is large, as was the case for their trial.\(^{24}\) In light of the correlation between the apparent treatment effect and the number of events, some have argued that interim analyses only be performed after a sufficient number of events have occurred to reduce the likelihood of overestimating the true treatment effect.\(^{14}\) It was also possible that population-related differences in pharmacogenomics may explain the divergent results of J9511 and S0124.\(^{34}\) S0124 examined different allelic variants in genes associated with irinotecan metabolism and found that ABCB1(C3435T) T/T and UGT1A1 (G-3156) A/A were associated with an increased risk of IP-related diarrhoea and neutropenia respectively.\(^{24}\) The characteristics of enrolled patients have changed over time for each included study, such as age, sex, patient demographics and PS. Another point to be noted is that the diagnostic criteria of extensive SCLC, and definition of OS and PFS were not unified, which might affect combined results. The present meta-analysis also showed that there was evidence of a difference or trend in the relative effect of chemotherapy in patient subgroups defined by demographics. This may reflect population differences in the frequencies of polymorphic alleles that influence the function of genes involved in irinotecan transport and metabolism.\(^{24,25}\) Our results are consistent with previous published meta-analyses of safety comparing IP with EP for patients with extensive SCLC.\(^{15}\)

Because IP regimens have been shown to produce a statistically significant improvement in the median overall survival of patients with extensive SCLC, these results are expected to improve the survival time approximately twice as long as that of single-agent therapy frequently used in the early 1970s,\(^{16}\) and produced a median survival time of 9–11 months.\(^{17}\) In the late 1980s, the EP regimen was introduced and investigated in RCT.\(^{18}\) A systemic review indicated a modest improvement over the years in the survival time

---

**Table 3** Meta-analysis of adverse events comparing IP versus EP

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>RCT,n</th>
<th>Treatment arm, n(N)</th>
<th>Control arm, n(N)</th>
<th>( P )-value</th>
<th>RR (95% CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 neutropenia</td>
<td>5</td>
<td>270 (840)</td>
<td>514 (741)</td>
<td>0.0001</td>
<td>0.43 (0.28, 0.66)†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 3/4 thrombocytopenia</td>
<td>5</td>
<td>31 (840)</td>
<td>94 (741)</td>
<td>0.007</td>
<td>0.29 (0.12, 0.72)†</td>
<td>0.54–0.99</td>
</tr>
<tr>
<td>Grade 3/4 anaemia</td>
<td>5</td>
<td>58 (840)</td>
<td>91 (741)</td>
<td>0.05</td>
<td>0.57 (0.32, 1.00)†</td>
<td>0.035</td>
</tr>
<tr>
<td>Grade 3/4 leucocytopenia</td>
<td>4</td>
<td>92 (624)</td>
<td>178 (635)</td>
<td>&lt;0.00001</td>
<td>0.53 (0.42, 0.66)†</td>
<td>0.48</td>
</tr>
<tr>
<td>Grade 3/4 diarrhoea</td>
<td>5</td>
<td>131 (840)</td>
<td>11 (741)</td>
<td>&lt;0.00001</td>
<td>10.43 (5.78, 18.82)‡</td>
<td>0.31</td>
</tr>
<tr>
<td>Grade 3/4 nausea/Vomiting</td>
<td>5</td>
<td>158 (840)</td>
<td>103 (741)</td>
<td>0.002</td>
<td>1.42 (1.13, 1.79)‡</td>
<td>0.032</td>
</tr>
<tr>
<td>Grade 3/4 anorexia</td>
<td>3</td>
<td>49 (735)</td>
<td>22 (633)</td>
<td>0.003</td>
<td>2.11 (1.29, 3.43)‡</td>
<td>0.09</td>
</tr>
<tr>
<td>Grade 3/4 fatigue</td>
<td>3</td>
<td>71 (735)</td>
<td>48 (633)</td>
<td>0.09</td>
<td>1.35 (0.95, 1.91)‡</td>
<td>0.24</td>
</tr>
<tr>
<td>Grade 3/4 infection</td>
<td>3</td>
<td>59 (569)</td>
<td>60 (559)</td>
<td>0.81</td>
<td>0.96 (0.69, 1.35)‡</td>
<td>0.58</td>
</tr>
</tbody>
</table>

†Random effects model; ‡Fixed-effect model. CI, confidence interval; RCT, randomised, controlled trial; RR, response rate.
of patients with extensive-stage SCLC treated with chemotherapy between 1972 and 1994. This improvement was potentially attributable to (i) introduction of the PE regimen in the late 1980s, and (ii) improvements in the supportive care and general management of the patients. Although multiple drug regimens have been introduced in the treatment of extensive-stage SCLC, the survival benefit from chemotherapy has reached a plateau, even with the introduction of the EP regimen in recent clinical trials. This difference in the time trend in OS is mainly attributable to differences in the study period (year of trial initiation 1972–1994 versus 1980–2006 in the earlier and preset study respectively).

Dose and schedule of EP regimen may influence results mentioned herein. In Hanna N et al.’s study, only 80.4% of the planned dose intensity of irinotecan was delivered, and 50% of the day-15 irinotecan doses were never administered. An RCT was performed to determine whether higher doses of EP regimen yield more complete responses or longer survival in SCLC patients, which showed that no therapeutic benefits resulted from increasing planned doses by 67% for the first two cycles of EP in patients with extensive-stage SCLC, and higher doses were associated with substantially worse toxicities. A meta-analysis of dose/cycle of EP and outcome of patients with extensive SCLC (16 RCT, 1419 patients), which also indicated that increasing the dose of cisplatin (60–135 mg/m²/cycle) did not improve the complete response rate, partial response rate or OS, and dose per cycle of either drug, had no influence on the toxic death rate (P = 0.08). Therefore, they concluded that dose/cycle of either etoposide or cisplatin had no impact on the response rate or survival in patients with extensive SCLC; lower doses of EP regimen appear to be as effective as higher doses in this patient population. Proposed subgroup analyses (by PS, dosage and duration, the second-line chemotherapy) were not conducted because the information was not reported or because the data were difficult to extract from the trial reports. A multiple regression analysis showed no significant improvement in survival for patients with extensive disease SCLC enrolled in phase III trials from 1981 to 2008. Additionally, the use of EP regimen did not affect survival, whereas the proportion of patients with good PS and the trial design of assigning prophylactic cranial irradiation were significantly associated with favourable outcome. An RCT evaluating different sequencing and administration schedules of E and P in the treatment of SCLC, the result indicated that the bolus administration of EP with E following P for the first two cycles of chemotherapy was the most effective regimen.

Our study has potential limitations. The analysis is based on published group data rather than individual patient data (IPD), where IPD meta-analyses have been described as the gold standard of systematic review. However, this approach is not always practical. Our results were based on observational studies and were therefore subject to the potential biases inherent in such studies.

Although multiple RCT have been performed between 1980 and 2006 involving 10 407 patients with 116 chemotherapy arms, the survival of patients with extensive disease-SCLC enrolled in phase III trials has not improved significantly over this time, suggesting the need for a breakthrough, such as the discovery of novel molecular target drugs. A 2009 study had shown that the addition of bevacizumab to EP in patients with ED-SCLC results in improved PFS and OS relative to historical controls who received this chemotherapy regimen without bevacizumab. This regimen appears to be well tolerated and has minimal increase in toxicities compared with chemotherapy alone. Everolimus is an orally available rapamycin analogue with antitumour activity. Single-agent everolimus and in combination with other anticancer agents have shown efficacy in cancer cell lines and xenograft non-SCLC (NSCLC) models, as well as in phase I studies. Everolimus monotherapy and in combination with chemotherapy agents has also been assessed in phase II trial involving patients with refractory advanced NSCLC, showing promising activity.

Conclusion
This study concludes that little progress has been made in the chemotherapy of extensive small-cell carcinoma of the lung. The search for new drugs remains a priority. Meanwhile, cost-effectiveness analyses taking into account people’s preferences are required to individualise optimal treatment in these patients.

References


48 Papadimitrakopoulou V, Blumenschein GR, Leigl NB, Benmouna J, Soria JC, Burris HA et al. A phase 1/2 study investigating the combination of RAD001 (R) (everolimus) and erlotinib (E) as 2nd and 3rd line therapy in patients (pts) with advanced non-small cell lung cancer (NSCLC) previously treated with chemotherapy (C): phase 1 results. *J Clin Oncol* 2008; 22: 20s (abstract 8051).
Prevalence of food allergy in Taiwan: a questionnaire-based survey

T.-C. Wu,1,3 T.-C. Tsai,3,4 C.-F. Huang,2,5 F.-Y. Chang,1 C.-C. Lin,7 I.-F. Huang,8 C.-H. Chu,9 B.-H. Lau,6 L. Wu,1 H.-J. Peng4 and R.-B. Tang1,3

1Children’s Medical Center and 2Department of Medical Research and Education, Taipei Veterans General Hospital, 3School of Medicine, National Yang-Ming University, 4Department of Medical Research and Education, National Yang-Ming University Hospital, 5Graduate Institute of Medical Sciences, National Defense Medical Center, 6Department of Pediatrics, Shin-Kong Memorial Hospital, Taipei, 7Department of Pediatrics, Taichung Veterans General Hospital, Taichung, 8Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, 9Department of Pediatrics, Hualien Tzu-Chi General Hospital, Hualien, Taiwan

Key words
food allergy, questionnaire survey, prevalence, food allergen, anaphylaxis.

Correspondence
Tzee-Chung Wu, Children’s Medical Center, Taipei Veterans General Hospital, 201, Sec. 2, Shih-Pai Road, Taipei 11217, Taiwan. Email: tczwu@vghtpe.gov.tw

Received 15 July 2011; accepted 19 March 2012.

Abstract

Aim: Food allergy is common in children and adults, and could be potentially fatal in minor groups. It is important for physicians to identify the prevalence of food allergies and to recognise common food allergens to make precise diagnosis and choose correct therapeutic approaches.

Methods: We used a nationwide, cross-sectional, random questionnaire-based survey to estimate the self-reported and expert-screened prevalence of food allergies and to identify the common food allergens in Taiwan. In this study, the perceptional diagnosis of food allergies was screened by physicians according to descriptions of convincing symptoms and medical recordings; in the meantime, non-allergic adverse reactions to foods, including food intolerance or food avoidance, were clarified.

Results: A total of 30 018 individuals who met the inclusion criteria was evaluated, and 6.95% of them were diagnosed as victims of food allergies. The prevalence was 3.44% in children under 3 years of age, 7.65% in children aged 4–18 years and 6.40% in adults respectively. About 77.33% of the food allergy population had experienced recurrent allergic attacks. Systemic reactions happened about 4.89% in food allergies group. The most commonly reported food allergen in Taiwan is seafood, including shrimp, crab, fish and mollusc. In addition, mango, milk, peanuts and eggs were also important food allergens in the general population; while milk, shellfish, peanuts and eggs were common in children.

Conclusions: Less than 10% of the Taiwan population suffers from food allergy with different allergic symptoms to variable food allergens in different age groups.

Introduction

Food allergy encompasses a range of disorders caused by adverse immune responses to dietary antigens. It affects all age groups and is increasingly encountered in daily life, especially among children. It is similar to other atopic disorders, such as asthma, allergic rhinitis and atopic dermatitis.

The prevalence of food allergy has dramatically increased in recent years, but there are few longitudinal studies.1–6 Exposure to allergens may result in a broad spectrum of symptoms ranging from minor discomfort to cardiopulmonary compromise and potentially fatal episodes. Food allergy is recognised as a major problem in Western countries and is a leading cause of anaphylaxis treatment in emergency departments in a number of countries.7 Thus, the importance for clinicians to understand the prevalence of food allergies and recognise common food allergens in their own regions cannot be overemphasised. Reports on the prevalence of food allergies or adverse reactions to food in Asia are limited, and epidemiologic studies on food allergies in the general population or among children are very few in Taiwan.

The aim of this study was to assess the prevalence of self-reported and expert-screened food allergy in an unselected population of children and adults in Taiwan.

Funding: This study was supported in part by grants (DOH Grants 94-stu-02 and 95-stu-02) from the Department of Health, Executive Yuan, Taiwan.

Conflict of interest: None.
Common food allergens were also identified, and allergic symptoms in different age groups were classified.

**Patients and methods**

**Study design and population**

A nationwide, cross-sectional, random, questionnaire-based survey was performed from 1 April to 31 October 2004. Preschool children were recruited from six outpatient departments in northern, middle, southern and eastern Taiwan as they were brought for routine health examination. School-age children and adolescents were randomly enrolled from 35 schools selected from each stratum of Taiwan, which was designated according to particular ethnic and geographical characteristics of residents using the probabilities proportional to sizes method similar to the research design of the ‘Nutrition and Health Survey of Taiwan Elementary School Children (2001–2002)’. Adult subjects were also randomly selected from each stratum.

The six experts who participated in this study were experienced paediatricians from six medical centres located in the northern, middle, southern and eastern Taiwan and were experts in either gastroenterology or immunology. They reviewed all of the questionnaires, and cases with equivocal statements or vague descriptions were excluded. They also analysed the descriptions of symptoms and records of physicians’ evaluations to distinguish food allergy from non-immunologic adverse food reactions. The subjects’ medical records were thoroughly reviewed for data, such as the duration between intake and symptoms, and the amount of ingested food. Briefly, cases diagnosed by clinicians and confirmed by positive laboratory tests, including serum immunoglobulin E (IgE), eosinophil count, multiple-allergy simultaneous test/coated allergen particle test, skin prick test (SPT), food challenge test or tissue biopsy, were enrolled as definite cases. On the other hand, cases that tended to be diagnosed as food intolerance (i.e. lactose intolerance), food avoidance and reactions to food contaminants, additives, toxins or infections were excluded. If the symptoms occurred within minutes, the diagnosis was presumed to be food allergy on the basis of type I immediate hypersensitivity reaction. Non-allergic food hypersensitivity was usually characterised by a delayed reaction, occurring hours or even days after eating certain food. Allergic reactions did not depend on the amount of ingested food, whereas food intolerance worsened as more food was consumed.

The Institutional Review Committee of Taiwan’s Veterans General Hospital approved the study. All of the participants or their parents provided informed consent.

**Questionnaire**

A standard, anonymous questionnaire was designed to obtain personal history and general information, including feeding history, dietary habits (e.g. vegetarian) and coexisting atopic disorders. The self-administered questionnaire was given to each subject to answer. If a subject answered ‘Yes’ to the question ‘Has your child/have you ever had an allergic reaction to food?’, then the respondent moved on to the other questions related to specifically identifying the possible foods, clinical symptoms, types of treatments and laboratory results. A panel of common foods, including those previously published9,10 and additional food with local importance, was listed for assessment with multiple options. In cases of positive allergic reaction to food, detailed descriptions, including the age of the first attack, clinical manifestations, duration of symptoms, number of episodes of food allergy, medical assessment, including treatments, and allergy tests were all obtained.

**Statistical analysis**

Data management was performed using the SAS statistical software for Windows (SAS version 9.2; Biostatistics Task Force, Taipei Veterans General Hospital, Taipei, Taiwan). Significance level was set at $P < 0.05$ for all of the tests.

**Results**

**Overall results**

From the 38,926 questionnaires distributed, 30,280 (77.8%) were completed. After review and interpretation by the expert physicians, 262 ineligible cases were excluded. A total of 30,018 cases, including 14,899 males and 15,119 females (sex ratio M/F 0.99), was valid for further analysis. There were 813 children aged less than 3 years, 15,169 aged between 4–18 years and 14,036 aged more than 19 years.

Of the 30,018 cases, 2086 (6.9%) were confirmed by the experts to have a food allergy. The percentage of food allergy was 3.4%, 7.7% and 6.4%, respectively, in the different age groups. Of the food allergy groups, 77.3% experienced more than one episode of food allergy (Table 1).

**Types of allergic foods**

Food frequently reported in previous studies and in the literature9,10 was included in the questionnaire. Food items listed in Table 2 were the most common causes of
Food allergies in Taiwan. Milk was one of the most important food allergens in toddlers; 32.1% (9 in 28 sensitised children) of children younger than 3 years of age with a food allergy had a milk allergy. As age increased, the major food allergen shifted from milk to seafood, including shrimp and crab, and some exotic fruit. In addition to the listed food, ‘other’ types of food included orange, almond, corn and nuts.

Clinical presentations of food allergies

Based on the severity of food-associated adverse reactions, 95.1% of subjects suffered from mild irritating symptoms without life-threatening events (Table 3). However, about one in every 714 patients with food allergy might suffer from cardiovascular collapse, with high morbidity and mortality (Table 3).

In this study, seafood, especially shrimp and crab, is the most common cause of severe food allergic reactions, while egg, milk and peanut are less important (Fig. 1). Three cases had anaphylactic reactions, including cardiopulmonary collapse. Two of them were sensitised to shrimp, while the other had a peanut allergy.

Clinical presentations of mild food allergy were grouped into three categories: oro-gastrointestinal symptoms, rhino-respiratory symptoms and dermatologic symptoms. Table 4 shows the frequency of these symptoms in the different age groups. Even though the allergic reaction occurred after food was ingested orally, oro-gastrointestinal symptoms did not dominate.

Discussion

To date, this cross-sectional study is the first nationwide questionnaire survey in an unselected population to assess the prevalence of food allergy in Taiwan. This study not only has a large sample size but also has a high return rate. The lifetime self-reported and expert-screened prevalence is around 6.9% in this study, which is less than those of similar studies in other countries. In the 1990s, the self-reported food allergy prevalence in the United Kingdom, Holland and the United States was 14.7%, 12.4% and 16.6% respectively.11–13 The Woods et al.’s study in 2001 that analysed incidences across

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. responses</th>
<th>Prevalence of food allergy</th>
<th>Prevalence of recurrent food allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>&lt;3</td>
<td>813</td>
<td>28</td>
<td>3.4</td>
</tr>
<tr>
<td>4–18</td>
<td>15 169</td>
<td>1160</td>
<td>7.7</td>
</tr>
<tr>
<td>&gt;19</td>
<td>14 036</td>
<td>898</td>
<td>6.4</td>
</tr>
<tr>
<td>Total</td>
<td>30 018</td>
<td>2086</td>
<td>6.9</td>
</tr>
</tbody>
</table>

 Clinical presentations of food allergies were grouped into three categories: oro-gastrointestinal symptoms, rhino-respiratory symptoms and dermatologic symptoms. Table 4 shows the frequency of these symptoms in the different age groups. Even though the allergic reaction occurred after food was ingested orally, oro-gastrointestinal symptoms did not dominate.

Table 2 Pattern of food allergens reported with allergic reactions in different age groups

<table>
<thead>
<tr>
<th>Food</th>
<th>No. sensitised cases</th>
<th>&lt;3 years old</th>
<th>4–18 years old</th>
<th>&gt;19 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrimp</td>
<td>1076 (51.6%)</td>
<td>5</td>
<td>612</td>
<td>459</td>
</tr>
<tr>
<td>Crab</td>
<td>710 (34.0%)</td>
<td>3</td>
<td>389</td>
<td>318</td>
</tr>
<tr>
<td>Fish</td>
<td>396 (19.0%)</td>
<td>4</td>
<td>227</td>
<td>165</td>
</tr>
<tr>
<td>Mango</td>
<td>385 (18.5%)</td>
<td>1</td>
<td>214</td>
<td>170</td>
</tr>
<tr>
<td>Molluscs</td>
<td>384 (18.4%)</td>
<td>1</td>
<td>170</td>
<td>213</td>
</tr>
<tr>
<td>Milk</td>
<td>217 (10.4%)</td>
<td>9</td>
<td>141</td>
<td>67</td>
</tr>
<tr>
<td>Peanut</td>
<td>207 (9.9%)</td>
<td>3</td>
<td>136</td>
<td>68</td>
</tr>
<tr>
<td>Egg</td>
<td>125 (6.0%)</td>
<td>3</td>
<td>78</td>
<td>44</td>
</tr>
<tr>
<td>Soybean</td>
<td>59 (2.8%)</td>
<td>0</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>Kiwi fruit</td>
<td>57 (2.7%)</td>
<td>1</td>
<td>43</td>
<td>13</td>
</tr>
<tr>
<td>Others</td>
<td>1125 (53.9%)</td>
<td>8</td>
<td>649</td>
<td>468</td>
</tr>
<tr>
<td>Total patients</td>
<td>2086</td>
<td>28</td>
<td>1160</td>
<td>898</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Table 3 The intensity and frequency of symptoms and signs of food allergy

<table>
<thead>
<tr>
<th>Classification and local reactions</th>
<th>Clinical presentation</th>
<th>Number</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddening</td>
<td>Itching</td>
<td>1984</td>
<td>95.11%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Angioedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhino-conjunctivitis</td>
<td>Cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable throat</td>
<td>Nausea, vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Diarrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe symptoms</td>
<td>Wheezing</td>
<td>99</td>
<td>4.75%</td>
</tr>
<tr>
<td>Stridor</td>
<td>Dyspnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Tachycardia and</td>
<td>3</td>
<td>0.14%</td>
</tr>
<tr>
<td>hypotension</td>
<td>Cardiopulmonary collapse</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
several countries had an average incidence of 12.2%, ranging from the lowest, 4.6% in Spain, to the highest, 19.1% in Australia. It also reported that people experienced illness following ingestion of particular food, presumably due to food allergy or intolerance. A 2007 meta-analysis on food allergies in communities revealed a self-reported prevalence of 3–35%. The prevalence and incidence of food allergies also varies immensely according to the diagnostic criteria used. In Germany, Zuberbier et al. reported a population-based study with an incidence of self-reported adverse reactions to food ranging from 35% to 3.6% in the same groups using double-blind, placebo-controlled food challenge (DBPCFC). Other results all showed that self-perceived food allergy/intolerance is higher than the point prevalence, which can be detected by objective assessments, including SPT, IgE titre or DBPCFC. Although further tests were not performed in the present study, the prevalence of food allergies was still lower than those of other similar reports based on questionnaires in Western countries. This result may reflect the special characteristic of food allergy in Taiwan, or even in Asia. Some claim that cultural differences and the consumption of certain dietary types may contribute to the difference between countries. Food allergy in Asia may be quite unique due to the different cultures and eating habits, which may result in occurrence of unique food allergens. Moreover, the screening by physicians in the present study may contribute to the elimination of some equivocal responders, making the diagnosis more reliable and definite.

Food allergy is more common in children and is increasing. Twenty years ago, the prevalence rate in children aged less than 4 years estimated by a US study was 6%. Without significant differences, the prevalence was about 5–6% in children in the first 3 years of life in the United Kingdom between 2001 and 2002 by a cohort study. The self-reported prevalence in school-age children was 6.7% and 7.2% in France and the Netherlands respectively. A 2005 cross-sectional study through questionnaire survey in Thailand reported that 6.25% of children had prior food reactions. The prevalence of parent-reported adverse food reaction was 8.1% in Hong Kong preschool children, and about 10.9% of elementary school children experienced allergic symptoms to foods in a nationwide questionnaire survey in Korea. In the present study, 7.4% of children aged less than 18 years had experienced food allergy, which was similar to data of most Western countries.

The availability of various foodstuffs and change in dietary habits may play important roles in the increasing prevalence in Asian communities. Nevertheless, the results of questionnaire studies should be interpreted with caution. For example, as to the first question of the questionnaire ‘has your child or have you ever had an allergic reaction to food’, our study revealed that the adult group displayed a definitely lower prevalence than the younger aged groups (4–18 years old), while the cumulative prevalence used to relatively rise as age and exposure time increase. This phenomenon points to a typical recovery tendency of some food allergies, such as milk or egg allergies, which resolve with time.

Table 4 Clinical manifestations of mild and local reactions in food allergy and the rate among different age groups

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>&lt;3 years old</th>
<th>4–18 years old</th>
<th>&gt;19 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>62.5%</td>
<td>21.9%</td>
<td>35.9%</td>
</tr>
<tr>
<td>Rhino-respiratory</td>
<td>12.5%</td>
<td>66.8%</td>
<td>44%</td>
</tr>
<tr>
<td>Oro-gastrointestinal</td>
<td>25%</td>
<td>11.3%</td>
<td>20.1%</td>
</tr>
</tbody>
</table>
Meanwhile, the effect of generational difference also complicate with this phenomenon. That is, younger patients have higher risk of morbidity from food allergy because modern-day children are exposed earlier to various exotic foods. Some studies indeed disclosed that the prevalence of food allergy is known to be lower in adults than children, implying that the prevalence of food allergy in children is increasing during these decades.\(^\text{29,30}\)

According to a meta-analysis in 2007, the self-reported prevalence rate of food allergy varies from 1.2–17% for milk, 0.2–7% for egg, 0–2% for peanut and fish, 0–10% for shellfish and 3–35% for other foods.\(^\text{1}\) Shellfish, which was reportedly a less common food allergen than egg, milk and peanut a decade ago in Asia, recently became a major sensitising food source in the region.\(^\text{25}\) The present study confirms this; our data reveal that the most common food allergen is seafood, including shrimp, crab, mollusc and fish. This may be due to the large consumption of seafood in Taiwan, which is a sea island.

In paediatric groups, cow’s milk and eggs are reported to be the most common causes of allergic reactions in younger children, and seafood, particularly shrimp, in older children. This is reported in Thailand,\(^\text{21}\) Singapore,\(^\text{22}\) and Hong Kong.\(^\text{27}\) The spectrum of food allergens in this Asian study is a little different from the prevalent food among white people. For example, tomatoes and hen’s eggs are the most common encountered allergens in a study in Turkey, while chocolate, apple and hazelnut are the prominent foods reported as ‘ill or trouble’ in some European countries.\(^\text{14,16}\) There are some distinctive food allergens in certain areas. Mango, a South-East Asian fruit, is the fourth most common food allergen in Taiwan in this study, while sesame is quite common in countries in the Middle East.\(^\text{28}\) It can be concluded that food allergens are influenced by dietary habits, which are usually influenced by geographic factors and living environment.

In the general population, allergic rhinitis is the most common self-reported allergic symptom, with 23.4% lifetime prevalence, followed by urticaria and allergic asthma with a total of 9.4% lifetime prevalence.\(^\text{31}\) The present study discloses that the common symptoms of food allergic reactions are rhino-respiratory symptoms and skin manifestations, with prevalence of 58.6% and 27% respectively. In younger children, the most common manifestation is urticaria. As they grow older, rhino-respiratory symptoms become more prominent. Oral-gastrointestinal symptoms are relatively less important in this study, although foods are ingested orally and contact the gastrointestinal mucosa.

Anaphylactic shock, the most severe complication of food allergy, accounts for 0.14% of allergic reactions in this survey, similar to the 0.19% in Young et al.’s study, wherein four anaphylaxis cases occurred in 2152 patients.\(^\text{11}\) Other studies reveal higher incidences of anaphylactic shock due to food in the paediatric group, about 4.9% in France and 5.3% in Hong Kong. These studies conclude that anaphylactic shock caused by food allergy occurs more frequently in adults than in children,\(^\text{29–32}\) which is not corroborated by data in the present study.

**Conclusion**

The self-reported and expert-screened prevalence of food allergy in the general population of Taiwan is 6.9%. Shrimp, crab, fish, mango, mollusc and milk are the main types of food associated with adverse allergic reactions. Peanut or tree nut allergies are not as common in Taiwan as they are in Western countries. Although positive cases may be indicative of IgE-mediated food allergy, the true prevalence of food allergy should be further assessed by DBPCFC, which is considered the gold standard for allergy testing.

**References**

9. Eriksson NE, Möller C, Werner S, Magnusson J, Bengtsson U, Zohubas M. Self-reported food hypersensitivity in Sweden, Denmark, Estonia, Lithuania,
Food allergy in Taiwan

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Appendix I Survey questions
Does a ‘code stroke’ rapid access protocol decrease door-to-needle time for thrombolysis?

Y. J. Tai, L. Weir, P. Hand, S. Davis and B. Yan

Department of Neurology, Royal Melbourne Hospital, Melbourne, Victoria, Australia

Key words
IV-tPA, emergency, ischaemic stroke.

Correspondence
Bernard Yan, Department of Neurology, Royal Melbourne Hospital, Parkville, Vic. 3050, Australia.
Email: bernard.yan@mh.org.au

Received 31 August 2011; accepted 18 December 2011.

Abstract

Background: Timely administration of intravenous tissue plasminogen activator (IV-tPA) for acute ischaemic stroke is associated with better clinical outcomes. Therefore, a coordinated hospital system of acute clinical assessment and neuroimaging will likely avoid delays in IV-tPA administration.

Aim: In July 2007, we implemented a ‘code stroke’ rapid access protocol at the Royal Melbourne Hospital with the aim of achieving rapid stroke assessment and treatment. This study investigates the quality of our ‘code stroke’ protocol and its impact on door-to-needle time and IV-tPA usage.

Methods: We included patients thrombolysed with IV-tPA from January 2003 to June 2007 (pre-code stroke era) and patients thrombolysed from July 2007 to December 2010 (code stroke era). Data collected were demographics, time points (stroke symptom onset, presentation to emergency department, neuroimaging and thrombolysis) and clinical outcomes (modified Rankin Scale) at discharge, symptomatic, intracerebral haemorrhage and death during admission. We compared the door-to-needle time and usage of IV-tPA between the two eras.

Results: Patient data on 98 ‘pre-code stroke’ thrombolysed patients and 189 ‘code stroke’ thrombolysed patients were collected. The median age was 71 (60–79), 56% were males, and the median baseline National Institute of Health Stroke Scale score was 13 ± 6.3. There was an 18-min reduction in the median door-to-needle time (90 min in ‘pre-code stroke era’ vs 72 min in ‘code stroke era’, \(P < 0.001\)). The rate of IV-tPA usage increased from 3.9% in 2004 to 17.3% in 2010.

Conclusion: Our study showed that ‘code stroke’ rapid access protocol decreased door-to-needle time and possibly contributed to the increased IV-tPA usage.

Introduction

In the setting of acute ischaemic stroke, intravenous tissue plasminogen activator (IV-tPA) has been proven to improve clinical outcomes when administrated within 4.5 h of symptom onset.1–3 It has been established that there is a gradation of efficacy over this time. In a pooled analysis of several multicentre, randomised and controlled thrombolysis stroke studies, it was reported that the odds of a favourable outcome at 3 months increased as onset-to-treatment time decreased.4 The number needed to treat to achieve a favourable clinical outcome (defined by modified Rankin Scale (mRS) 0 or 1) when administered IV-tPA between 0 and 90 min, 91 and 180 min, and 181 and 270 min was 4.5, 9.0 and 14.1 respectively.5 Despite recognition of the benefits, wide promotion in guidelines and public health campaigns, IV-tPA usage remains disappointingly low with a reported 2–10% usage rate in Europe and North America.1

The diagnosis of ‘time-critical therapy’ such as stroke made in emergency departments has been reported to be delayed and less accurate in the absence of effective protocols. This results in uncertainty in decision-making, leading to reduced efficiency and increased system costs.3 With a time limit factor and risk of intracerebral haemorrhage (ICH) in the use of IV-tPA, rapid and accurate neurological assessment and recognition of stroke is vital. Code stroke is an integrated and efficient strategy carried out by a specialised team of emergency, radiology and neurology staff who conduct patient assessment, imaging, investigation and treatment from the time of presentation (‘door’) to emergency services to the time that IV-tPA can be instituted (‘needle’). Certain studies conducted in Australia and internationally have shown benefits of a safe and effective ‘code stroke’ protocol on reducing door-to-needle times, morbidity, mortality and increasing thrombolysis rates, with reported door-to-
needle times of 50–120 min. However, the impact of ‘code stroke’ on door-to-needle time has not been studied adequately.

Code stroke was implemented at the Royal Melbourne Hospital (RMH) in July 2007 and involves emergency triage, assessment by an emergency physician, ordering of investigations and prompt referral to the stroke team through switchboard to all members of the Code stroke team, each of whom possess a linked pager. This allows for quick referrals and rapid induction of the code stroke protocol by each member of the team. Prior to code stroke, referrals were slow and often erroneously directed to the neurology registrar rather than the stroke registrar resulting in significant delays. Upon arrival at the patient’s bedside, the stroke team performs neurological assessment using the National Institute of Health Stroke Scale (NIHSS) score, orders imaging review, carries out further investigations, reviews the diagnosis and assesses patient eligibility for thrombolysis.10 The protocol (see Fig. 1) is similar to a study done by University of San Diego with the exception of unmixed IV-tPA at the bedside pending further investigations and does not involve multicentre referrals as with de la Ossa et al.’s and Sattin et al.’s studies in Spain. The code stroke system aims to reduce delays in assessment and investigation of patients, thereby increasing rates of thrombolysis. We aimed to carry out a comprehensive qualitative analysis of the code stroke service at the RMH to determine if code stroke resulted in a reduction in door-to-needle time and door-to-computed tomography (CT) time, and increased the percentage of patients treated with thrombolysis.

**Methods**

**Patients**

We included all patients thrombolysed with IV-tPA from January 2003 to June 2007 (pre-code stroke era) and all

![Figure 1 Flowchart of patient presentation and code stroke protocol. CT, computed tomography; ECG, electrocardiogram; ED, emergency department; IV-tPA, intravenous tissue plasminogen activator; NIHSS, National Institute of Health Stroke Scale.](image-url)
patients thrombolysed from July 2007 to December 2010 (code stroke era). We excluded patients who were treated with intra-arterial tPA or mechanical clot retrieval. Patients with incomplete data were also excluded.

**Data collection**

Patient data were collected retrospectively. The clinical data recorded were demographics (age and gender), medical history and risk factors, including hypertension, atrial fibrillation, diabetes mellitus, smoking history, structural heart disease, ischaemic heart disease, dyslipidaemia, peripheral vascular disease, migraines, previous stroke, previous transient ischaemic attack and premorbid mRS score. Time points included stroke symptom onset, presentation to emergency department, clinical assessment, neuroimaging and initiation of thrombolysis. Stroke characteristics and outcomes recorded were stroke arterial territory location, baseline and 24-h NIHSS score, Oxfordshire Community Stroke Project classification, symptomatic ICH, duration of admission and discharge mRS score.

We determined incidence of ICH from follow-up CT scan and defined it as symptomatic if the patient had any associated neurological deterioration attributable to the presence of parenchymal haemorrhage by the treating neurologist. Neurological improvement was defined as an improvement of 4 points on NIHSS score, or a score of 0 or 1 at 24 h. NIHSS and mRS assessments were performed by fully accredited neurologists or neurology trainees.

**Statistics**

Statistical analyses were performed on SPSS program (SPSS, Chicago, IL, USA). Data was analysed using t-test or Mann–Whitney test as deemed appropriate. The impact of code stroke on clinical outcomes was tested through multiple logistic regression adjusting for baseline variables. A P-value of <0.05 was selected to indicate significance.

**Results**

During the pre-code stroke era, 96 patients received IV-tPA. During the code stroke era, 213 patients received IV-tPA. Of this number, 24 (11.3%) patients were excluded, as 21 had received intra-arterial interventions and the remaining 3 (1.4%) had missing data. The median age of all patients was 71, 56% of patients were males, and the median NIHSS score was 13.5–19

The baseline characteristics of patients in the code stroke era and pre-code stroke era were well matched (Table 1). The only observed difference between the two groups was a prior history of stroke (P = 0.01). The median pre-code stroke group onset-to-door time was 61.50 (interquartile range (IQR) 49.0–73.8) min, and the median code stroke onset-to-door time was 72.0 (IQR 56.0–111.5) min (P < 0.001). There was an 18-min (20%) absolute reduction in the median door-to-needle time (90.0 (IQR 77.3–111) min pre-code stroke vs 72.0 (IQR 50.5–93.5) min code stroke, P < 0.001) and a 19.5-min reduction (46.4%) in the median door-to-CT time (42.0 (IQR 29.0–56.0) min pre-code stroke vs 23.0 (IQR 16.0–39.0) min code stroke, P < 0.001) – refer to Figures 2 and 3. There was also an observed difference between the median CT-to-treatment time: 48.5 (IQR 32.8–67.3) min pre-code stroke versus 39.0 (IQR 25.0–62.0) min code stroke, P = 0.044 (Fig. 4). Overall, median onset-to-treatment time was 160 (IQR 133–175) min in the pre-code stroke group and 160 (IQR 128–195) min in the code stroke group (P = 0.339). Comparison of onset-to-door times between patients treated within 0–3 h and patients treated within 3–4.5 h of symptom onset yielded a 67-min difference (133.75 min (onset-to-treatment time 3–4.5 h) vs 65.9 min (onset-to-treatment time 0–3 h), P = 0.0001) (Fig. 5).

Multiple logistic regression revealed patients who presented during working hours (WH) (P = 0.001) had a higher NIHSS score (P = 0.048), history of atrial fibrillation (P = 0.02) and dyslipidaemia (P = 0.014), and had a shorter door-to-needle time.

Patients who presented outside business hours had longer door-to-needle time, CT-to-treatment time and onset-to-treatment time in both groups. The median door-to-needle time in the WH group was 73.0 min versus 87.0 min in the non-WH (NWH) group, P = 0.001. Further comparisons drawn between code stroke and pre-code stroke groups revealed an observed 5.0 min median CT-to-treatment time reduction (49.6 min WH vs 54.6 min NWH, P = 0.045) and 14.8 min median door-to-needle time reduction (85.3 min WH vs 100.1 min NWH, P = 0.013) during the pre-code stroke era. Code stroke era yielded similar results with an observed 4.0 min median CT-to-treatment time reduction (45.2 min WH vs 49.2 min NWH, P = 0.109) and 11.4 min median door-to-needle time reduction (69.2 min WH vs 80.6 min NWH, P = 0.013; Fig. 6). The median CT-to-treatment time in the WH group was 36 min versus 46 min in the NWH group, P = 0.005. The median onset-to-treatment time in the WH group was 150 min versus 167 min in the NWH group, P = 0.003.

A difference in neurological improvement was observed between the groups with 32% in pre-code stroke group and 47% in code stroke group (P = 0.021). Overall, average symptomatic ICH was 7%, with a
reported 5% in the pre-code stroke group and 7% in code stroke group \((P = 0.483)\), and the proportion of death was 13% in both groups. There was no noted difference in the median duration of admission between the groups \((13 \pm 19 \text{ days vs } 11 \pm 17 \text{ days}, P = 0.348)\) nor was there a difference in discharge mRS with patients with a mRS score of less than 2 in the pre-code stroke group reported to be 68% and code stroke group 74% \((P = 0.303)\).
IV-tPA usage of all ischaemic stroke patients from year to year was 3.9% in 2004, 6.6% in 2005, 8.2% in 2006, 9.0% in 2007, 12.2% in 2008, 15.6% in 2009 and 17.3% in 2010. IV-tPA usage for 2003 were not reported, as data on all ischaemic patients were not available (Fig. 7).

Discussion

Our analysis shows that an implemented code stroke system was associated with a 20% relative reduction in door-to-needle time, 18% relative reduction in door-to-CT time, and an increase in IV-tPA usage from 3.9% to 17.3% while maintaining a low proportion of death. The median door-to-needle time of 72 min is lower than the 85 min reported in the Canadian Alteplase of Stroke Effectiveness Study (CASES) but longer than the recommended 60 min by National Institute of Neurological Disorders and Stroke (NINDS). This discrepancy could be attributable to confounding factors relating to levels of staff experiences, as the role of the stroke nurse was undertaken by the same
The median onset-to-treatment time of 160 min is similar to CASES reported 155 min, but within NINDS recommended 180 min. The observed increase in onset-to-door time and onset-to-treatment time after implementation of code stroke is supported by our findings that patients treated within 3 h of symptom onset during code stroke have shorter onset-to-door times than patients who were treated 3–4.5 h of symptom onset. It can also be accounted for by the alteration of onset-to-treatment time limit from 3 to 4.5 h in December 2008 after studies showed benefits of thrombolytic therapy between 3 and 4.5 h.

**Figure 5** Working hours versus non-working hours.

**Figure 6** Comparison of onset-to-door time with onset-to-treatment time, 0–3 h versus 3–4.5 h. IQR, interquartile range.
A difference in mean door-to-needle time, CT-to-treatment time and onset-to-treatment time was observed between patients who present during WH or NWH, with patients who present within WH more likely to receive treatment in a shorter period of time (Fig. 5, Table 2). The ‘weekend effect’ has been investigated with no consistent findings regarding the influence of business hours on thrombolysis rates. Some studies have reported a higher mortality rate for ischaemic stroke patients admitted on weekends and have attributed it to lower staffing levels and lower staff experiences. A lack of staff and experience could be a possible explanation for an increase in door-to-needle time observed during NWH. This is supported by a study that reported longer CT scan times for stroke patients who present to emergency on evenings and weekends. More research is needed to identify the factors underlying the correlation we found between business hours and door-to-needle times. One possible reason for the lengthened door-to-needle time observed during NWH could be due to a longer time required for the team to reach the emergency department after hours. In regards to the association of a higher NIHSS score, history of atrial fibrillation and dyslipidaemia with a shorter door-to-needle time, increased severity of stroke and positive cardiovascular risk could cause physicians to speed up processes, although we are unclear of the factors. The increase of IV-tPA usage, although partly attributable to the implementation of code stroke, could also be explained by other possible factors. The first being that our time frame window was increased from 3 to 4.5 h in 2008 that would have contributed to the increase in thrombolysis rates as more patients now qualify for treatment, especially those that arrive later, as indicated by the significant difference in median onset-to-door time between patients treated within 3 h and 3–4.5 h (Fig. 6). Second, it is important to acknowledge that given the long period of study from 2003–2008, there would have been confounding factors that would have had an influence on the code stroke protocol. Such factors, such as staff experience, infrastructure and system improvements, would all have had a positive or negative impact on the efficiency of the code stroke protocol.

Our proportions of symptomatic ICH of 7% is higher than the national average rate of 1% and worldwide Safe Implementation of Treatment in Stroke (SITS) rate of 1.7%. In both groups, we found our study’s proportion of death of 13% to be lower than the national rate of 18% and worldwide SITS rate of 14%. Our definition of symptomatic ICH differs from SITS definition of symptomatic ICH that is defined as a local or remote parenchymal haemorrhage type 2 on the imaging scan at 22–36 h after treatment combined with a neurological deterioration of 4 or more points on the NIHSS from baseline or from the lowest NIHSS score between baseline and 24 h or leading to death. This stricter definition could explain the lower incidence rate of ICH compared with our study, as our definition classifies more patients as symptomatic ICH as long as there was a neurological deterioration.

### Table 2  Multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.99–1.02</td>
<td>0.618</td>
</tr>
<tr>
<td>Gender</td>
<td>1.29</td>
<td>0.91</td>
<td>0.160</td>
</tr>
<tr>
<td>Pre-admission mRS</td>
<td>0.99</td>
<td>0.86–1.14</td>
<td>0.864</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.06</td>
<td>0.74–1.52</td>
<td>0.756</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.47</td>
<td>0.99–2.20</td>
<td>0.059</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.28</td>
<td>0.90–1.82</td>
<td>0.164</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.58</td>
<td>1.08–2.33</td>
<td>0.020</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>1.07</td>
<td>0.51–2.24</td>
<td>0.866</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1.02</td>
<td>0.70–1.48</td>
<td>0.914</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.67</td>
<td>0.68–4.11</td>
<td>0.266</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>0.66</td>
<td>0.47–0.92</td>
<td>0.014</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>0.74</td>
<td>0.47–1.17</td>
<td>0.197</td>
</tr>
<tr>
<td>Prior TIA</td>
<td>1.15</td>
<td>0.64–2.08</td>
<td>0.639</td>
</tr>
<tr>
<td>Working hours</td>
<td>1.69</td>
<td>1.23–2.33</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>0.998</td>
<td>0.995–1.00</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Adjusted for baseline variables: age, pre-admission mRS and baseline NIHSS.

---

Figure 7  Intravenous tissue plasminogen activator (IV-tPA) usage rates in all ischaemic strokes and projected usage by year. (–) Reported IV-tPA usage; (–) Projected IV-tPA usage without code stroke. *Projected values calculated using rate of IV-tPA usage increase from year-to-year basis using values from 2004 to 2007.
When comparing patient outcomes, despite a significant difference in early improvement in NIHSS score post-thrombolysis in the code stroke era, there was no difference in the discharge mRS score between the two eras. This could be attributed to a lack of reduction in the onset-to-treatment time in both code stroke and pre-code stroke eras as well as difference in categorising patients based on the NIHSS and mRS scale. Given that more patients were treated between the 3- and 4.5-h time frame during the code stroke era, this may offset any benefits of IV-tPA treatment administered within a shorter time even though IV-tPA has been proven beneficial up to 4.5 h.

There are a few limitations to our study. The retrospective nature of the study resulted in the exclusion of patients with missing data or patients who received other forms of thrombolytic therapy. These patients make up 11.3%. With such a small sample size, such exclusion may have impacted on the results. Given the long period of study from 2003 to 2010, there would have been changes to the infrastructure, staff experiences systems and protocols that may have confounded our results. Lastly, the 3-month mRS score is standard for measuring patient outcome, and in circumstances of data unavailability, we have used the discharge mRS score to determine patient outcome, as certain studies have shown that discharge mRS is associated with long-term survival as well.20

Our results have highlighted the importance of a code stroke protocol as well as a need for continual assessment, improvement of systems and seeking of avenues to allow for more patients to be thrombolysed safely.

In a study by Sattin et al., unmixed IV-tPA is brought to the bedside pending further investigation and is mixed and administered immediately when the patient meets all criteria.11 This process, not currently part of the standard protocol, is done ad hoc at RMH and therefore could be implemented in the current code stroke system. General feedback as well as studies in the literature have highlighted the benefits of prehospital notification and its importance as a strategy for increasing IV-tPA rates and door-to-needle times.21 This system is currently under development and should be part of emergency and acute management of ischaemic stroke patients.

We found that ‘code stroke’ rapid access protocol was associated with a decreased door-to-needle time and possibly contributed to increase IV-tPA usage. However, further studies of system protocols with emphasis on minimising time delays to treatment are warranted.

References
16 Jauss M, Schutz HJ, Tanislav C, Misselwitz B, Rosenow F. Effect of daytime, weekday and year of admission...
Obesity does not affect sodium picosulphate bowel preparation


Department of Gastroenterology, Campbelltown Hospital, and University of Western Sydney, Sydney, New South Wales, Australia

Key words
Obesity, sodium picosulphate, bowel preparation, colonoscopy.

Abstract

Background: A previous study utilising oral polyethylene-glycol by Borg et al. concluded that obesity is an independent predictor of inadequate bowel preparation at colonoscopy.

Aim: To compare bowel preparation quality between obese and non-obese individuals as assessed by Boston bowel preparation scale (BBPS) after using sodium picosulphate.

Methods: Prospective recruitment of patients at a day surgical unit in a New South Wales academic hospital. Bowel preparation was with Picoprep in all patients. Body Mass Index and epidemiological details were collected. Bowel preparation efficacy was assessed using the Boston Bowel Preparation Score.

Results: One hundred and four patients were enrolled prospectively. Five (4.8%) were excluded owing to poor mental capacity. Sixty-three (64%) were non-obese, and 36 (36%) were obese. Fifty-seven (90%) non-obese and 32 (89%) obese patients had good bowel preparation. There was no statistical difference for sodium picosulphate bowel preparation between obese and non-obese individuals ($P > 0.99$) using Fisher’s exact probability tests. The BBPS score in the left colon predicted the overall BBPS score in all patients ($P < 0.001$). Three of 99 patients (3%) did not tolerate sodium picosulphate, with nausea being the most common side-effect.

Limitations: Non-randomised study

Conclusions: There was no difference in bowel preparation quality between obese and non-obese patients using a low-volume bowel preparation (sodium picosulphate) and without dose modification of the bowel preparation. Sodium picosulphate was a well-tolerated and an effective bowel preparation for obese individuals. With an increasing incidence of obesity and expanding colonoscopic indications within Australia and other Western countries from government-sponsored programs, it is paramount that procedural quality not be compromised in the obese patient.
Introduction

Successful visualisation of colonic mucosa depends on a good bowel preparation, the position of lesions in respect to colonic folds (distal vs proximal), the skill of the endoscopist and colonoscopic withdrawal time. Good bowel preparations are essential in colonoscopy for the identification and therapy of relevant abnormalities with emphasis upon pre-cancerous and cancerous lesions. Trautwein et al. determined that an imperfect bowel preparation can prolong procedure time, increase the chance of an aborted examination and increase costs by 22%. In response to the earlier, professional bodies such as the American Society of Gastrointestinal Endoscopy (ASGE) produced a consensus statement on multiple bowel preparation options. Although multiple commercial preparations exist, none fulfils all the goals of a perfect bowel preparation, as described by the Society of American Gastrointestinal and Endoscopic Surgeons in 2006.

Obesity remains a significant public health concern in Australia and other parts of the developed world. In gastroenterology, obesity is associated with an increased incidence of diverticular disease, gastroesophageal reflux disease, colonic polyps and colonic cancer. The National Institutes of Health – American Association for Retired Persons Diet and Health study on 307,708 men and 209,436 women over 4.5 years had shown a strong positive correlation of body mass index (BMI) with colon cancers. While several studies had noted an inverse relationship between colo-rectal cancer screening compliance and obesity (odds ratio 0.75; 95% confidence interval 0.62–0.91), conclusive evidence of the effects of obesity on preparation quality remains elusive. Examples of conflicting evidence include Borg et al. who described obesity as an independent predictor of inadequate bowel preparation and Ness et al. who found no impact of obesity on bowel cleanliness.

Early studies looking to quantify bowel preparation cleanliness utilised a subjective visual grading scale (Aronchick scale) as described in Table 1. Although recommended by the American College of Gastroenterology Taskforce on Quality in Endoscopy, a lack of standardised definitions that were open to subjective interpretation had limited its utility in research. Addressing these deficiencies, the Boston bowel preparation scale (BBPS) has minimal interobserver variability and scores the right, transverse and left colon separately (Table 2), with a composite final score of >5 defining an inadequate bowel preparation.

Funding: None.
Conflict of interest: None.

<table>
<thead>
<tr>
<th>BBPS score</th>
<th>Score description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Unprepared colon segment with mucosa not seen because of solid stool that cannot be cleared</td>
</tr>
<tr>
<td>1</td>
<td>Portion of mucosa of the colon segment seen, but other areas of the colon segment are not well seen because of staining, residual stool and/or opaque liquid</td>
</tr>
<tr>
<td>2</td>
<td>Minor amount of residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment is seen well</td>
</tr>
<tr>
<td>3</td>
<td>Entire mucosa of colon segment seen well, with no residual staining, small fragments of stool or opaque liquid</td>
</tr>
</tbody>
</table>

Picoprep is a mixture of cathartic agents (citric acid and magnesium oxide) and a low volume picosulphate cleansing solution in the form of sodium picosulphate. The efficacy of picosulphate cleansing has been shown to be non-inferior to phospho-soda-buffered saline (Fleet) with superior taste and tolerability compared with Fleet.

The current study aims to determine whether a difference exists in bowel preparation quality as assessed by the BBPS between obese and non-obese individuals with a low-volume bowel preparation (sodium picosulphate – Picoprep).

Methods

Ethics approval for the study was obtained from the Sydney South West Area Health Service Human Ethics Committee (QA2010/19).

Prospective recruitment occurred over 3 months (March 2010 to May 2010) from outpatient colonoscopies performed in the day surgery unit at Campbelltown Hospital (CTH). All colonoscopies were performed by gastroenterologists.

Picoprep (Australian Pharmaceutical Industries, Camelia, Australia) was used for all bowel preparations as per three-sachet (30 mg picosulphate) protocol at CTH.

Weight and height data were identified at admission to CTH, and BMI was calculated (BMI = weight(kg)/
height (m$^2$). Obesity was defined as a BMI $\geq$ 30 kg/m$^2$ in Caucasians$^{13}$ and $\geq$ 27.5 kg/m$^2$ in Asians.$^{16}$ Patient characteristics, time of procedure (morning vs afternoon), history of diabetes mellitus, cardiovascular comorbidities, medications (specifically narcotics, antidepressants, anti-hypertensive agents, proton pump inhibitors), mental capacity, diverticular disease and a history of inflammatory bowel disease were recorded. BBPS scores were obtained for the right colon, transverse colon and left colon. Ancillary history of tolerability, effectiveness and compliance with Picoprep was obtained pre-anaesthesia. Bowel preparation efficacy was graded during colonoscopy with the BBPS for the right, transverse and left colon. All three gastroenterologists used the BBPS. Scores were agreed on between the gastroenterology advanced trainee and the supervising consultant gastroenterologist for the procedure. A composite score was derived from adding the three scores. Poor bowel preparation was defined as a BBPS score $>5$. Patients with poor mental capacity from a history of dementia or intellectual impairment were excluded from analyses on the basis that bowel preparation compliance would be of issue. Polyp detection was recorded. Polyp detection rates were calculated and used as a surrogate for colonoscopy quality.$^{17}$

The measured primary outcome was a BBPS score relating to bowel preparation effectiveness, with secondary outcomes of tolerability and polyp detection. Time of procedure (morning vs afternoon) was investigated with respect to bowel preparation quality. Because of the observational nature of this study, blinding was not possible.

Statistical analyses were performed on Statistical Package for the Social Sciences (SPSS) for Windows version 12 (SPSS, Inc., Chicago, IL, USA). Fisher’s exact probability tests were performed on continuous and categorical variables. A $P$ value of $>0.05$ was considered significant.

### Results

Within 3 months, 104 patients were recruited, with five (4.8%) excluded from analyses for reasons of poor mental capacity (intellectual disability and dementia). The median age of the 99 patients was 51.5 years old (range 16–77 years old) with 60.6% female and 93% Caucasian (Table 3).

Thirty-six per cent of recruited patients met the definition for obesity in this study. The composite BBPS was $\geq 5$ in 89% of patients with a colonoscopy completion rate of 97%. Of the 62 non-obese patients, 57% (90%) had a good bowel preparation, and of the 37 obese patients, 32 (89%) had a good preparation. There were no statistical differences for Picoprep bowel preparation between obese and non-obese patients ($P > 0.99$) using Fisher’s exact probability tests, with further data in Table 4. There were no correlations seen between BBPS scores and BMI, as seen in Figure 1.

Colon polyps were identified in 37.4% of all patients, with an adenoma rate of 26.3% (26.7% female; 25.5% male). A past history of intra-abdominal surgery did not affect preparation quality ($P > 0.99$). A good bowel preparation in the left colon predicted a good bowel preparation in the whole colon ($P < 0.01$). Although the presence of diabetes suggested a difference between BBPS scores

<table>
<thead>
<tr>
<th>Table 3 Population characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
</tr>
<tr>
<td>Median age (years)</td>
</tr>
<tr>
<td>Female/male</td>
</tr>
<tr>
<td>Caucasians (%)</td>
</tr>
<tr>
<td>Comorbidities (%) Cardiovascular risk factors</td>
</tr>
<tr>
<td>Diabetes mellitus (Type 1 and 2)</td>
</tr>
<tr>
<td>Diverticular disease</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Mean BMI (kg/m$^2$)</td>
</tr>
<tr>
<td>Percentage non-obese (%)</td>
</tr>
<tr>
<td>Good bowel preparation (BBPS = 5) (%)</td>
</tr>
<tr>
<td>Morning/afternoon procedure (%)</td>
</tr>
<tr>
<td>Polyp detection rate (%)</td>
</tr>
<tr>
<td>Adenoma rate</td>
</tr>
<tr>
<td>Previous abdominal surgery (%)</td>
</tr>
</tbody>
</table>

BBPS, Boston bowel preparation scale; BMI, body mass index.

<table>
<thead>
<tr>
<th>Table 4 Primary and secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Obese vs non-obese</td>
</tr>
<tr>
<td>Number of obese (female vs male)</td>
</tr>
<tr>
<td>Number of non-obese (female vs male)</td>
</tr>
<tr>
<td>Diverticular disease (obese vs non-obese)</td>
</tr>
<tr>
<td>Inflammatory bowel disease (obese vs non-obese)</td>
</tr>
<tr>
<td>Previous abdominal surgery</td>
</tr>
<tr>
<td>Patients with polyps found (female vs male)</td>
</tr>
<tr>
<td>Patients with adenomas found (female vs male)</td>
</tr>
<tr>
<td>Females with adenomas (obese vs non-obese)</td>
</tr>
<tr>
<td>Males with adenomas (obese vs non-obese)</td>
</tr>
<tr>
<td>Females with hyperplastic polyps (obese vs non-obese)</td>
</tr>
<tr>
<td>Males with hyperplastic polyps (obese vs non-obese)</td>
</tr>
<tr>
<td>Medication use (B-blockers, anticholinergics, antidepressants, anti-emetics, constipation medications)</td>
</tr>
<tr>
<td>Time of day of procedure (morning vs afternoon)</td>
</tr>
<tr>
<td>Obese</td>
</tr>
<tr>
<td>Non-obese</td>
</tr>
</tbody>
</table>

— , not significant.
(6 vs 7) \( (P = 0.013) \), it did not affect the overall effectiveness of bowel preparation. Opinions on bowel preparation effectiveness by the patient were not a reliable indicator of bowel preparation cleanliness \( (P > 0.99) \) (Table 3).

This study was underpowered to analyse if diverticular disease \( (P = 0.28) \) or inflammatory bowel disease \( (P = 0.42) \) predicted a poor bowel preparation. Medication effects (narcotics, antidepressants, antihypertensive agents, proton pump inhibitors) on bowel preparation quality were insignificant \( (P = 0.72) \), as was the time of day of procedure (morning vs afternoon) \( (P = 0.32) \).

Ninety-seven per cent of patients tolerated Picoprep. Nausea was the most common side-effect. There was no difference in Picoprep tolerability between obese and non-obese groups.

**Discussion**

In this prospective study, we demonstrated that BMIs \( \geq 30 \) in Caucasians and \( \geq 27.5 \) in Asians were not independent predictors of inadequate bowel preparation with sodium picosulphate. A good bowel preparation in the left colon predicted a good preparation in the whole colon, and a past history of abdominal surgery did not affect bowel preparation quality. The study of Borg *et al.* \(^8\) was important in suggesting that clinicians might not be performing colorectal cancer screening as effectively as they could for a higher risk population group (obese patients); our results differ and reassure that excellent colonoscopy viewing can be achieved with a standard picosulphate preparation in obese as well as non-obese individuals.

The strengths of this study include its prospective design with the use of a highly reproducible bowel preparation scoring tool between gastroenterologists with scoring performed by a small group of three consultant gastroenterologists adequately trained in the use of the BBPS prior to subject recruitment. Comparatively, Borg *et al.* (the only other significant study in this area) was conducted retrospectively with a significant recall bias where the quality of bowel preparation was extracted from a descriptive procedural report using the Aronchick scale. As recognised by Borg *et al.*, the descriptive use of the Aronchick scoring system in retrospective records with procedures done by 26 different gastroenterologists had meant that interobserver variability was a significant confounding factor with unclear, subjective interpretations of what constitutes an ‘adequate preparation’.

Inherent flaws within a retrospective data set also challenged a definitive conclusion of an association between a high BMI and poor bowel preparation given confounders of compliance, socioeconomic status and education level. \(^7\) While Borg BB *et al.* had looked at several different bowel preparation options in their study (a significant confounding factor), the current study looked at the adequacy of bowel preparation with one bowel preparation product only – Picoprep thus reducing the influence of compliance on study conclusions. Previous studies had shown that 5–15% of patients do not complete their prescribed preparation because of poor palatability and/or the large volume needed compared with Picoprep \(^18,19\). It is a strength of the current study that the best tolerated bowel preparation has been studied to determine obesity’s influence on bowel preparation.

Study weaknesses include the lack of data on diabetic complications and of diabetic control. The study was underpowered to analyse for the effects of diverticular disease, inflammatory bowel disease, medication use or time of procedure on the adequacy of bowel preparation. The study was observational and lacked blinding; therefore, patient physical size could be observed with BMI estimated preprocedure potentially introducing bias into the study. However, the use of the BBPS in the study design as an objective measure does mitigate any significant impact on our study. The prevalence of obesity in the Macarthur region of New South Wales in this study of colonoscopy in adults was also higher than the 2008 national average of 24.8\%\(^20,21\), which could hint upon different ethnic and lifestyle factors that could not be excluded in our study as potential confounding factors.

ASGE quality guidelines on minimum adenoma detection rates suggest a minimum adenoma pickup rate of 15\% in females and 25\% in males. Given that colonoscopies were performed by the advanced trainee in gastroenterology closely supervised at all times by
experienced consultant gastroenterologists, it was likely that 25.5% represented the true male adenomas prevalence and 26.7% the true female adenoma prevalence in the Macarthur region in Sydney, New South Wales indicating accurate colonoscopy results. The zero adenoma rate found in the obese male cohort can be attributed to a Type 2 error with this study not designed to prove an existing effect previously already well elucidated by other studies.5

These results show sodium picosulphate to be an excellent bowel preparation solution for obese patients with 3% of the obese study group failing bowel cleansing necessitating a repeat procedure and 89% of all patients achieving a good preparation where Picoprep failure rates are comparable with phospho-soda enemas in colonoscopy.14,18,19

Obesity has a significant impact on colonoscopies in Australia with 2005–2006 Medicare data estimating a total of 444 689 public and private colonoscopies done per year,22 of which approximately 110 000 (24.8%) procedures are in obese patients.20,21,22 This number is likely to be significantly higher now with an increasing population, the advent of the Australian National Bowel Cancer Screening Programme (NBCSP), and increased public awareness of bowel cancer screening. With the NBCSP currently funded for 1 million faecal occult blood testings or $34 million over 4 years, any reduction in procedural repeat rates secondary to poor bowel preparation as high as 20%23 can be of significant impact to the success of the former. The efficacy of sodium picosulphate on obese patients in the Macarthur region in New South Wales benefits bowel cancer colonoscopy screening programmes by demonstrating that a good colonoscopy preparation is readily achievable in obese patients as well as the nonobese population.

Future studies into bowel preparation in obese patients could compare high-volume and low-volume preparations with various dosing regimens.

**Conclusion**

There was no difference in bowel preparation quality between obese and non-obese patients using a lowvolume bowel preparation (sodium picosulphate). Sodium picosulphate was well tolerated and effective in obese patients with favourable implications on NBCSP in Australia and similar programs overseas. With an increasing incidence of obesity and expanding colonoscopic indications within Australia and other Western countries from government-sponsored programmes, it is paramount that procedural quality not be compromised in the obese patient.

**References**

16. Singapore Health Promotion Board. Revision of body mass index (BMI) cut
Introduction

Atherosclerosis and atherosclerosis-associated conditions, such as coronary heart disease and ischaemic cerebrovascular disease, are major causes of morbidity and mortality among middle aged and older adults in developed countries. Hyperlipidaemia and low levels of high density lipoprotein cholesterol (HDL-C) increase atherogenic risk. Multiple well-controlled clinical trials have...
documented the safety and efficacy of HMG-CoA reductase inhibitors (statins) in reducing fatal and non-fatal coronary heart disease events, strokes and overall mortality.6

Whilst clinical trials have demonstrated statins to be generally safe and well tolerated, there is emerging evidence that statins cause proximal muscle weakness with or without creatine kinase elevation.7–11 Little is known about the mechanism of statin-induced muscle toxicity. Several theories have been proposed suggesting that myopathy is caused by metabolic abnormalities.10,11 Flint et al. suggests that GTP-binding proteins’ depletion caused by inhibition of mevalonate participates in statin myotoxicity.12,13 Urso et al. found that statins plus exercise resulted in changes in gene expression for the ubiquitin proteasome pathway (UPP) whereas this did not occur in a control group or a statin without exercise group. UPP is responsible for protein transcription and degradation in skeletal muscle and if protein degradation is enhanced through this pathway, it may explain the mechanism underlying statin-related myotoxicity.14,15

Older adults have increased falls risk because of age-related muscle decline, impaired balance, co-morbidities, medication use and increasing frailty and it has been postulated that statins may exacerbate age-related muscle decline, potentially increasing falls risk.8,16–23

The evidence for an association between statin use and muscle weakness, however, is inconsistent. In a recent Tasmanian study, Scott et al. assessed percentage of lean muscle mass in arms and legs, isometric strength of quadriceps and hip extensors as well as falls risk in 774 statin and non-statin users and reported that statin users had a greater decline in strength, muscle quality and modest increases in fall risk scores. There were no significant differences between the type of statin used.24 Other smaller studies have suggested that people experience difficulty walking and rising from a chair between 3 and 12 months after commencing statin therapy25 and that proximal strength and other functional symptoms recover within 3 months of statin cessation.5,9,11

In contrast, other studies have found either small beneficial effects or no detrimental effects of statin use in older people. Agostini et al. found statin use to be associated with slightly improved performance in timed chair stands in a study of ambulatory, community-dwelling males (mean age 75 years).25 Similarly, McDermott et al. found elderly statin users with peripheral arterial disease performed better in the 6-min walk, walking velocity test and summary performance score than elderly non-statin users,26 and this improvement was sustained over time.27

In those without peripheral arterial disease, there was no difference in strength measures between statin and nonstatin users.26,27 Ashfield et al. found no association between statin use and grip strength in women and men aged 59–73 years.28

The conflicting evidence in relation to statin use and physical performance is possibly caused by inconsistencies in the types of functional tests used, sample sizes, co-morbidities and/or gender of participants.8,9,23,26 Further, most previous studies have included only a limited range of physical performance measures and none has examined the relationship between statin use and prospectively measured falls.

The aims of this study, therefore, were to investigate: (i) whether there are significant associations between statin use and muscle strength, balance and mobility and (ii) whether statin use increases the risk of falls in community-dwelling older people.

**Method**

**Participants**

Five hundred community-dwelling people aged 70 to 90 years participated in the prospective cohort study with a 1-year follow-up for falls. They were randomly recruited from a cohort of 1037 community-dwelling men and women living in eastern Sydney and participating in the first stage of the Sydney Memory and Ageing Study (January 2006 to October 2007).29

Exclusion criteria were severe neurological, cardiovascular or major musculoskeletal impairments (determined at a baseline physiological assessment) that precluded participants from walking 20 m without a walking aid, and cognitive impairment determined by a score of <24 on the Mini-Mental State Examination (MMSE). All participants provided informed consent, approved by the University of New South Wales Human Studies Ethics Committee (HREC #05224).

**Assessments**

At baseline, all participants underwent an extensive assessment of medical, physical and cognitive measures by trained research personnel.50

**Medical assessment**

A complete medical history was recorded, including the presence of medical conditions, medication use and falls history. Participants brought containers for all current medications to the assessment and research staff recorded all medications, including the type and prescribed dosage. Statins used by those in the survey included fluvastatin, pravastatin, rosuvastatin, simvastatin and atorvastatin. Length of statin use and dosage regimens for the different
statins were not used in this analysis and no differentiation was made between the types of statin used.

Physical assessment

The Physiological Profile Assessment (PPA)\(^{14}\) has been developed by the Falls and Balance Research Group at Neuroscience Research Australia, Sydney and uses an individual's physiological profile to estimate falls risk.\(^{31,32}\) A standardised fall risk score is obtained from data collected from five measures of sensorimotor function with validity and reliability established in previous studies: (i) visual contrast sensitivity was assessed using a lower limb-matching task. Participants were seated with their eyes closed and asked to align their lower limbs simultaneously on either side of a vertical acrylic sheet (60 × 60 × 1 cm) inscribed with a protractor and placed between the legs. Errors in alignment of the great toes were recorded in degrees. The average of five trials was recorded. (ii) Proprioception was measured using a light as stimulus and a finger press score out of two trials recorded. (iii) Quadriceps strength was measured isometrically in the dominant leg, while participants were seated with the hip and knee flexed to 90 degrees. Participants were required to pull against the strain gauge – with maximal force for 2–3 s with the best score out of two trials recorded. (iv) Simple reaction time was measured using a light as stimulus and a finger press as response. The average of 10 trials was recorded. (v) Postural sway was measured using a sway meter recording displacements of the body at the level of the pelvis, while participants stood on a foam rubber mat (40 × 40 × 7.5 cm) with eyes open. The distance in millimetres traversed by the pen attached to the sway meter in 30 s was recorded.\(^{31,32}\) The PPA validity and reliability has been evaluated in several studies and has been shown to predict those community-dwelling people who are at risk of multiple falls with 75% accuracy.\(^{31,35}\)

In addition, postural sway (area in mm\(^2\)) was also assessed on a firm base with eyes open using the same technique as in the PPA. The maximal balance range (MBR) tests (mm), adjusted for height, assessed how far participants could lean forwards and backwards from the ankles without moving the feet or bending the hips.\(^{31,32,34}\) The coordinated stability test, adjusted for height, assessed participants’ ability to adjust body position in a steady and coordinated way while placing them at or near the limits of their base of support.\(^{31,32,34}\) Gait was measured as the time (in seconds) needed to walk 3 m, turn and walk back at normal pace. The Timed Up and Go Test measured the time required for a person to rise from a chair, walk 3 m, turn, walk back and sit down.\(^{31-33}\) The Sit to Stand (in seconds) test assessed the time it took participants to rise as fast as possible from a 45-cm high chair five times with their arms folded across the chest.\(^{35-37}\)

Number of falls

A fall was defined as ‘an unexpected event in which the person comes to rest on the ground, floor or lower level’.\(^{32}\) The number of falls in the previous year was assessed at baseline. Fall frequency during the 1-year follow-up period was monitored with monthly falls diaries and follow-up telephone calls. Questionnaires were given to participants each month, seeking details on the number of falls in the past month, such as the location, cause and any physical injuries suffered, such as bruises, lacerations or fractures. This method for collection of falls data has been used by the investigators in previous studies and is recommended in best practice.\(^{38}\) Participants were classified as multiple fallers if they fell more than twice during the follow-up period.

Statistical analysis

Statistical analyses were performed using SPSS Statistics Version 17 for Windows (SPSS Inc, Chicago, USA). Data were explored for normal distribution and linearity. Variables with skewed distribution were transformed, after initial assessment of outliers, by logarithim (positive) or square root (negative) transformation prior to further analyses.\(^{39,40}\) Chi-squared tests were used to assess differences between statin and non-statin users on concomitant medications and to investigate the number of falls during the 12 month follow-up survey.

Differences in the strength, balance and mobility tests between statin and non-statin users were assessed using analyses of covariance while controlling for age and general health.

Results

Characteristics of sample

The mean age of participants was 77.9 years (standard deviation (SD) 4.6), and 270 (54%) were women. Of a possible nine system-related medical conditions, the sample had a mean of 3.1 (SD 1.5.) The most common co-morbidities were arthritis (55.3%), cardiovascular disease (34.8%) and type 2 diabetes (12.3%). Half the sample (n = 250 participants) were taking statin medications. There was no evidence of any differences in age, gender, height (gender specific) and body mass index (gender specific) between those taking and not taking statins associated with impaired balance
statins (Table 1), nor of a difference in gender proportions between the two groups. The non-statin group had a higher proportion of people in very good to excellent health ($P = 0.009$) than the statin group.

### Effect of statin use on measures of fall risk

Table 2 shows the mean scores for the strength, balance and mobility tests for the statin and non-statin users (Table 2). After controlling for age and health status, performance only in the MBR test was significantly inferior in the statin users. Results remained after using a Hochberg correction for multiple comparisons.

### Effect of statin use on falls during 12-month follow-up period

In all, 149 (30%) participants reported one or more falls in the previous year, and 214 (43%) reported one or more falls during the 1-year follow-up (six participants were lost during follow-up for falls). A Chi-squared test for independence (Table 1) indicated that the proportions of statin users and non-statin users who suffered multiple falls in the follow-up year were not significantly different, relative risk $= 0.75$ (0.48–1.18).

### Discussion

The current study could not confirm associations between use of statins and reduced muscle strength, postural sway and mobility. However our findings did suggest an association between statin use and dynamic leaning balance. Leaning balance is partly influenced by ankle flexibility and toe plantar flexor muscle strength. The possible myotoxic effect of statins on proximal skeletal muscle strength could potentially explain this relationship, however more research is warranted to understand the mechanisms.

Several studies have found a significant age-related decline in the ability of people to reach forward as far as possible without taking a step. The most commonly used test is the functional reach test developed by Duncan et al., which has been correlated with age, performance in activities of daily living and falls. Reduced dynamic balance is associated with reduced

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Statin†</th>
<th>Non-statin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>250</td>
<td>249</td>
<td></td>
</tr>
<tr>
<td>Gender, frequency (%)</td>
<td>121 (24.7%)</td>
<td>106 (21.7%)</td>
<td>0.42‡</td>
</tr>
<tr>
<td>Male</td>
<td>129 (26.4%)</td>
<td>133 (27.2%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>129 (26.4%)</td>
<td>133 (27.2%)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD) (years)</td>
<td>78 (4.47)</td>
<td>78 (4.59)</td>
<td>0.82</td>
</tr>
<tr>
<td>Males</td>
<td>78 (4.60)</td>
<td>77 (4.72)</td>
<td>0.36</td>
</tr>
<tr>
<td>Females</td>
<td>170 (9.66)</td>
<td>171 (6.74)</td>
<td>0.76</td>
</tr>
<tr>
<td>Female</td>
<td>156 (6.92)</td>
<td>159 (6.61)</td>
<td>0.61</td>
</tr>
<tr>
<td>Height, mean (SD) (cm)</td>
<td>282.22 (4.78)</td>
<td>274.3 (4.95)</td>
<td>0.31</td>
</tr>
<tr>
<td>Males</td>
<td>275.4 (4.21)</td>
<td>265.2 (4.78)</td>
<td>0.19</td>
</tr>
<tr>
<td>Females</td>
<td>125 (25.6%)</td>
<td>86 (17.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>Good</td>
<td>72 (14.8%)</td>
<td>90 (18.4%)</td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>15 (3.1%)</td>
<td>29 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>15 (3.1%)</td>
<td>29 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Number of falls during 12 month follow-up, frequency (%)</td>
<td>242 (100%)</td>
<td>244 (100%)</td>
<td></td>
</tr>
<tr>
<td>Non-faller ($\leq 1$)</td>
<td>201 (83.1%)</td>
<td>191 (78.3%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Multi faller ($\geq 2$ falls)</td>
<td>41 (16.9%)</td>
<td>53 (21.7%)</td>
<td></td>
</tr>
</tbody>
</table>

†Fluvastatin, pravastatin, rosuvastatin, simvastatin or atorvastatin.‡Yates continuity correction. SD, standard deviation.

### Table 2

<table>
<thead>
<tr>
<th>Function test</th>
<th>Non-statin users</th>
<th>Statin users</th>
<th>F</th>
<th>Significance (two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadriceps strength, kg</td>
<td>248 26.4 11.8</td>
<td>249 27.5 11.9</td>
<td>1.344</td>
<td>0.445†</td>
</tr>
<tr>
<td>Floor sway path, mm</td>
<td>244 77.0 39.3</td>
<td>245 81.1 45.4</td>
<td>0.526</td>
<td>0.468</td>
</tr>
<tr>
<td>Foam sway path, mm</td>
<td>240 185.0 94.6</td>
<td>239 182.1 94.9</td>
<td>0.083</td>
<td>0.773</td>
</tr>
<tr>
<td>Coordinated stability, errors</td>
<td>238 14.7 12.6</td>
<td>238 16.2 13.4</td>
<td>1.591</td>
<td>0.208</td>
</tr>
<tr>
<td>Maximum balance range, mm</td>
<td>239 153.0 59.6</td>
<td>243 141.8 51.1</td>
<td>5.744</td>
<td>0.017</td>
</tr>
<tr>
<td>PPA score, z-score</td>
<td>239 0.87 0.94</td>
<td>238 0.85 0.91</td>
<td>0.190</td>
<td>0.663</td>
</tr>
<tr>
<td>Timed up and go, s</td>
<td>230 9.9 3.4</td>
<td>228 9.6 2.5</td>
<td>2.427</td>
<td>0.120</td>
</tr>
<tr>
<td>Sit to stand, s</td>
<td>215 16.0 5.5</td>
<td>229 16.8 5.0</td>
<td>1.914</td>
<td>0.167</td>
</tr>
<tr>
<td>Gait speed, m/s</td>
<td>238 8.6 2.8</td>
<td>246 8.9 2.9</td>
<td>1.053</td>
<td>0.305</td>
</tr>
</tbody>
</table>

†Adjusted for gender. For the physiological profile assessment, sway, coordinated stability test, timed up and go, sit to stand and gait speed, high scores indicate impaired performance. For the quadriceps strength and maximum balance range, low scores indicate impaired performance (see Methods section for details of assessment tests). SD, standard deviation.
ability to correct displacements during movement as well as reduced gait speed and step length that can lead to increased fall risk. 46,47

As far as we are aware, this is the first study to examine the relationship between statin use and prospective falls. There was no indication that statin use increased the number of falls in a 12-month follow-up period. In fact, our findings show a trend indicating statin use may be protective for falls. It is possible that statins may adversely affect some factors associated with falls and ameliorate others. For example, the harmful effect of statins on leaning balance found here and muscle strength in others studies could lead to falls related to loss of balance and/or tripping. On the other hand, the cardioprotective effects of statins 46,47 could reduce falls caused by episodes of dizziness, syncope and/or drop attacks. A larger sample size is needed to determine whether statin use is related differently to different fall types.

The limitations of our study mainly relate to the constraints of the existing dataset, sample size and length of the study. It was necessary to investigate statins as a class as the number taking statins (n = 250) was considered too small for analysis of the five different statin medications used, dosage regimens and length of use. This was based on the assumption that the muscle complications are a class effect though some variability may be related to dose, duration or the individual drug. We also did not have data on participants’ compliance with statin use during the follow-up period. Previous small studies found myopathic weakness improved on cessation of statins, but symptoms returned within 2 weeks of recommencement of a statin 8,11 with patients complaining of muscle aches, decreased exercise tolerance or unsteadiness when walking or turning. 8,11

The multiple covariates in the analysis, due to comorbidities and medications, need to be taken into account when concluding that reduced performance is caused by statins alone. As mentioned, higher doses and long-term use may result in a stronger association between statins and muscle strength decline and therefore fall risk. A larger study with greater statistical power may be able to determine if this association exists. Lastly, we acknowledge that our findings are only generalisable to mainly healthy, community-dwelling adults aged between 70 and 90 years.

Conclusion

In a cohort of healthy, older people, the use of statins was not associated with impaired muscle strength, postural sway, reduced mobility or falls. However, statin users performed worse in an MBR test that may potentially increase fall risk. More research is needed to ascertain any (positive or negative) relationship between falls and statin use in older people.

Acknowledgements

The authors would like to thank the participants in this study who were drawn from the Memory and Ageing Study of the Brain and Ageing Program, School of Psychiatry, UNSW, funded by a NHMRC Program Grant (No. 350833) to Professors P. Sachdev, H. Brodaty and G. Andrews.

References

Awareness regarding venous thromboembolism among internal medicine practitioners in Mexico: a national cross-sectional study

A. Majluf-Cruz,1 G. Castro Martinez,3 M. A. Herrera Cornejo,3 G. Liceaga-Cravioto,3 F. Espinosa-Larrañaga2 and J. Garcia-Chavez4

1Medical Research Unit in Thrombosis, Hemostasis, and Atherogenesis, Mexican Institute of Social Security, 2Office for Health Education, Mexican Institute of Social Security, 3Mexican College of Internal Medicine, and 4Clinical Epidemiology Research Unit, UMAE La Raza, Mexican Institute of Social Security, Mexico City, Mexico.

Key words venous thromboembolism, internal medicine, deep vein thrombosis, pulmonary embolism, thromboprophylaxis.

Correspondence
Abraham Majluf-Cruz, Apartado Postal 12-1100, Mexico, D.F., Mexico.
Email: amajlufc@gmail.com

Received 9 April 2011; accepted 13 November 2011.

Abstract

Background: Venous thromboembolism (VTE) affects millions of patients worldwide and is responsible for thousands of hospitalisations annually.

Aims: To evaluate the awareness regarding VTE among Mexican internists.

Methods: We designed a cross-sectional survey using a questionnaire applied to Mexican internists mainly during academic meetings.

Results: We collected 1220 questionnaires. VTE was considered a potential complication for medical inpatients by 85% of the respondents, whereas 69% and 63%, respectively, considered pulmonary embolism to be a complication of deep vein thrombosis (DVT) and a cause of death. Awareness of some VTE risk factors was adequate, and 85% of those physicians surveyed routinely observed patients for these risk factors, although only 58% performed global risk stratification. Only 12% of the respondents considered length of hospital stay as a risk factor, and 58% assumed that the risk decreases after hospital discharge; 64% and 49% responded that the risk is higher, and VTE risk factors are more frequent in surgical versus medical inpatients respectively. VTE diagnosis was reported as easy or very easy for 59% of the respondents, but only 41% regarded phlebography as the gold standard for diagnosing DVT, although 85% of the respondents reported that D-dimer + Doppler ultrasound was an alternative. Pulmonary arteriography or helical computed tomography CT scan was the gold standard for diagnosing pulmonary embolism for 60% of the physicians, but 55% responded that electrocardiogram, arterial gasometry and chest X-ray are also useful.

Conclusions: Awareness regarding VTE risk factors and the degree of diagnostic skills among Mexican internal medicine specialists are low.

Introduction

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a major public health issue affecting thousands of patients worldwide and is responsible for a high number of hospitalisations annually.1-2 VTE implies a substantial risk of morbidity and mortality in patients hospitalised for acute medical or surgical conditions.3 For example, PE accounts for 5–10% of deaths in hospitalised patients, making VTE the most common preventable cause of in-hospital death.4-7 However, medical inpatients represent a more vulnerable subgroup with a higher clot burden than surgical patients because they exhibit a ~43% higher relative incidence of PE8 and experience proximal DVT (with and without calf extension) more often, and isolated DVT less often than surgical patients.9 Furthermore, hospitalised medical patients appear to be at higher risk for more extensive and aggressive clot burden than surgical patients. Although the impact of VTE in the surgical setting has been well studied, its prevalence among hospitalised medical inpatients has only recently been investigated in large clinical trials. Finally, in addition to the acute risk of mortality, VTE is associated with long-term complications that substantially contribute to patient morbidity and the economic burden of long-term management.10

The incidence of DVT among hospitalised patients has increased,11 mainly during and after hospitalisation for an
acute medical illness. A higher frequency of DVT has been demonstrated among hospitalised medical patients compared with surgical patients.9,12 However, thromboprophylaxis in medical patients is still largely underused.4,9,12–15 Several factors may explain why thromboprophylaxis is less used in hospitalised medical patients, but two factors deserve special attention: (i) low physician awareness of VTE risk4 and (ii) the fact that the assessment of VTE risk in surgical patients is easier than in medical patients due to the high number of risk factors affecting patients with medical conditions. Consequently, although thromboprophylaxis consensus guidelines for medical patients have been available for several years, these guidelines remain largely underused.13

Although the frequency of medical patients at risk for VTE is not very likely to vary significantly among countries, there are differences regarding use of thromboprophylaxis, 4,14 which have been attributed to the availability of guidelines, educational factors, reimbursement policies and national healthcare resources. However, it is possible that the most important factor may be the level of awareness among physicians. In Mexico, the majority of hospitalised patients are cared for directly or indirectly by internal medicine specialists. Therefore, our objective was to determine the degree of awareness regarding VTE among Mexican internists.

Methods

A national cross-sectional survey was designed using a survey instrument that was applied to graduate internists and internal medicine residents attending the National Internal Medicine Meeting and the International Meeting organised by the Colegio de Medicina Interna de Mexico, one of the largest internal medicine medical colleges in Latin America. Currently, this academic entity has a membership of 6608 physicians, including 1644 women (24.8%) and 4964 men (75.2%). Also, upon invitation, the instrument was answered and returned through mail or directly answered through email. Internists were invited to participate after a brief introduction explaining the purposes of the study. Participation was voluntary and anonymous. Demographical data were recorded from all participants.

Because there is no widely accepted guideline to carry out risk factor stratification for VTE in hospitalised medical patients, we explored the level of awareness of the risk factors for DVT according to published evidence and from clinical consensus specifically addressing these patients.4,8,12,15–29 Based on this body of evidence, an initial survey instrument was designed by the authors. It was then submitted to a validation process in which 10 academically recognised internists responded to the questionnaire in order to calibrate each item. The calibrated instrument was returned to the authors to be modified according to the suggestions and calibration scores. Once the instrument was modified, a second calibration round was required in order to optimise the instrument. The recalibrated instrument was finally returned to the authors who then performed the final adjustments. The instrument is comprised of 151 items, most offering five options to be answered according to a Likert scale ranging from ‘completely agree’ to ‘completely disagree’. The survey contained two parts. The first part was designed to assess the knowledge regarding the disease, risk factors and diagnosis. The second part was designed in order to explore the awareness with regard to thromboprophylaxis. This report addresses only the findings of the first part of the survey.

We compared awareness of atherothrombotic risk factors versus risk factors for VTE. We decided to explore the atherothrombotic problem because it represents a significant issue in internal medicine, and because it is associated with several related risk factors analogous to VTE.

This study had no external funding source.

Statistical analysis

Continuous data are expressed as means, and categorical data according to percentages. Differences between categorical variables were evaluated using a χ² test; P-value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences software (v.16; SPSS Inc., Chicago, IL, USA).

Results

We collected the survey instrument responded to by 1675 graduate internists and internal medicine residents from January 2010 to December 2010. After a first analysis, 445 instruments (27.2%) were excluded because they were inadequately completed. Hence, our final sample included 1220 instruments. Table 1 shows the general characteristics of this group of respondents. This is a representative sample of the distribution of internists throughout our country as well as those internists affiliated with the most important public health institutions because we gathered information from practicing physicians in the 32 states of the Mexican Republic.

Table 2 shows an analysis of the general concepts regarding VTE. Most of the internists had an appropriate and clearly defined global concept of VTE. Also, most considered VTE as a potential complication in hospitalised medical patients, but fewer respondents considered...
PE as a potential complication. A high percentage of participants considered that PE does not represent a cause of death. Surprisingly, the search for atherothrombotic risk factors versus VTE risk factors during the first clinical evaluation of patients was quite similar in hospitalised patients. However, in medical outpatients, most of the interviewees evaluate atherothrombotic risk factors, but only a minority seeks VTE risk factors. Although most of the respondents routinely search for VTE risk factors in medical in-hospital patients, global risk stratification for VTE is carried out to a lesser degree, a fact that appears contradictory because the identification of specific risk factors for VTE is high. Moreover, when we explored the criteria used for global risk stratification, only a minority of the respondents used any published evidence, and the majority of the respondents did not consider cumulative risk factors in hospitalised medical patients likely to increase the global risk for VTE. Therefore, the relatively high awareness of individual risk factors for VTE does not translate into an appropriate stratification of global risk for DVT in medical patients.

Results regarding the identification of specific risk factors for DVT based on published evidence are shown in Table 3. Awareness of some risk factors for VTE appears to be very high, but other findings in this survey deserve special attention. For example, only a minority of the participants agreed completely that age >75 years is a risk factor for VTE. Moreover, a very low percentage of respondents considered length of hospital stay as a risk factor for VTE. The majority of the respondents considered that the risk for VTE decreases significantly after hospital discharge.

Although most respondents agreed that assessment of VTE risk is mandatory when surgical risk evaluation is performed, survey results clearly show that specific

Table 1  General characteristics of the participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>413 (34.4)</td>
</tr>
<tr>
<td>Male</td>
<td>807 (65.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>21–30</td>
<td>298 (24.3)</td>
</tr>
<tr>
<td>31–40</td>
<td>274 (22.3)</td>
</tr>
<tr>
<td>41–50</td>
<td>356 (29.1)</td>
</tr>
<tr>
<td>51–60</td>
<td>260 (21.2)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>32 (3.1)</td>
</tr>
<tr>
<td>Medical practice</td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>178 (14.6)</td>
</tr>
<tr>
<td>Public</td>
<td>464 (38.0)</td>
</tr>
<tr>
<td>Both</td>
<td>578 (47.4)</td>
</tr>
<tr>
<td>Academic activities</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>371 (30.4)</td>
</tr>
<tr>
<td>School of medicine (undergraduate)</td>
<td>317 (26.0)</td>
</tr>
<tr>
<td>Internal medicine residency</td>
<td>243 (19.9)</td>
</tr>
<tr>
<td>Both</td>
<td>289 (23.7)</td>
</tr>
<tr>
<td>Clinical research</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>362 (29.7)</td>
</tr>
<tr>
<td>No</td>
<td>858 (70.3)</td>
</tr>
<tr>
<td>In-hospital appointment</td>
<td></td>
</tr>
<tr>
<td>Postgraduate interns</td>
<td>947 (77.6)</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>618 (65.2)</td>
</tr>
<tr>
<td>Emergency room</td>
<td>94 (9.9)</td>
</tr>
<tr>
<td>Intensive care units</td>
<td>80 (8.4)</td>
</tr>
<tr>
<td>Teaching</td>
<td>71 (7.5)</td>
</tr>
<tr>
<td>Administration</td>
<td>47 (5.1)</td>
</tr>
<tr>
<td>Other</td>
<td>37 (3.9)</td>
</tr>
<tr>
<td>Internal medicine residents</td>
<td>279 (22.9)</td>
</tr>
<tr>
<td>Year 1</td>
<td>94 (33.7)</td>
</tr>
<tr>
<td>Year 2</td>
<td>65 (23.3)</td>
</tr>
<tr>
<td>Year 3</td>
<td>68 (24.4)</td>
</tr>
<tr>
<td>Year 4</td>
<td>52 (18.6)</td>
</tr>
</tbody>
</table>

Table 2  General concepts about venous thromboembolism (VTE) among internists

<table>
<thead>
<tr>
<th>Concept</th>
<th>Yes (%)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE is a continuum where DVT is likely to cause PE</td>
<td>98.4</td>
<td>1.6</td>
</tr>
<tr>
<td>VTE is a potential complication in hospitalised medical patients</td>
<td>84.8</td>
<td>5.2</td>
</tr>
<tr>
<td>PE may affect medical patients</td>
<td>68.9</td>
<td>31.1</td>
</tr>
<tr>
<td>When PE is suspected, internationally accepted diagnostic criteria are used to perform the diagnosis</td>
<td>29.6</td>
<td>70.4</td>
</tr>
<tr>
<td>PE is a cause of death</td>
<td>62.9</td>
<td>47.1</td>
</tr>
<tr>
<td>DVT is most frequently diagnosed among medical inpatients versus non-hospitalised medical patients</td>
<td>57.9</td>
<td>37.1</td>
</tr>
<tr>
<td>Searching of atherothrombotic risk factors is performed at the initial evaluation of in-hospital medical patients</td>
<td>86.7</td>
<td>13.3</td>
</tr>
<tr>
<td>Search for VTE risk factors is performed at the initial evaluation of in-hospital medical patients</td>
<td>83.1</td>
<td>16.9</td>
</tr>
<tr>
<td>Search for atherothrombotic risk factors is performed at the initial evaluation of medical outpatients</td>
<td>94.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Search for VTE risk factors is performed at the initial evaluation of medical outpatients</td>
<td>27.8</td>
<td>72.2</td>
</tr>
<tr>
<td>Global risk factor stratification is routinely performed</td>
<td>58.1</td>
<td>41.9</td>
</tr>
<tr>
<td>Global risk stratification is performed based on published evidence</td>
<td>33.2</td>
<td>66.8</td>
</tr>
<tr>
<td>Accumulation of risk factors in hospitalised medical patients increases the global risk for VTE</td>
<td>29.6</td>
<td>70.4</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; PE, pulmonary embolism
surgery-related risk factors for VTE are not properly evaluated (Table 4). Most internists considered that the risk is higher among surgical inpatients, and almost half of the respondents believe that risk factors for VTE are more frequently found among hospitalised surgical patients. As shown in Table 4, the level of awareness of other surgical scenarios that may imply a risk for VTE was not always high.

### Table 3  
Awareness about risk factors for venous thromboembolism (VTE) in hospitalised medical patients

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Completely agree</th>
<th>Agree more than disagree</th>
<th>Neither agree nor disagree</th>
<th>Disagree more than agree</th>
<th>Completely disagree</th>
<th>AAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>75</td>
<td>18</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>9.12</td>
</tr>
<tr>
<td>Obesity</td>
<td>72</td>
<td>20</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8.95</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>69</td>
<td>21</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>8.80</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>68</td>
<td>22</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>8.80</td>
</tr>
<tr>
<td>Neurological disease including stroke</td>
<td>68</td>
<td>21</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>8.77</td>
</tr>
<tr>
<td>Poli-trauma</td>
<td>64</td>
<td>25</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>8.65</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>64</td>
<td>24</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>8.60</td>
</tr>
<tr>
<td>Length of orotracheal intubation</td>
<td>62</td>
<td>25</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>8.55</td>
</tr>
<tr>
<td>Immobilisation</td>
<td>65</td>
<td>23</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>8.55</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>62</td>
<td>24</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>8.50</td>
</tr>
<tr>
<td>COPD</td>
<td>62</td>
<td>23</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>8.50</td>
</tr>
<tr>
<td>Gender</td>
<td>61</td>
<td>27</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>8.50</td>
</tr>
<tr>
<td>Hospitalisation in ICU</td>
<td>42</td>
<td>48</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>8.17</td>
</tr>
<tr>
<td>Use of casts</td>
<td>54</td>
<td>27</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>8.00</td>
</tr>
<tr>
<td>ICVC</td>
<td>43</td>
<td>30</td>
<td>12</td>
<td>8</td>
<td>7</td>
<td>7.35</td>
</tr>
<tr>
<td>Orotracheal intubation</td>
<td>44</td>
<td>27</td>
<td>13</td>
<td>9</td>
<td>7</td>
<td>7.30</td>
</tr>
<tr>
<td>Primary thrombophilia</td>
<td>32</td>
<td>24</td>
<td>13</td>
<td>15</td>
<td>16</td>
<td>6.02</td>
</tr>
<tr>
<td>Acute lung disease</td>
<td>23</td>
<td>27</td>
<td>13</td>
<td>9</td>
<td>7</td>
<td>7.30</td>
</tr>
<tr>
<td>Personal history of VTE</td>
<td>7</td>
<td>28</td>
<td>27</td>
<td>31</td>
<td>7</td>
<td>4.92</td>
</tr>
<tr>
<td>Family history of VTE</td>
<td>12</td>
<td>19</td>
<td>26</td>
<td>30</td>
<td>13</td>
<td>4.67</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td>5</td>
<td>16</td>
<td>32</td>
<td>28</td>
<td>19</td>
<td>3.95</td>
</tr>
</tbody>
</table>

AAI, appropriate answer index = Σ (degree of appropriateness: completely agree = 10; agree more than disagree = 7.5; neither agree nor disagree = 5; disagree more than agree = 2.5; completely disagree = 0) (percentage of responses)/100; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ICVC, indwelling central venous catheter.

### Table 4  
Awareness in regard to surgery-related risk factors for venous thromboembolism (VTE) among internists

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Completely agree</th>
<th>Agree more than disagree</th>
<th>Neither agree nor disagree</th>
<th>Disagree more than agree</th>
<th>Completely disagree</th>
<th>AAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>If necessary, thromboprophylaxis may be used before surgery</td>
<td>68</td>
<td>22</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>8.72</td>
</tr>
<tr>
<td>Evaluation of the risk of VTE is mandatory in surgical patients</td>
<td>58</td>
<td>24</td>
<td>7</td>
<td>9</td>
<td>2</td>
<td>8.17</td>
</tr>
<tr>
<td>Risk of VTE increases when surgery is &gt;30 min</td>
<td>54</td>
<td>29</td>
<td>9</td>
<td>4</td>
<td>4</td>
<td>8.12</td>
</tr>
<tr>
<td>Risk of VTE is higher for cancer surgery as compared with non-cancer surgery</td>
<td>34</td>
<td>22</td>
<td>9</td>
<td>16</td>
<td>19</td>
<td>5.90</td>
</tr>
<tr>
<td>Risk is not equal in all elective surgeries</td>
<td>29</td>
<td>19</td>
<td>6</td>
<td>26</td>
<td>20</td>
<td>5.27</td>
</tr>
<tr>
<td>Risk for VTE is higher for urgent surgery as compared with elective surgery</td>
<td>25</td>
<td>22</td>
<td>8</td>
<td>21</td>
<td>24</td>
<td>5.07</td>
</tr>
<tr>
<td>Risk factors for VTE are more frequently found in medical versus surgical patients</td>
<td>17</td>
<td>15</td>
<td>19</td>
<td>25</td>
<td>24</td>
<td>4.70</td>
</tr>
<tr>
<td>Risk of VTE is higher for orthopaedic surgery versus abdominal surgery</td>
<td>24</td>
<td>17</td>
<td>5</td>
<td>21</td>
<td>33</td>
<td>4.45</td>
</tr>
<tr>
<td>The risk of VTE changes with the type of cancer</td>
<td>13</td>
<td>16</td>
<td>11</td>
<td>27</td>
<td>33</td>
<td>3.72</td>
</tr>
<tr>
<td>Risk of VTE is higher for medical versus surgical patients</td>
<td>15</td>
<td>13</td>
<td>8</td>
<td>29</td>
<td>35</td>
<td>3.60</td>
</tr>
<tr>
<td>Risk of VTE is higher for open versus laparoscopic surgery</td>
<td>9</td>
<td>10</td>
<td>14</td>
<td>36</td>
<td>31</td>
<td>3.25</td>
</tr>
</tbody>
</table>

AAI, appropriate answer index (obtained as described in Table 3).
Regarding VTE diagnosis, 59.2% of the respondents considered that VTE diagnosis is easy or very easy. However, only 40.8% considered that the gold standard for diagnosis of DVT is phlebography; 84.9% believe that the combination of D-dimer + Doppler ultrasound is an appropriate diagnostic alternative. In contrast, only 60.2% believe that the gold standard for PE diagnosis is either pulmonary arteriography or helical computed tomography scan; 55.1% answered that combined data of electrocardiogram, arterial gasometry and chest X-ray are sufficient for the diagnosis of PE.

Discussion

Thromboprophylaxis should be considered for all hospitalised medical patients after carefully evaluating the risks and benefits associated with available therapies; however, it has been demonstrated that it is widely underused. Even within the high-risk setting of intensive care units, medical patients received VTE prophylaxis prior to the diagnosis of DVT only about two-thirds as often as compared with surgical patients. Consequently, thousands of medical patients worldwide are at high risk of suffering from VTE.3,15,30–36

Medical patients represent a high proportion of individuals receiving care in hospitals, and most of them are at high risk for VTE.4 As a consequence, the identification of individuals at risk for VTE and the subsequent implementation of thromboprophylaxis would provide an effective and less expensive strategy to reduce significantly the overall burden of this disease.3,9,30,31 We sought to determine the level of awareness regarding VTE because it is impossible to conceive of high-quality thromboprophylaxis without an appropriate assessment of VTE risk in a patient, a goal that depends on an accurate understanding of the specific risk factors affecting an individual. Indeed, the first step to increase thromboprophylaxis is to recognise properly VTE global risk in a patient.

The Mexican hospital system is public (primarily managed by the government) and also private. Almost 80% of the Mexican population has access to public medical services, with only a minority having the availability of private medical care provided by medical insurance companies. Due to the aging process of the Mexican population in the last two decades,37 the number of hospitalisations in public institutions has grown significantly. For example, in the Instituto Mexicano del Seguro Social, the largest public institution, 1 957 616 patients were hospitalised during 2008 (9 236 168 in-hospital days).38 Patients hospitalised in internal medicine wards in 2008 represented 38% of total hospitalisations.

Several risk factors for VTE in medical patients have been described in recent years; however, their importance varies significantly among studies. Additional research is needed to determine the optimal VTE scale for risk stratification. Although these risk factors are not equally significant for medical in-hospital patients, we explored the awareness of all published risk factors regardless of their epidemiological classification (high, possible or probable risk). The underuse of thromboprophylaxis in internal medicine wards may also be due to the false perception that patients do not have sufficient risk factors for developing VTE, and that the global risk for VTE is low. Therefore, we also decided to evaluate the ability to integrate global risk for VTE.

Some results of this survey agree with those results previously published, and they demonstrate low awareness of risk factors for VTE among internists. We found that Mexican internists cannot identify at which age the risk for VTE begins, a fact that may be due to the highly variable information gathered from several studies that impedes to establish the cut-off age at which it becomes an independent risk factor for VTE. Also, as previously described, upon hospital discharge, the risk of VTE is assumed to abate, and thromboprophylaxis is discontinued, even when the risk often persists because of the prevalence of various ongoing risk factors. We found a similar behaviour because most of the respondents believe that the risk decreases after hospital discharge and, therefore, thromboprophylaxis is discontinued. This practice is inappropriate because patient risk should be regarded as a continuum, where several risk factors are present before, during and after hospitalisation. Assessment of the remaining risk factors at the time of discharge is important in order to decide which patients should receive extended thromboprophylaxis to minimise the risk of thrombotic events post-discharge. Additionally, we found an inadequate level of awareness regarding the length of hospital stay as a risk factor for VTE. There is a direct relationship between the days of hospitalisation and the degree of immobilisation. Consequently, as the length of hospitalisation increases, the risk of VTE is increased. According to our data, this risk factor is not properly weighed, even though it is critically important among a population of physicians treating patients who usually require in-hospital care for long periods of time.

Due to the characteristics of the Mexican healthcare system, internists perform the majority of preoperative risk evaluations. However, we found that the evaluation of independent surgery-related risk factors for VTE as well as the approach to global risk stratification is poor. If we consider medical and surgical patients, internists in Mexico are responsible for the evaluation and VTE risk stratification of thousands of patients; however, because awareness regarding VTE is low, we may assume that thromboprophylaxis is not properly prescribed.

© 2011 The Authors
Internal Medicine Journal © 2011 Royal Australasian College of Physicians
Therefore, we may hypothesise that each year, hundreds of patients are at high risk for VTE because of the low indication for thromboprophylaxis. These disappointing facts are not solely attributable to internists. We explored the existence of thromboprophylactic programmes in both public and private hospitals and found that such preventive programmes are practically non-existent. An explanation may be the high degree of resources assigned to atherothrombotic diseases, mainly diabetes mellitus and obesity. Although it would be absurd to minimise the importance of atherothrombotic entities, VTE is clearly another major challenge for our health system, as it is worldwide. It is our hope that our results will alert medical authorities in Mexico regarding the urgent necessity of creating a national programme for VTE prophylaxis. Continuing education is required to increase VTE awareness among healthcare providers in order to encourage them to provide additional resources for VTE prophylaxis.

Our data are important from a national healthcare perspective because they enable estimating both patient well-being and the economic benefits of fully applying evidence-based thromboprophylaxis. Previous studies have shown gaps between guidelines and recommendations and practice in the hospital setting. The absence of a global overview of this problem may be a barrier to physicians who are uncertain of the prevalence of VTE risk factors in their patients. Therefore, our data continue to demonstrate a gap between ideal and realworld practices.

One important finding from this survey must be highlighted. Most internists report that VTE diagnosis is clinically easy to perform; however, diagnostic tools are not properly used, which is a fact that contributes to a low index of objective VTE diagnoses. Certainly, it should be noted that, although a significant proportion of internists do not know the precise diagnostic resources available in their hospitals, an important factor in determining the low degree of objective diagnosis is the lack of diagnostic resources in both private and public hospitals throughout Mexico.

This study may have significant limitations. First, it is a random survey with the well-known methodological limitations of this type of research. However, we consider that the instrument itself, the high number of questionnaires applied and the exclusion of inappropriately completed questionnaires confirm that our results closely reflect the level of VTE awareness among Mexican internists. We included participants from the 32 states of the Mexican Republic, who treat patients from a wide range of ethnic, social, economic and healthcare environments. Second, because of the cross-sectional design of this study, it is only able to assess the awareness until the date of the survey. Third, the instrument was applied only among internists attending academic meetings. We may assume that this specific population is interested in maintaining a higher level of clinical skills than those not regularly attending these meetings. Therefore, it is quite possible that the results obtained may overestimate the degree of awareness of VTE among internists in Mexico.

Conclusion

We believe that awareness of risk factors and diagnostic skills for VTE among Mexican internists is inadequate. Therefore, it seems obvious that the first step to improve the rates of appropriate thromboprophylaxis use among internists in Mexico requires an ongoing educational process in order to increase awareness of the risk factors related to medical patients.

References


**SPAST mutations in Australian patients with hereditary spastic paraplegia**

H. Vandebona,1 N. P. Kerr,1 C. Liang2 and C. M. Sue1,2

1Department of Neurogenetics, Kolling Institute of Medical Research, University of Sydney and 2Department of Neurology, Royal North Shore Hospital, Sydney, New South Wales, Australia

Key words
autosomal dominant hereditary spastic paraplegia, AD-HSP, spastin, SPAST, SPG4.

Correspondence
Carolyn M. Sue, Department of Neurology, Royal North Shore Hospital, St Leonards, NSW 2065, Australia.
Email: carolyn.sue@sydney.edu.au

Received 18 October 2011; accepted 30 March 2012.

Abstract

Background: Hereditary spastic paraplegia (HSP) is often caused by mutations in the SPAST gene. The frequency of SPAST mutations causing HSP in Australian patients is currently unknown.

Aim: We aimed to determine the frequency of SPAST gene mutations in our cohort of HSP patients.

Methods: We recruited 30 unrelated patients with HSP for clinical and genetic assessment. DNA or RNA was extracted from patients’ samples to perform direct DNA sequencing of the SPAST gene, multiplex ligation-dependent probe amplification (MLPA) and/or cDNA analysis.

Results: We identified 13 heterozygous SPAST mutations in 16 unrelated patients. Most mutations (75%) were detected by DNA sequence analysis. We identified nine-point mutations (n = 9), insertion (n = 1), one type of splice site mutation (n = 2), one type of exonic deletion (n = 2) and one type of exonic amplification (n = 2). Missense mutations (n = 7) were the most frequent mutation type (44%). Heterozygous exonic deletion (n = 2) and heterozygous exonic amplification (n = 2) were identified by MLPA and cDNA screening (25%). We also identified the single heterozygous p.Ser44Leu polymorphism in two other patients without pathogenic mutations in SPAST.

Conclusion: We conclude that SPAST mutations are responsible for the majority of HSP in Australia. Most of the patients with SPAST mutations had pure forms of HSP and a positive family history to suggest autosomal dominant (AD) HSP. Not all mutations were identified by direct sequencing of the SPAST gene, necessitating further molecular analysis. Given that SPAST mutations cause AD-HSP, these findings are important when providing genetic counselling for affected patients.

Introduction

Hereditary spastic paraplegia (HSP) is a progressive neurodegenerative disorder that typically presents with lower limb spasticity and gait abnormalities. Pathological studies demonstrate the degeneration of the long axons in the descending corticospinal tracts and ascending dorsal columns. Clinically, patients are categorised as having pure (uncomplicated HSP)1 or complicated HSP. Complicated forms of HSP exhibit additional neurological signs such as ataxia, mental retardation, dementia, extrapyramidal disturbances, visual or auditory dysfunction or epilepsy. Pure HSP is the most common form1 comprising about 90% of all patients with HSP.

HSP may follow autosomal dominant (AD), autosomal recessive, X-linked and sporadic patterns of transmission. AD-HSP is the most common inheritance pattern, accounting for about 70% of all HSP.2 Mutations in spastin (SPAST) are the most frequent cause of HSP. SPAST (previously referred to as SPG4) is located on chromosome 2p22, has 17 exons and encodes a 616 amino acid protein that plays an important role in axonal transport as it regulates microtubule organisation.3 Frequencies of SPAST mutations in various HSP cohorts range between 13% and 40%.4–7 The prevalence of SPAST mutations in Australian patients with HSP is currently unknown. In this study, we aimed to determine the frequency of SPAST mutations in Australian subjects with HSP.
Patients and Methods

Thirty consecutive unrelated patients with HSP referred to the neurogenetics clinic at Royal North Shore Hospital, Sydney, were assessed. Clinical features are summarised in Table 1. This study was approved by the Northern Sydney Central Coast Area Health Service Human Research Ethic Committee and all participants gave written informed consent.

Mutation analysis

Genomic DNA was extracted from blood and used to amplify all 17 exons in the SPAST gene. Direct nucleotide sequencing was performed using an ABI 3730 sequencer. Multiplex ligation-dependent probe amplification (MLPA) analysis (http://www.mlpa.com) of genomic DNA was carried out using the P165 MLPA kit (MRCHolland, Amsterdam, the Netherlands) according to the manufacturer’s instructions to identify heterozygous deletions, duplications and rearrangements. When necessary, RNA was extracted from patients’ cell lines and cDNA was constructed using standard methods. Polymerase chain reaction (PCR) and direct sequencing of cDNA of SPAST was performed to confirm exonic deletions or duplications. All abnormal results were performed in duplicate to confirm results. To confirm heterozygosity, mutations detected were also assessed by specific PCR/restriction fragment length polymorphism analysis. The likely pathogenicity of novel point mutations was determined by protein change due to nucleotide change and also using a mutation prediction programme PolyPhen-2 (Polyorphism Phenotyping v2) (http://genetics.bwh.harvard.edu/pph2/).

Results

Of the 30 patients recruited for this study, 20 were male and 10 were female. Twenty-five had pure HSP and five patients had complicated HSP (Table 1). In addition, another patient (ID: 05033) had saccadic abnormalities; an additional clinical feature to the pure form of HSP, but not enough to warrant the diagnosis of complicated HSP. Age at onset (AAO) of disease ranged from infancy to late adulthood. Twenty-four patients had a positive family history. Clinical manifestations of the patients in this study are summarised in Table 1.

We identified 13 heterozygous spastin mutations in 16 unrelated patients (53% of total). By sequencing all 17 exons of SPAST gene, we detected seven missense mutations, two nonsense mutations, one insertion (which caused an exonic deletion as detected by MLPA and cDNA) and one splicing mutation at intron 11. Further sequencing analysis of cDNA from the patient with the splice-site mutation detected a deletion of exon 11. Two other mutations, a heterozygous exonic deletion (exons 8–9; n = 2) and a heterozygous exonic amplification (exon 16; n = 2) were identified by MLPA and cDNA sequencing analysis. We also identified two unrelated patients with heterozygous p.Ser44Leu in exon 1, a known rare polymorphism and a phenotypic modifier of the SPAST gene by DNA sequencing analysis. Neither of these patients had other SPAST mutations. SPAST mutation analysis results are summarised in Table 2. Mutations spanned over the gene although the majority of mutations were located in the AAA domain (85%; 11/13). The other two mutations, which were located in exons 2 and 3 were localised in the MIT domain (15%). Both MIT region alterations were point mutations, with early onset disease. Twelve of the 16 patients with SPAST mutations had clinical features of pure or uncomplicated HSP (75%). Positive family history for the disease is identified in 87.5% (14/16) of SPAST mutated patients. There was no correlation between other clinical features, age of onset and mutation location or type.

Discussion

We found SPAST gene mutations in 53% of unrelated HSP patients (16/30) in our study group, thus confirming that mutations in this gene cause the majority of HSP in Australian patients. Gene abnormalities with point mutations were mainly identified by direct sequencing of the SPAST gene, but the identification of other causative mutations due to exonic rearrangements, deletions and duplications required additional molecular analysis with MLPA and/or cDNA sequencing. This finding suggests that multiple methods of genetic analysis are required to identify mutations in this gene in patients where the diagnosis is clinically suspected.

We found a higher frequency of SPAST mutations (53%) in our cohort of AD-HSP patients compared to some reported studies.4-7 The higher frequency of identified SPAST mutations in our study is most likely due to the combined molecular techniques used in our mutation analysis and possible ascertainment bias due to our patient selection of affected subjects.

The majority of patients with SPAST mutations in our cohort had pure HSP. One of our patients (ID: 06042) who had complicated HSP with clinical features of upper limb weakness, dysarthria and amyotrophy, had a c.1392A>T nucleotide change in exon 11 causing a p.Glu464Asp (E464D) change in the SPAST gene. While glutamic acid (E) and aspartic acid (D), both are acidic amino acids, the nucleotide change was considered as...
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>AAO (years)</th>
<th>Disease duration (years)</th>
<th>Spasticity</th>
<th>Gait abnormalities</th>
<th>Sphincter dysfunction</th>
<th>Leg/arm weakness</th>
<th>Muscle wasting</th>
<th>Hyperreflexia</th>
<th>Upgoing plantar responses</th>
<th>Cerebellar signs</th>
<th>Loss of vibration sense</th>
<th>Abnormal saccades</th>
<th>Kyphosis/ lordosis</th>
<th>Walking aid</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>04011</td>
<td>48</td>
<td>16</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1,4</td>
</tr>
<tr>
<td>10088</td>
<td>50</td>
<td>15</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>04060</td>
<td>ch</td>
<td>50+</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>UL,LL</td>
<td>-</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>NK</td>
<td></td>
</tr>
<tr>
<td>06042</td>
<td>2</td>
<td>46</td>
<td>LL</td>
<td>+</td>
<td>+</td>
<td>UL,LL</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>06028</td>
<td>4</td>
<td>69</td>
<td>LL</td>
<td>+</td>
<td>+</td>
<td>LL</td>
<td>LL</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>05062</td>
<td>68</td>
<td>9</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>LL</td>
<td>LL</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>05033</td>
<td>17</td>
<td>9</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>LL</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>04065</td>
<td>15</td>
<td>38</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>LL</td>
<td>-</td>
<td>UL,LL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>06075</td>
<td>ch</td>
<td>27+</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>LL</td>
<td>LL</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>05038</td>
<td>3</td>
<td>36</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>06048</td>
<td>41</td>
<td>24</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>06061</td>
<td>19</td>
<td>16</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>LL</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>06040</td>
<td>62</td>
<td>10</td>
<td>LL</td>
<td>-</td>
<td>-</td>
<td>LL</td>
<td>LL</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>06045</td>
<td>9 months</td>
<td>45</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>07076</td>
<td>20s</td>
<td>40+</td>
<td>LL</td>
<td>+</td>
<td>LL</td>
<td>LL</td>
<td>LL</td>
<td>UL,LL</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>07078</td>
<td>16</td>
<td>30</td>
<td>LL</td>
<td>+</td>
<td>+</td>
<td>LL</td>
<td>LL</td>
<td>UL,LL</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>07083</td>
<td>ch</td>
<td>20+</td>
<td>LL</td>
<td>-</td>
<td>-</td>
<td>LL</td>
<td>-</td>
<td>LL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>08080</td>
<td>13</td>
<td>44</td>
<td>LL</td>
<td>+</td>
<td>LL</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>04078</td>
<td>20s</td>
<td>30</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>LL</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>1,2,3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>08083</td>
<td>12</td>
<td>9</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>08094</td>
<td>37</td>
<td>2</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>08077</td>
<td>20</td>
<td>34</td>
<td>LL</td>
<td>+</td>
<td>LL</td>
<td>-</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1,2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08079</td>
<td>48</td>
<td>10</td>
<td>LL</td>
<td>+</td>
<td>LL</td>
<td>-</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>1</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>09006</td>
<td>24</td>
<td>1</td>
<td>LL</td>
<td>-</td>
<td>-</td>
<td>LL</td>
<td>-</td>
<td>LL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>09016</td>
<td>32</td>
<td>6</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>LL</td>
<td>LL</td>
<td>LL</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>08074</td>
<td>1.5</td>
<td>58</td>
<td>LL</td>
<td>+</td>
<td>LL</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>4,1,3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>09065</td>
<td>10</td>
<td>38</td>
<td>UL,LL</td>
<td>+</td>
<td>LL</td>
<td>LL</td>
<td>LL</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1,3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>09061</td>
<td>Inf</td>
<td>54</td>
<td>LL</td>
<td>+</td>
<td>LL</td>
<td>-</td>
<td>UL,LL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12,3,4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>09062</td>
<td>33</td>
<td>35</td>
<td>LL</td>
<td>+</td>
<td>UL,LL</td>
<td>UL,LL</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>2,5,3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61808</td>
<td>57</td>
<td>3</td>
<td>LL</td>
<td>+</td>
<td>LL</td>
<td>LL</td>
<td>LL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- normal/absent; +, present; AAO, age at symptom onset; ch, childhood; Inf, infant; LL, lower limb; mo, months; NK, not known as adopted; UL, upper limb; Walking aids, 1, walking stick; 2, orthotics; 3, wheelchair for distance; 4, calipers/splints; 5, walker; 6, wheelchair bound.
Pathogenic (Polyphen-2 predicted the mutation is probably damaging with a score of 1.000) as the change is located in the main functional and highly conserved AAA cassette region of the SPAST.

Mutations in our patients were found to be scattered throughout the conserved domains of the spastin. Most of these mutations are predicted to disrupt the AAA domain or MIT region. Crystallography studies have revealed that spastin is a ring-shaped hexamer with a narrow central pore molecule and indicate that the integrity of the functional domains is critical for the normal function of spastin.

The majority of our patients with SPAST mutations had a positive family history. Only two patients (12.5%) with SPAST mutations seemed to be sporadic cases. Both had complicated HSP. Our findings are consistent with previous population studies that report that 12–18% of patients with sporadic HSP have mutations in the SPAST gene.11,12

Proukakis et al., reported a significant excess of affected males by HSP by literature review of 31 studies related to SPAST mutation analysis.13 Similarly, our study group had twice as many males as females affected with HSP. Also, patients found to have SPAST mutations in this study (11 males and five females), also showed a male predominance. Counting the family members we examined for mutations, a total of 16 males and 13 females were diagnosed with SPAST mutations consistent with other reports that males may be more severely affected by HSP.

We also identified two unrelated patients with heterozygous p.Ser44Leu in exon 1. The pathogenicity of this nucleotide change has been questioned. It is most likely a disease-modifying polymorphism when coexisting with another SPAST mutation11 although homozygotes for this mutation (and no others) have been found to be symptomatic.5 It has been reported that <0.6% (5 of 900) alleles in a North American control population,9 0.6% in Italian population 11 and 3.1% (11/350) in a healthy control group in United Kingdom7 carry a heterozygous p.Ser44Leu change. One of our patients (ID: 04078) with the p.Ser44Leu had a mother and another sibling who also carried the same point mutation but were asymptomatic for HSP. The second patient (ID: 07083) had no family history for the disease. These findings support the notion that the p.Ser44Leu is not pathogenic, but rather may act as a genetic modifier in the setting of an additional SPAST mutation.

Currently, haploinsufficiency, due to loss of spastin function, is the favoured mechanism for the effect of disease-related mutations in SPAST. Several other mechanisms, including a dominant-negative effect of SPAST mutations13 and mitochondrial involvement due to presence of impaired mitochondrial transport in HSP patients have also been proposed to contribute to the pathogenesis of HSP. It has been also suggested that some mutations may produce truncated spastin isoforms that would act in a dominant manner via a gain of function mechanism causing the disease.17,18

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Exon/intron</th>
<th>Nucleotide change†</th>
<th>Protein change‡</th>
<th>Mutation type</th>
<th>Relatives having mutation</th>
<th>HSP phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>06028</td>
<td>2</td>
<td>c.444G&gt;A</td>
<td>p.Trp148X</td>
<td>Nonsense</td>
<td></td>
<td>Pure</td>
</tr>
<tr>
<td>08077</td>
<td>3</td>
<td>c.583C&gt;G</td>
<td>p.Leu195Val</td>
<td>Missense</td>
<td>2 siblings</td>
<td>Pure</td>
</tr>
<tr>
<td>08074</td>
<td>7</td>
<td>c.1096G&gt;A</td>
<td>p.Glu366lys</td>
<td>Missense</td>
<td></td>
<td>Pure</td>
</tr>
<tr>
<td>06075</td>
<td>8–9</td>
<td>Exonic deletion</td>
<td></td>
<td>Exonic deletion</td>
<td></td>
<td>Pure</td>
</tr>
<tr>
<td>09065</td>
<td>8–9</td>
<td>Exonic deletion</td>
<td></td>
<td>Exonic deletion</td>
<td></td>
<td>Complicated</td>
</tr>
<tr>
<td>04011</td>
<td>9</td>
<td>c.1196C&gt;T</td>
<td>p.Ser399Leu</td>
<td>Missense</td>
<td>2 children</td>
<td>Pure</td>
</tr>
<tr>
<td>09061</td>
<td>9</td>
<td>c[1214_1215insT]</td>
<td>Frameshift mutation</td>
<td></td>
<td>1 child</td>
<td>Pure</td>
</tr>
<tr>
<td>06040</td>
<td>10</td>
<td>c.1291C&gt;T</td>
<td>p.Arg431X</td>
<td>Nonsense</td>
<td>1 child</td>
<td>Pure</td>
</tr>
<tr>
<td>06042</td>
<td>11</td>
<td>c.1392A&gt;T</td>
<td>p.Glu464Asp</td>
<td>Missense</td>
<td></td>
<td>Complicated</td>
</tr>
<tr>
<td>07076</td>
<td>Intron 11</td>
<td>c.1413 + 3_1413 + 6del</td>
<td>Missplicing</td>
<td>Exon 11 skipped</td>
<td></td>
<td>Pure</td>
</tr>
<tr>
<td>61808</td>
<td>Intron 11</td>
<td>c.1413 + 3_1413 + 6del</td>
<td>Missplicing</td>
<td>Exon 11 skipped</td>
<td></td>
<td>Complicated</td>
</tr>
<tr>
<td>09062</td>
<td>12</td>
<td>c.1466C&gt;G</td>
<td>p.Pro489Arg</td>
<td>Missense</td>
<td></td>
<td>Complicated</td>
</tr>
<tr>
<td>06045</td>
<td>15</td>
<td>c.1642G&gt;A</td>
<td>p.Asp548Asn</td>
<td>Missense</td>
<td></td>
<td>Pure</td>
</tr>
<tr>
<td>06048</td>
<td>16</td>
<td>Exonic amplification</td>
<td></td>
<td>Exonic amplification</td>
<td>1 aunt</td>
<td>Pure</td>
</tr>
<tr>
<td>09016</td>
<td>16</td>
<td>Exonic amplification</td>
<td></td>
<td>Exonic amplification</td>
<td>1 parent</td>
<td>Pure</td>
</tr>
<tr>
<td>09006</td>
<td>17</td>
<td>c.1789A&gt;G</td>
<td>p.Ser597Gly</td>
<td>Missense</td>
<td>1 parent</td>
<td>Pure</td>
</tr>
</tbody>
</table>

†Nucleotide numbers refer to the open reading frame of SPAST mRNA sequence, NM_014946.3. ‡Amino acid numbers refer to the spastin peptide sequence NP_055761.2.
Conclusions

Patients with AD-HSP are more likely to have mutations in the SPAST gene. Mutations were confined mainly in the functional regions of the gene, with the majority of them being located in the AAA domain. If full sequencing of the gene does not identify a mutation, then other molecular analysis such as MLPA and cDNA sequencing to identify exonic deletions or duplications, or splice junction abnormalities, are warranted. Identification of SPAST mutations, even in sporadic cases, is important for genetic counselling of affected families.

References


Acknowledgements

We thank JGL Morris (Westmead Hospital, Westmead, NSW), R Joffe (Royal North Shore Hospital, St Leonards, NSW), D Sharpe (Concord Hospital, Concord, NSW), V Fung (Westmead Hospital), P Clouston (Westmead Hospital), M Theiben (Nepean Hospital, Kingswood, NSW), E Thompson (Women’s & Children’s Hospital, North Adelaide, SA), C Yiannikas (Concord Hospital, Concord, NSW) and the HSP Foundation of Australia for referring their patients to our clinic and Wendy Welsh (Royal North Shore Hospital, St Leonards, NSW) for clinical assistance.
BRIEF COMMUNICATION

Changes in serum phosphate during treatment of diabetic ketoacidosis: predictive significance of severity of acidosis on presentation

T. Shen¹ and S. Braude²

¹Intensive Care Unit, Bankstown Hospital and ²Intensive Care Unit, Bankstown Hospital and The University of Sydney, Sydney, New South Wales, Australia

Key words
serum phosphate, diabetic ketoacidosis, hypophosphataemia, metabolic acidosis.

Correspondence
Stanley Braude, Manly Hospital, Darley Road, Manly, NSW 2095, Australia.
Email: sbraude@nsccahs.health.nsw.gov.au

Abstract
Changes in serum phosphate during diabetic ketoacidosis (DKA) treatment are not well characterised, although it is known that serum phosphate falls with treatment. We sought to define the nature of these changes and whether the severity of acidosis on admission influenced the severity of subsequent hypophosphataemia. We retrospectively reviewed data on all patients with confirmed DKA presenting to our unit between 2007 and 2010 inclusive. Forty-three patients with 64 episodes of DKA were evaluated. At presentation, 62.5% of patient episodes were hyperphosphataemic. Initial serum phosphate in all patient episodes correlated significantly with the initial serum creatinine ($r = 0.694$, $P < 0.01$) and the initial blood glucose ($r = 0.593$, $P < 0.01$). Serum phosphate fell during the course of treatment in all episodes (mean absolute fall $1.28 \pm 0.77$ (SEM) mmol/L). The mean nadir phosphate was $0.58 \pm 0.19$ mmol/L. Ninety per cent of nadir phosphate levels were hypophosphataemic ($<0.8$ mmol/L), and 11% were severely hypophosphataemic ($<0.32$ mmol/L). Mean initial bicarbonate differed significantly between those with nadir phosphates $<0.5$ mmol/L (9.26 ± 4.55) and those with nadir phosphates $>0.5$ mmol/L (13.0 ± 4.59, $P = 0.0031$). Similar significant bicarbonate differences were noted between those with nadir phosphates less than and more than 0.32 mmol/L respectively (7.42 ± 2.44 and 12.2 ± 4.87, $P < 0.01$). The initial hyperphosphataemia is reflective of intravascular volume depletion and pre-renal renal impairment. The severity of subsequent hypophosphataemia can be predicted by the degree of metabolic acidosis on presentation. As profound hypophosphataemia can be associated with serious complications, clinicians should recognise the likelihood of this biochemical derangement in those DKA patients presenting with profound acidosis.
analyses were done using Student’s t-test for parametric and non-parametric data respectively. Multiple regression analysis was performed using the -test and Mann–Whitney U-test for parametric and non-parametric data respectively. Multiple regression analysis was performed to assess the individual impact of different variables.

Table 1 lists the basic demographic and initial biochemistry data for the study group. Table 2 summarises the changes in serum phosphate during admission. At time zero, 63% of episodes were hyperphosphataemic, 33% within the normal range and 5% hypophosphataemic. Initial serum phosphate level correlated significantly with the initial serum creatinine (R = 0.69, \( P < 0.01 \)) and initial blood glucose level (BSL) (R = 0.59, \( P < 0.01 \)) with initial serum creatinine having greater explanatory power and impact on the initial phosphate level from multiple regression analysis (Fig. 1).

Serum phosphate dropped during the course of the admission in all episodes, with a mean absolute fall of 1.28 ± 0.77 mmol/L, reaching a mean nadir of 0.58 ± 0.19 mmol/L on average 22 h after initiating treatment. Ninety per cent of nadir phosphate levels were considered hypophosphataemic (<0.8 mmol/L), and 10.9% were severely hypophosphataemic (<0.32 mmol/L). At the time of nadir phosphate, the mean corresponding bicarbonate level was 22.1 ± 4.2 mmol/L, demonstrating resolution of acidosis. Episodes with lower nadir phosphate levels had significantly lower initial venous bicarbonate, suggesting greater degree of metabolic acidosis on presentation (Fig. 2). For example, those who were severely hypophosphataemic (nadir <0.32 mmol/L) had a mean bicarbonate of 7.42 ± 2.44 mmol/L at presentation compared with 12.2 ± 4.87 mmol/L in those with nadir phosphate <0.32 mmol/L (\( P = 0.01 \)). In addition, there appeared to be a significant continuous inverse relationship between the extent of fall in serum phosphate and the time to nadir phosphate.

Table 1 Clinical data and initial laboratory values (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>43</td>
</tr>
<tr>
<td>Episodes of diabetic ketoacidosis</td>
<td>64</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>37.5 ± 19.6</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>34/30</td>
</tr>
<tr>
<td>Average length of HDU admission (days)</td>
<td>2</td>
</tr>
<tr>
<td>Blood glucose level (mmol/L)</td>
<td>34.5 ± 14.2</td>
</tr>
<tr>
<td>Venous bicarbonate (mmol/L)</td>
<td>11.7 ± 4.9</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.2 ± 0.1</td>
</tr>
<tr>
<td>Serum creatinine (mmol/L)</td>
<td>143.0 ± 60.0</td>
</tr>
<tr>
<td>Serum urea (mmol/L)</td>
<td>12.7 ± 7.4</td>
</tr>
</tbody>
</table>

Table 2 Changes in serum phosphate (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial serum phosphate</td>
<td>1.86 ± 0.73</td>
</tr>
<tr>
<td>Hyperphosphataemic (&gt;1.5 mmol/L)</td>
<td>40 (63%)</td>
</tr>
<tr>
<td>Normophosphataemic (0.8–1.5 mmol/L)</td>
<td>21 (33%)</td>
</tr>
<tr>
<td>Hypophosphataemic (&lt;0.8 mmol/L)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Nadir serum phosphate</td>
<td>0.58 ± 0.19</td>
</tr>
<tr>
<td>Nadir phosphate &lt;0.5 mmol/L</td>
<td>23 (36%)</td>
</tr>
<tr>
<td>Nadir phosphate &lt;0.32 mmol/L</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Mean drop in serum phosphate (mmol/L)</td>
<td>1.28 ± 0.77</td>
</tr>
<tr>
<td>Time to nadir phosphate from admission (h)</td>
<td>22 ± 14</td>
</tr>
</tbody>
</table>
phosphate and the initial bicarbonate level (R = -0.49, P < 0.01).

Our study demonstrated that in most patients presenting with DKA, there is an initial hyperphosphataemic phase followed by a marked fall in serum phosphate with the initiation of insulin and fluid therapy. Nevertheless, it is important to note that initial hyperphosphataemia occurs despite total body phosphate depletion.5,12 Our study demonstrated a significant and positive correlation of initial serum phosphate with both initial serum creatinine and BSL. This finding can be most plausibly explained by recognising that with increasing intravascular volume depletion in DKA, the initial osmotic drive for urinary phosphate excretion is counteracted by worsening renal impairment which leads to phosphate retention. Therefore, initial serum creatinine appears to be a surrogate marker for the extent of intravascular volume depletion. The effect of hyperglycaemia per se would be to cause an osmotic diuresis which would promote both fluid and phosphate loss, although according to our multiple regression analysis, the former appears to be dominant in influencing serum phosphate concentration on presentation.

In keeping with previous studies,6,7,13,14 serum phosphate was seen to drop in all episodes with the initiation of therapy. The mean time for nadir phosphate to be reached was 22 h similar to a previous report.7 The precipitous decline in serum phosphate is thought to reflect mainly intracellular translocation of phosphate.1,2,4 This phosphate redistribution unmasks a state of total body phosphate depletion, which can result in profound hypophosphataemia. It has been suggested that phosphate concentration decreases in parallel with serum potassium during DKA treatment.15 However, our data seem to suggest that the drop in serum potassium precedes the fall in phosphate, as the former is historically known to reach nadir rapidly within 4–6 h of starting treatment.15

Changes in acid–base are also known to cause transcellular phosphate movements. For example, during respiratory alkalosis, the decrease in carbon dioxide causes a rise in the intracellular pH. In the present study, it was interesting to note that the mean venous bicarbonate at time of nadir phosphate was 22.1 mmol/L. Our data would suggest that the normalisation of acid–base status in itself during the process of DKA resolution may contribute to the transcellular flux of phosphate and subsequent hypophosphataemia; this is reflected by our finding of the virtually complete resolution of metabolic acidosis by the time of maximum phosphate fall.

In our study, we found a significant relationship between the severity of initial metabolic acidosis and the extent of hypophosphataemia subsequently. Physiologically, phosphate acts as a major urinary buffer for the excretion of fixed acids. Thus, in those patients with DKA who are significantly acidic on admission, it may be reasonable to assume that they have a low total

![Figure 1](image1.jpg)  
(a) Correlation between initial creatinine and initial serum phosphate. (b) Correlation between initial blood glucose level (BSL) and initial serum phosphate.

![Figure 2](image2.jpg)  
Nadir phosphate and initial venous bicarbonate (mean ± SD). *P = 0.01 when compared to nadir phosphate >0.32. **P = 0.0031 when compared to nadir phosphate >0.5.

© 2012 The Authors  
Internal Medicine Journal © 2012 Royal Australasian College of Physicians
body phosphate to start with (irrespective of their initial serum phosphate level) and are at greater risk of developing severe hypophosphataemia with the institution of therapy. For this at-risk group, prophylactic replacement of phosphate may be justified.

There are several limitations in our study. As the study was retrospective, the intervals of blood sampling were inconsistent across the study population. Nevertheless, the conventional protocol-driven management of DKA dictated relatively frequent blood samplings (maximum intervals of 6 h). Our study is also limited by the reliance on biochemical data alone. As a result, possible contribution of clinical factors, such as length of illness prior to presentation, premorbid medications, insulin dose received as well as fluid replacement were not specifically assessed.

In conclusion, the overwhelming majority of patients demonstrated a fall in serum phosphate during their treatment of DKA, and 11% of episodes recorded a fall in the severely hypophosphataemic range. The initial hyperphosphataemia appears to reflect intravascular depletion and pre-renal impairment. The severity of subsequent hypophosphataemia can be predicted by the degree of metabolic acidosis on presentation. An important caveat to these findings, however, is that statistical relationships do not necessarily imply causality, and these findings need to be interpreted accordingly. To our knowledge, this is the first study to define a risk factor for severe hypophosphataemia during DKA treatment and specifically the prognostic importance of initial acid–base status. Clinicians should be alerted to these findings and their implications for clinical management.

References
Ironic case of hepatic dysfunction following the global withdrawal of sitaxentan

G.W. Don, F. Joseph, D.S. Celermajer and T.J. Corte

Royal Prince Alfred Hospital and Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

Key words
pulmonary arterial hypertension, systemic sclerosis, management, sitaxentan, hepatic dysfunction.

Abstract
A patient with pulmonary arterial hypertension secondary to systemic sclerosis was successfully treated with sitaxentan prior to its worldwide withdrawal (because of hepatotoxicity concerns), but then ironically experienced acute hepatic dysfunction during substitute bosentan therapy, and was eventually stabilised on a phosphodiesterase-5 inhibitor.

Pulmonary arterial hypertension (PAH) is a relatively common complication of systemic sclerosis (SSc) with an estimated prevalence ranging from 4.9% to 26.7%.1 In the modern treatment era with specific therapy for PAH, survival rates for isolated SSc-PAH are improved at 78% at 1 year and 47% at 3 years.2 Data from preceding decades indicated survival rates as poor as 45% and 30% at 1 and 3 years respectively.3 Specific drug therapies available for the treatment of PAH include prostanoids, phosphodiesterase (PDE)-5 inhibitors and endothelin receptor antagonists (ERA).4 ERA therapy has been associated with hepatotoxicity that is typically dose-related and reversible, but there have been seven documented cases of a more severe and apparently idiosyncratic hepatitis that have resulted in two deaths from acute liver failure with sitaxentan.5 One of these deaths occurred during an early premarketing trial,6 and the second was documented in a recent case report.7 In December 2010, following a further two cases of fatal hepatitis during clinical trials, sitaxentan was withdrawn from the global market.8

We report a case where, following successful mono-therapy with sitaxentan, the patient developed acute hepatic dysfunction while taking bosentan, which had been substituted for her well-tolerated sitaxentan after the mandatory withdrawal. She eventually stabilised on a PDE-5 inhibitor. We discuss the alternative therapeutic options available to such patients and the factors involved in choosing the ideal alternative agent in such cases.

A 53-year-old woman from the Philippines presented to the emergency department in October 2010 with a 2-month history of exertional dyspnoea (World Health Organisation (WHO) Class III), orthopnoea and peripheral oedema. She had a 6-month history of skin tightening over her hands and face, arthralgia of the small joints of the hands, hypopigmentation, and Raynaud’s phenomenon. She had no dysphagia, syncope, fever or chest pain. Her background history included peptic ulcer disease and uterine fibroids. She was a current smoker (15 pack years).

On examination, there was skin thickening and hypopigmentation to the mid-forearms. She had clear lung fields but was in right heart failure, with a raised jugular venous pressure at 7 cm, a third heart sound, parasternal heave and pulsatile hepatic margin.

Chest X-ray showed normal lung fields with dilated pulmonary arteries and right heart (Fig. 1). Electrocardiogram revealed right axis deviation. Pulmonary function tests showed a mild restrictive ventilatory defect (forced expiratory volume in 1 s 1.95 L, 81%; forced vital capacity 2.42 L, 79%) and reduced gas transfer capacity (diffusing capacity of carbon monoxide 71%). She had positive antinuclear antibodies with a speckled pattern (>1:2560), double-stranded DNA antibodies and ribonu-
cleoprotein antibodies, although anti-Scl-70 antibodies were not detected. Her liver function was acutely deranged (likely secondary to antibiotics given for a concomitant respiratory tract infection; Fig. 2) but resolved spontaneously over 48 h. Her 6-min walk distance was 376 m.

Transthoracic echocardiography confirmed right atrial and right ventricular (RV) enlargement, with mildly impaired RV contraction. There was severe tricuspid regurgitation with an estimated systolic pulmonary arterial pressure of 55 mmHg. Right heart catheterisation confirmed PAH with a mean pulmonary arterial pressure of 37 mmHg and mean pulmonary capillary wedge pressure below 15 mmHg.

A diagnosis of PAH associated with SSc (group 1 PAH) was made, and she was commenced on sitaxentan 100 mg daily, with improvement of dyspnoea within 48 h. Less than 1 month later, sitaxentan was withdrawn from the global market (10 December 2010), and she was prescribed bosentan 62.5 mg twice daily, as her liver function had improved. Following the change in therapy, her liver function tests deteriorated (Fig. 2) despite cessation of bosentan. One week after ceasing bosentan, she presented with scleral icterus, jaundice and worsening hepatic function. Hepatic ultrasound showed no biliary obstruction. Her liver function tests stabilised over the following week without further intervention. She was subsequently commenced on sildenafil 20 mg three times daily for PAH. Four months post-discharge, her liver function tests are normal, and her dyspnoea much improved with a 6-min walk distance of 416 m (WHO Class I).

This case highlights the fact that discontinuation of a successful monotherapy agent can have serious repercussions for individual patients, notwithstanding hepatotoxicity concerns regarding sitaxentan. It is somewhat ironic in this case that the cessation of sitaxentan because of these concerns resulted in serious hepatic complications and an unnecessary period of clinical functional deterioration.

Current guidelines recommend that the first-line management of PAH patients in WHO functional Class III PAH in the absence of a positive vasoreactivity test is either with ERA or PDE-5 inhibitors. The choice of agent depends upon a variety of factors including comorbidities, side-effect profiles, local prescription regulations and cost restrictions. Our patient was initially commenced on the ERA sitaxentan, as she had had acute hepatic dysfunction, and sitaxentan was considered to have a better side-effect profile with regard to hepatic function. Following mandated withdrawal of sitaxentan, her liver function had improved, and she was prescribed the ERA bosentan. However, following a period of acute but eventually reversible hepatic dysfunction with bosentan, it was discontinued, and she was commenced on the PDE-5 inhibitor sildenafil. It is possible that our patient’s initial liver test abnormalities prior to commencing ERA therapy may have indicated that she was more likely to respond with hepatic dysfunction when commenced on bosentan; however, to our knowledge, this has not been specifically reported in the literature.
In our patient, in Australia, the available alternative therapeutic options for the treatment of WHO functional class III PAH included an alternative ERA agent (bosentan or ambrisentan) or class-switching to a PDE-5 inhibitor (sildenafil). In other locations, alternative PDE-5 inhibitors such as tadalafil are possible considerations. Individual agent choice is likely to be primarily influenced by the side-effect profile and risk of hepatotoxicity, relative efficacy and cost of each agent.

All ERA show varying degrees of hepatotoxicity in clinical trials. The incidence of liver function test abnormalities with bosentan ranges from 3% to 10% at the standard dose of 125 mg twice daily. Further increases in the incidence of liver function abnormalities up to 14% are seen at higher doses (250 mg twice daily) indicating a dose effect. All cases of liver function abnormalities improved with dose adjustment or drug cessation.

In contrast, ambrisentan and sitaxentan were traditionally considered to have lower incidence of hepatic dysfunction. Ambrisentan has an incidence of hepatic dysfunction of 0–2%. The annual incidence of liver function abnormalities during a 2-year trial of ambrisentan was 2%, with just 2 of 383 subjects requiring drug cessation. In fact, in a study specifically assessing the safety of ambrisentan in patients requiring the cessation of bosentan or sitaxentan because of liver function abnormalities, no patient had any significant rise in liver function tests. The incidence of significant hepatic dysfunction associated with short-term sitaxentan administration ranges from 0% to 3% at the standard dose of 100 mg daily, increasing up to 10% at higher doses. Longer term studies of sitaxentan (100 mg daily) up to 58 weeks have indicated that the cumulative incidence of hepatic dysfunction ranges from 3% to 8%. Following reports of four fatal liver injuries because of sitaxentan and an additional four cases of severe reversible liver toxicity, sitaxentan has now been withdrawn from the market.

PDE-5 inhibitors, however, have not been associated with significant hepatotoxicity. The relative efficacy of these agents has not been tested in head-to-head trials, and only indirect inferences can be made. However, there are data supporting the use of each potential PAH therapy as monotherapy over placebo. In the randomised placebo-controlled trial of sildenafil (SUPER-1), sildenafil was associated with improved 6-min walk distance, WHO functional class and pulmonary haemodynamics. There are similar data available for tadalafil, with improvement in pulmonary haemodynamics, exercise capacity and time to clinical worsening.

Bosentan is also associated with improvement in exercise capacity, WHO functional class, decrease in pulmonary vascular resistance, increase in cardiac output and increased time to clinical worsening. Ambrisentan has been associated with improvement in pulmonary haemodynamics, exercise capacity, and WHO functional class and increased time to clinical worsening.

In our case, successful monotherapy with sitaxentan was followed by severe hepatic derangement and worsened clinical function after the withdrawal of this agent from the global market. Our case highlights the fact that discontinuation of a successful monotherapy agent may lead to serious repercussions for individuals. In fact, in this case that the withdrawal of sitaxentan because of concerns with regard to liver dysfunction actually led (indirectly) to serious hepatic complications. Our patient continues on sildenafil as an alternative monotherapy in view of its relatively equivalent clinical efficacy, low incidence of hepatotoxicity and cost-effectiveness.

References

8 European Medicines Agency. Thelin (sitaxentan) to be withdrawn due to...
Brief Communication


Leukaemia cutis in chronic lymphocytic leukaemia following varicella zoster virus reactivation

G. Hapgood, 1 E. Mooney, 2 H. V. Dinh, 2 D. Gin, 2 C. McLean 3 and S. B. Ting 1, 4

Department of 1Clinical Haematology, Alfred Hospital, Melbourne, Victoria, Australia; Department of 2Dermatology, Alfred Hospital, Melbourne, Victoria, Australia and Department of 3Anatomical Pathology, Alfred Hospital, Melbourne, Victoria, Australia and Department of 4Australian Centre for Blood Diseases, Alfred Hospital, Melbourne, Victoria, Australia

Key words
leukaemia cutis, chronic lymphocytic leukaemia, varicella zoster.

Correspondence
Greg Hapgood, Department of Clinical Haematology, Alfred Hospital, Commercial Road, Prahran, Vic. 3181, Australia.
Email: greghapgood@hotmail.com

Received 20 December 2011; accepted 6 May 2012.
doi:10.1111/imj.12000

Abstract
We report a case of a 75-year-old male with indolent chronic lymphocytic leukaemia (CLL) for 8 years, who presented with a 6-month history of a painful, zosteriform eruption in a T3-4 distribution that evolved into an unusual crop of papular nodules. Upon biopsy and immunostaining of these lesions CLL was proven consistent with leukaemia cutis related to varicella-zoster virus reactivation. In the absence of other treatment indices, he was commenced on chlorambucil with successful resolution of both his pain and the lesions.

Chronic lymphocytic leukaemia (CLL) is a monoclonal proliferation of functionally incompetent B lymphocytes. It is the most common leukaemia in Western countries accounting for approximately 25% of leukaemia presentations. The age-adjusted incidence of CLL is 4.1 per 100 000 per year with a median age at diagnosis of 72 years.1 Most commonly, patients are asymptomatic and present with incidental lymphocytosis after a non-related full blood count or with asymptomatic lymphadenopathy in up to 50–90% of cases. Occasionally, patients may have systemic symptoms such as the classical ‘B symptoms’ of unintentional weight loss, fevers and night sweats. Although the natural history of CLL is variable, clinical predictors for initiating treatment include: patients with B symptoms, bulky symptomatic lymphadenopathy or organomegaly, anaemia, thrombocytopenia and/or a lymphocyte doubling time of less than 6 months.2 Patients without these indicators can simply be observed.

Skin lesions in CLL occur in up to 25% of patients. These lesions can be direct through the cutaneous seeding of leukaemic or other malignant cells or indirect due to a range of non-malignant processes such as purpura, pruritus, urticaria, cutaneous vasculitis, Sweet’s syndrome, exaggerated arthropod reactions and infection.3 Leukaemia cutis is the term used to describe the infiltration of neoplastic leukocytes or their precursors into the epidermis, the dermis or subcutis resulting in cutaneous lesions. Leukaemia cutis is a rare phenomenon in CLL and remains much less common than in T cell leukaemias and lymphomas.4

The patient was referred to our clinic with a 6-month history of left-sided painful papules and nodules that had coalesced into plaques on the back and chest in a T3-T4 distribution (Fig. 1). He had no previous episode of varicella zoster virus (VZV) infection or recollection of chickenpox. The lesions began as painful vesicular eruptions that progressed to brown papules and nodules with central follicular plugging. This appeared to represent a classic description of VZV reactivation.

The patient’s CLL had been diagnosed 8 years prior and had not required any treatment based on regular clinical assessments and full blood counts. At the time of these skin eruptions, he had no constitutional symptoms and was Binet stage B with stable bilateral cervical lymphadenopathy and no evidence of hepatosplenomegaly. He had a haemoglobin of 122 g/L, platelet count of 164 × 10^9/L, total white cell count of 93 × 10^9/L and a lymphocyte count of 82 × 10^9/L. His other medical history included diverticulosis and mild-moderate aortic regurgitation under observation.
Amitryptiline had been started for pain 2 months after the lesions arose with some effect. Five months after developing the lesions, he was treated with oral valaciclovir (500 mg tds for 4 weeks) under the guidance of the infectious diseases unit, but this provided no significant improvement in pain or appearance, and he was referred to the dermatology unit. The lesions were dry at this stage, and material for polymerase chain reaction testing for VZV could not be obtained. VZV serology was not performed at this time.

Two punch biopsies of the lesions revealed a dermal infiltrate composed of predominantly small cells interspersed with intermediate-sized cells, both with ovoid nuclei and a high nuclear : cytoplasmic ratio. The intact surface epidermis appeared normal. Scattered single-plasma cells and histiocytes were noted. Immunohistochemistry revealed diffuse activity of the infiltrate with the classic CLL immunophenotype of CD5 and CD23 positivity. There was also granular cytoplasmic CD20 reactivity and a population of CD3 cells. The biopsies were consistent with CLL.

The patient was then referred to the haematology unit where restaging for his CLL was performed. During the progression of the painful zosteriform eruption, there were no associated B symptoms. The examination findings of cervical lymphadenopathy and the absence of hepatosplenomegaly remained stable during this period. His haematologic parameters had not worsened. Serum immunoglobulins revealed hypogammaglobulinemia with an IgG of 5 g/L (7–16.5 g/L) and a mildly elevated β2 microglobulin of 3.8 mg/L (1.2–2.5 mg/L). Computed tomography staging revealed stable lymphadenopathy of the neck, mediastinum, axillae, para-aortic, mesenteric and inguinal regions and no evidence of hepatosplenomegaly. Bone marrow biopsy revealed a markedly hypercellular marrow with a diffuse pattern of infiltration by lymphocytes that were identical in size and shape to the lymphocytic infiltration seen in skin biopsies. Cytogenetic analysis revealed a complex karyotype that included monosomy 5, and deletions in 6q and 13q. In summary, although he had stable Binet stage B CLL, associated biochemical tests together with the complex cytogenetics,5 may suggest the leukaemia cutis to be a portent of active clinical disease.

In order to treat his pain and the leukaemia cutis, chlorambucil was initiated at a dose of 0.1 mg/kg per day. It resulted in a reduction of his pain to the degree that he was able to cease his amitryptiline after 4 weeks. In parallel, his skin lesions began to subside, and significant aesthetic improvement was noted after 2 months of chlorambucil (Fig. 2). Correlative blood parameters showed a fall in his lymphocyte count to $33 \times 10^9/L$ without impairment to his haemoglobin or platelet counts.

Cutaneous manifestations of CLL are not uncommon. However, our case study of leukaemia cutis associated with CLL is very infrequent, and the patient’s presentation in a dermatomal area of VZV reactivation further highlights this unusual case. There have been reports of new onset CLL presenting as leukaemia cutis at the site of herpes zoster scars4,6 and patients with CLL developing leukaemia cutis at the site of herpes zoster eruption.7 In our case, as in other reports, the CLL infiltrate appears to be a secondary phenomenon after VZV infection has regressed. It has been proposed that malignant B lymphocytes are recruited to the area in response to the antigenic stimulus. Recruitment should be regarded as reactive rather than a true metastatic process.8 Malignant B lymphocytes may koebnerise at dorsal root ganglia and become activated under certain infectious (e.g. VZV reactivation) and/or non-infectious stimuli. This activation could enable malignant B lymphocytes to migrate along nerve roots and lead to skin deposition. An alternative hypothesis is that circulating malignant B lymphocytes are attracted to a site of antigenic stimulation, and this leads to skin deposition. The acquisition and/or loss of certain adhesion molecules by malignant B lymphocytes may modulate their interactions with cell wall proteins.
and extracellular matrix proteins thereby facilitating their migration into the skin. 

Although the data regarding the prognostic significance of leukaemia cutis in CLL are sparse, the occurrence does not seem to adversely affect outcome. Earlier work suggested that leukaemia cutis in patients with CLL conferred a poor prognosis, often followed by blast crisis and death. While this certainly is the case in Richter’s syndrome (large cell transformation), it appears that patients with CLL infiltrates have a better prognosis than was originally thought. In the largest report of cutaneous infiltrates in CLL, the 5-year survival in 42 patients was 66%. The same study suggested that the mean duration of disease before skin manifestations was 39 months, and in seven patients, skin lesions were the first sign of disease. In four of these patients, lesions were confined to the sites of previous herpes zoster scarring.

There is a paucity of information available regarding the treatment options for leukaemia cutis in CLL. The literature consists of isolated case reports. The management of cutaneous B and T cell leukaemias and lymphomas is complex and based on staging and patient comorbidities. Although treatments used previously include intralesional steroids, radiotherapy and systemic chemotherapy, there are too few cases in the literature for firm recommendations to be made.

Local therapy for skin disease may delay or obviate the need for systemic chemotherapy. Colburn et al. reported two cases of leukaemic cutis in CLL involving the ear. One patient received intralesional steroid injections to no avail followed by successful radiotherapy. The other patient was simply observed.

Ultraviolet (UV) B phototherapy has been used in the management of recurrent leukaemia cutis in a CLL patient. The patient had extensive lesions over his abdomen, nose, arms and upper back. Twenty four treatments with UVB therapy resulted in marked resolution of the lesions as well as improvements in his haematological indices. His lesions recurred 6 months after, and he received a second successful course of UVB. The mechanism of action of UV therapy is not well understood despite its use in cutaneous T cell lymphomas. It may alter the cutaneous cytokine profile thereby driving migration of lymphocytes from the skin into the blood.

Systemic chemotherapy has also been successfully used. Gibbs et al. presented two cases of CLL presenting with cutaneous involvement that were both successfully managed with oral chlorambucil. One patient was treated for 4 months and remained in complete remission at 10 months. The other patient achieved partial remission after 6 months. In an example with systemic symptoms, Claeyss et al. used fludarabine and cyclophosphamide to treat a case of painful facial leukaemia cutis. In this case, chemotherapy resulted in regression of the lesions after one cycle.

Given the only indication for treatment commencement in our patient was the pain and aesthetics associated with his skin lesions, we elected to use chlorambucil, which is well tolerated in the elderly. Within 4 weeks of starting treatment, his pain resolved and his lesions markedly reduced in size. Treatment of the underlying CLL with an active chemotherapy agent may result in improvement of leukaemia cutis. Clinicians should consider leukaemia cutis in patients with CLL presenting with unusual or persistent cutaneous lesions.

References

Successful treatment of macrophage activation syndrome complicating adult Still disease with anakinra

N. K. Loh,1 M. Lucas,2,3 S. Fernandez4 and D. Prentice1

Departments of 1Internal Medicine, 2Immunology and Pathwest Laboratory Medicine, Royal Perth Hospital, 3Centre for Clinical Immunology and Biomedical Statistics, Murdoch University and 4School of Pathology and Laboratory Medicine, University of Western Australia, Perth, Western Australia, Australia

Key words
anakinra, macrophage activation syndrome, adult Still’s disease, haemophagocytic lymphohistiocytosis, natural killer cell.

Abstract
A previously healthy 20-year-old man presented with adult Still disease (ASD). He developed life-threatening macrophage activation syndrome (MAS), which was refractory to standard immunosuppression but responded dramatically to the IL-1 receptor antagonist anakinra. Subsequent immunological investigations included assessment of the perforin expression of natural killer (NK) cells and CD8+ T cells, which confirmed MAS.

A previously fit and healthy 20-year-old recent Afghani migrant of Hazari ethnicity presented with a 2-week history of daily spiking fevers in excess of 39°C, myalgia, sore throat, a truncal rash and diarrhoea. On examination, mild hepatosplenomegaly and mild generalised lymphadenopathy was elicited. An evolving maculopapular rash over his upper trunk was noted.
Investigations revealed a normocytic anaemia, marked leukocytosis, elevation of inflammatory markers and hyperferritinaemia (18 500 ng/mL) (see investigation time line, Fig. 1). Empiric treatment with parenteral broad-spectrum antibiotics was initially commenced for a suspected infective cause, with no clinical response. A comprehensive screen for infection, malignancy, autoimmune disease and vasculitis was unremarkable, and a clinical diagnosis of adult Still disease (ASD) was established.

During his second week of admission, his fever became unremitting, and he developed pancytopenia, acute renal failure and a consumptive coagulopathy. Persistent elevation of inflammatory markers, plasma levels of IL-6, TNF-α and fasting triglycerides were demonstrated. The ferritin had risen to 155 000 ng/mL. Imaging studies

![Investigation timeline](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Admission</th>
<th>Pre-anakinra</th>
<th>Pre-discharge</th>
<th>Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/L)</td>
<td>96</td>
<td>70</td>
<td>105</td>
<td>109</td>
</tr>
<tr>
<td>Platelet count (x 10^9/L)</td>
<td>327</td>
<td>15</td>
<td>179</td>
<td>250</td>
</tr>
<tr>
<td>Leucocyte count (x 10^9/L)</td>
<td>21.2</td>
<td>2.85</td>
<td>6.35</td>
<td>7.25</td>
</tr>
<tr>
<td>INR</td>
<td>1.3</td>
<td>2.2</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.5</td>
<td>0.3</td>
<td>0.7</td>
<td>3.6</td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
<td>-</td>
<td>&gt;20</td>
<td>3.82</td>
<td>2.39</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>60</td>
<td>139</td>
<td>48</td>
<td>57</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>240</td>
<td>210</td>
<td>11</td>
<td>1.3</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>18 500</td>
<td>155 000</td>
<td>15 000</td>
<td>-</td>
</tr>
<tr>
<td>IL-6 (mg/L)</td>
<td>-</td>
<td>95</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TNF-α (ng/L)</td>
<td>-</td>
<td>17</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Triglycerides (fasting, mmol/L)</td>
<td>-</td>
<td>3.8</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>ASD</th>
<th>MAS plus ASD</th>
<th>Convalescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments</td>
<td>Glucocorticoids</td>
<td>Anakinra</td>
<td>Cyclosporine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>40</td>
<td>39</td>
<td>39</td>
</tr>
</tbody>
</table>

Figure 1 Investigation timeline.
demonstrated interval progression in hepatosplenomegaly, pelvic, inguinal and axillary lymphadenopathy. Multiple organ biopsies revealed reactive histiocytosis, with haemophagocytosis seen on an inguinal lymph node biopsy. A diagnosis of macrophage activation syndrome (MAS), complicating ASD was established.

Systemic immunosuppression was initiated (high-dose pulse IV methylprednisolone followed by hydrocortisone) during the second week of the hospital stay. Despite an initial transient response, the continuous fever returned, and the patient developed acute respiratory distress syndrome (ARDS) and a severe inflammatory response syndrome requiring intubation and inotropic support. In week 3, anakinra (200 mg IV) was administered. The patient rapidly defervesced – inotropes were weaned, and he was extubated 3 days later. Six days post-anakinra, he was commenced on maintenance anakinra (100 mg subcutaneous, once daily) and cyclosporine A (100 mg, twice daily). The patient was discharged from hospital 12 days following commencement of anakinra functionally normal, with normalised inflammatory markers, renal biochemistry and improving haematological parameters. Cyclosporine and prednisolone were de-escalated with introduction of methotrexate. He developed recrudescence of symptoms when anakinra was inadvertently ceased. He remains clinically well with normal inflammatory markers and ferritin, dependent on a maintenance regimen of anakinra (100 mg subcutaneous, once daily) with methotrexate (10 mg, weekly).

We subsequently analysed total cell numbers and perforin expression of natural killer (NK) cells and CD8+ T cells in our patient at two time-points, shortly after initial presentation prior to anakinra therapy (Fig. 2, marked by arrow), and 1 year later while on daily anakinra. Flow cytometric analysis was performed using a BD Biosciences (San Jose, CA, USA) FACSCalibur flow cytometer. All antibodies used in the analysis were purchased from Becton Dickinson and used according to the manufacturer’s guidelines. Analysis revealed a significant reduction in total NK-cell numbers (CD3-/CD56+dim) at both time-points when compared with the numbers detected in 10 healthy age-matched controls (Fig. 2a). Interestingly, we also observed a reduction of CD56++bright NK-cells, which has been described previously in MAS1-2 (Fig. 2b). Although the exact role of the CD56++bright NK cell subset remains to be clarified, it is thought that these cells have immunoregulatory properties via the secretion of cytokines and may contain CD56+dim NK cell precursors.1 A reduction in total CD8+ T cell numbers was not seen (Fig. 2c). Overall, no significant change of total NK cell numbers or the CD56++bright NK-cell subset was seen between the two time-points, namely before and during treatment with anakinra. This may indicate that anakinra itself does not rectify any underlying immune dysregulation but serves as symptomatic treatment. Furthermore, perforin levels within the NK-cell and CD8+ T cell population were not significantly reduced when compared with the control group (n = 10; data not shown). We can, however, not exclude functional perforin deficiency. Given the persistent immunological changes observed, further genetic analysis for underlying germ-line mutations in this case may be warranted.

Although ASD and MAS share common features, several features distinguish the two conditions. After the initial diagnosis of ASD, clinical deterioration with an unrelenting fever, pancytopenia, acute renal failure and consumptive coagulopathy heralded the onset of MAS. The development of pancytopenia in MAS is a consequence of phagocytosis.3,4 The coagulopathy associated with MAS related to hepatic dysfunction or endothelial damage and resembles disseminated intravascular coagulation.5 ARDS has also been reported and associated with high mortality.6 The degree of hyperferritinaemia observed in MAS is over an order of magnitude higher (averaging >60 000 ng/mL) than seen in ASD alone (averaging 4700 ng/mL).6,7 As a result of considerable clinical overlap, recognition of MAS complicating ASD is difficult, and its incidence is probably underestimated.6 The diagnostic pathological finding in MAS is the haemophagocytosis of red cells, leukocytes or platelets.8

MAS is a secondary form of haemophagocytic lymphohistiocytosis (HLH). Immunological characteristics in MAS include a marked reduction in NK-cell function and/or numbers and a reduction in cytotoxic activity of CD8+ T-cells, leading to defective clearance of activated macrophages.5,9 In a subtype of familial HLH, mutations in the gene encoding perforin (PRF-1), a protein important for the cytotoxic activity of T and NK cells, have been described, which lead to low or absent perforin protein expression.10 Furthermore, studies in patients with soJRA also demonstrated decreased perforin expression, which may account for the association between MAS and soJRA.10 In a series of patients with MAS complicating soJRA, two subsets of patients were identified, one with profoundly decreased NK-cell numbers but normal perforin levels and the other with mildly decreased NK-cell numbers but very low levels of perforin expression.11 The marked reduction in NK-cell numbers with only a mild decrease in perforin levels in our patient was consistent with the diagnosis of MAS.

There is currently no established protocol for the treatment of MAS complicating ASD. Cyclosporine and high-dose glucocorticoids have been used with success in MAS secondary to soJRA.12 Intravenous immunoglobulin has
been used with limited success.\textsuperscript{13} Etoposide is usually reserved for patients who fail to respond to cyclosporine and glucocorticoids as adjunctive therapy or as part of the HLH-2004 protocol.\textsuperscript{14} Experience with biological agents is limited. TNF-\(\alpha\) inhibition to block CD8\(^+\) T-cell mediated macrophage stimulation was postulated as a promising target for treatment. In the paediatric setting, Etanercept, an anti-TNF-\(\alpha\) agent, has been used with dramatic response in MAS secondary to soJRA\textsuperscript{15} but worryingly, was also thought to have induced MAS in the treatment of soJRA\textsuperscript{16} as well as worsening of disease and exacerbations of autoimmune disease.\textsuperscript{17}

Interleukin-1 also plays a central role in the pathogenesis of ASD and MAS. Two underlying defects are likely to contribute to the dysregulation of IL-1 in these diseases. First, the possible loss of control of IL-1 secretion as seen in soJRA\textsuperscript{17} in conjunction with unopposed macrophage activation in MAS, and second, reduced inhibition of IL-1 by its specific competitive antagonist IL-1 receptor antagonist (IL-1RN) as described for ASD and other similar autoinflammatory conditions.\textsuperscript{18} This combination likely culminates in the IL-1-driven clinical picture of unremitting fever, severe constitutional symptoms, and significant tissue damage seen in ASD plus MAS. Anakinra, an IL-1R antagonist, has shown reliable efficacy in the treatment of soJRA,\textsuperscript{19,20} ASD,\textsuperscript{18,21–23} and paediatric MAS secondary to histiocytic panniculitis plus soJRA.\textsuperscript{24,25}

Anakinra was chosen in our patient rather than cyclosporine alone, which takes weeks to achieve a biological effect. The dramatic and rapid resolution following treatment with anakinra in this case adds further evidence to the important pathogenic role of dysregulation of IL-1

\begin{figure*}[h]
\centering
\includegraphics[width=\textwidth]{flow_cytometry.png}
\caption{Flow cytometric analysis of lymphocyte subsets. (a) Significant persistent reduction of the proportion of CD56\(^+\) natural killer (NK) cells per CD3\(^{-}\)lymphocytes in Case MAS/ASD pre- (arrow) and during 1 year into the anakinra therapy as compared with healthy controls \((n=10)\). (b) Reduction of the proportion of CD56\(^{++}\) bright NK cells per CD3\(^{-}\)lymphocytes in Case MAS/ASD pre- (arrow) and during anakinra therapy as compared with healthy controls. (c) Proportion of CD8\(^+\) T cells/total lymphocytes in Case MAS/ASD pre- (arrow) and during anakinra therapy and healthy controls.}
\end{figure*}
in ASD plus MAS. Accordingly, other agents, such as anti-IL 1β monoclonal antibodies of IL-1 Trap molecule, which reduce IL-1 activity, are also likely to be effective.

Acknowledgements

The authors acknowledge Janet Roddy, Nicola Cook and Mark Reed (Department of Rheumatology, Royal Perth Hospital) for input to the patient’s care and to Kathie Tymms (ANU Medical School) for the patient’s ongoing management. We thank Katja Pafferrott (Centre for Clinical Immunology and Biomedical Statistics) for her assistance with the flow cytometric analysis and Martyn French for the helpful discussion. Canberra Rheumatology donated anakinra for several months prior to a government subsidy becoming available.

References


LETTERS TO THE EDITOR

Clinical-scientific notes

Rapid recovery of renal function after pulse steroid therapy in a human immunodeficiency virus-infected patient with glomerulonephritis

Renal disease is an important complication of human immunodeficiency virus (HIV) infection and its prevalence is increasing. HIV-specific renal lesions are well described and include HIV-associated nephropathy as well as HIV immune complex disease of the kidney and thrombotic microangiopathy. These HIV-associated lesions are seen less commonly in the era of highly active antiretroviral therapy (HAART), but still remain important in those patients with a late diagnosis of HIV, or those patients not on therapy. In the HAART era, toxicities from antiretroviral drugs and complications from non-infectious comorbidities have become more frequent causes of chronic kidney disease in this patient cohort. Concurrent primary kidney diseases are also seen with the increased survival of this patient cohort. Clinically, it is often difficult to distinguish these aetiologies in the absence of a renal biopsy.

For the first time, we describe an HIV-infected patient with acute kidney injury secondary to anti-neutrophil cytoplasm antibody (ANCA)-negative pauci-immune mesangial proliferative glomerulonephritis on a background of acute tubular necrosis, with rapid response to treatment with steroid therapy. The absence of ANCA is unusual; ANCA are frequently found in the sera of HIV-positive patients, often in patients with no signs of vasculitis. ANCA-associated microscopic polyangiitis has previously been described in HIV-infected patients.

A 63-year-old white man presented to the emergency department short of breath in September 2011. At presentation, he had acute respiratory distress, with a respiratory rate of 44 breaths per minute, and an oxygen saturation level of 66% on room air. He was afebrile with spontaneous clearance and renal impairment, which had not been investigated. In December 2010, his serum creatinine was 125 μmol/L; estimated glomerular filtration rate (eGFR) 54 mL/min/1.73 m².

After resuscitation, he was admitted to the intensive care unit (ICU) and treated for proven Pneumocystis jiroveci pneumonia. He had acute kidney injury, presumed secondary to his acute illness. The creatinine on admission to ICU was 881 μmol/L; eGFR 6 mL/min/1.73 m². He required invasive ventilation and continuous venous haemodialysis and was commenced on sulphamethoxazole and trimethoprim. He remained in the ICU for 2 weeks and gradually improved.

Upon renal review after discharge from ICU, he was dialysis dependent. Further investigations revealed dysmorphic microhaematuria and a 24-h protein excretion of 0.6 g. Renal ultrasound demonstrated normal-sized kidneys without obstruction. Autoantibodies against neutrophil cytoplasm, glomerular basement membrane and double-stranded DNA were negative, as was his antinuclear antibody. No cryoglobulins were detected in the serum. The serum electrophoresis and complement levels were normal. Hepatitis B virus (HBV)-DNA and hepatitis B surface antigen were not detected, nor was hepatitis C antibody. A renal biopsy was performed (Fig. 1). Histologically, the primary diagnosis was pauci-immune mesangial proliferative glomerulonephritis with crescents in 30% of glomeruli sampled. There were no immune deposits on electron microscopy and the immunofluorescence was negative. In addition, the tubules demonstrated degenerative changes consistent with acute tubular necrosis.

Despite concerns regarding the use of immunosuppressive treatment in a profoundly immunodeficient patient, therapy with intravenous bolus methylprednisolone (500 mg daily) was commenced to test for reversibility of the glomerular lesion. After 3 days, the patient was converted to oral prednisone therapy (1 mg/kg). He was placed on prophylaxis against other infective complications with azithromycin, valacyclovir and fluconazole. There was a rapid improvement in renal function (Fig. 1c). At review in December 2011, his creatinine was 124 μmol/L; eGFR 54 mL/min/1.73 m². The patient has also commenced abacavir, lamivudine and nevirapine, agents chosen to avoid renal toxicity. He continues on prophylactic dose sulphamethoxazole and trimethoprim.

The broad spectrum of renal diseases seen in HIV-infected patients often results in difficulty in making an accurate diagnosis in the absence of a renal biopsy.
Figure 1 Renal biopsy; (a) cellular crescent in an affected glomerulus (periodic acid-Schiff stain, ×10). Crescents were present in 30% of glomeruli sampled. (b) Mesangial hypercellularity without focal necrosis (haematoxylin–eosin stain, ×10). Typical changes of acute tubular necrosis can also be seen. The primary histological diagnosis was pauci-immune mesangial proliferative glomerulonephritis with crescents, and concurrent acute tubular necrosis. (c) Time-course of the patient’s serum creatinine (μmol/L) before and after treatment with steroids. i.v., intravenous.
Drug reaction with eosinophilia and systemic symptoms associated with H1N1 vaccination

A 19-year-old Asian woman presented with a 10-day history of lethargy, fevers, pharyngitis, abdominal pain, lymphadenopathy, pruritic maculopapular rash and petechiae. She had a history of seronegative rheumatoid arthritis, treated for 12 months with sulphasalazine, and underwent H1N1 vaccination 4 days prior to symptom onset.

Laboratory findings revealed abnormal liver function, eosinophilia and thrombocytopenia (Table 1). Abdominal ultrasound showed hepatitis, cholecystitis, periportal lymphadenopathy, splenomegaly and ascites. Sulphasalazine was ceased. Punch biopsy of cutaneous lesions were consistent with drug-induced eruptions. Human Herpes Virus 6 (HHV6) serology confirmed reactivation and lymph node biopsy revealed reactive necrotising lymphadenitis. Recovery was complicated by pneumonia, warm antibody haemolytic anaemia, disseminated intravascular coagulation plus thrombosis and methicillin-resistant Staphylococcus aureus septicemia related to peripherally inserted central catheter insertion. Based on the clinical course and the RegiSCAR scoring system, this is a probable/definite case of drug reaction with eosinophilia and systemic symptoms (DRESS).1

DRESS syndrome is a severe, idiopathic drug-induced delayed hypersensitivity syndrome characterised by skin rash, fever, lymphadenopathy, haematological abnormalities and internal organ involvement.2,3 The clinical presentation of DRESS syndrome is variable and occurs in response to a range of drugs, usually 3 weeks to 3 months after initiation, with multiple reported cases attributable to sulphasalazine.4–6

There is no accepted treatment for DRESS syndrome beyond cessation of the culprit drug. In sulphasalazine-induced DRESS syndrome, symptom onset has reportedly occurred after 2, 4 and 8 weeks drug treatment.6–9 The mechanism responsible for the unpredictable temporal relationship between drug initiation and onset is undetermined. This case highlights the potential for DRESS to occur after longer drug exposure than generally accepted and in association with immune response to H1N1 vaccination.

References

Patch and lymphocyte transformation testing have revealed drug-specific T-cell expansion in response to drug antigens in DRESS, with this T-cell expansion a potential mechanism in the development of DRESS. Reactivation of herpes viruses, in particular HHV6, has been confirmed in this and many other cases of DRESS syndrome and is suggested to contribute to hypersensitivity reactions. It is believed the drugs capable of causing DRESS reactions potentially induce immunosuppression. This immunosuppressed environment triggers reactivation of latent viruses and consequently a non-specific mass immune system response through virus-specific and non-specific T cells. It is possible that the non-specific immune response to H1N1 vaccination may have contributed in a similar way to the development of DRESS in this patient. Despite reported association of viral infection and DRESS, there is no published association of DRESS and H1N1 vaccination. Perhaps, sulphasalazine combined with the immune response post vaccination triggered a pathogenic antiviral CD8+ immune response. Alternative theories of reactive oxidative metabolite accumulation due to abnormal production and detoxification of drug metabolites or genetically determined slow acetylation of the sulphapyridine component of sulphasalazine would not explain the delay in the development of DRESS.

This case fits the clinical presentation of DRESS syndrome and occurred during drug therapy with sulphasalazine, a known causative agent. The onset of symptoms occurring more than 12 months after drug initiation has not previously been reported in the literature.

Received 9 May 2012; accepted 16 July 2012.

doi:10.1111/imj.12012

N. Hewitt,1 M. Levinson2,3 and G. Stephenson3
1Department of Infectious Diseases, St Vincent’s Hospital,
2Professorial General Medicine Unit, Cabrini Hospital and
3Cabrini-Monash Department of Medicine, Cabrini Hospital,
Melbourne, Victoria, Australia

Table 1 Results of pathology tests performed during admission

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference range</th>
<th>Day of admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>20–105</td>
<td>70</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>5–35</td>
<td>152</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>5–30</td>
<td>237</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>10–35</td>
<td>133</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>3–15</td>
<td>23</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>115–160</td>
<td>115</td>
</tr>
<tr>
<td>Platelets (x10⁹/L)</td>
<td>150–450</td>
<td>155</td>
</tr>
<tr>
<td>INR</td>
<td>0.8–1.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Eosinophils (x10⁹/L)</td>
<td>0–0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Lymphocytes (x10⁹/L)</td>
<td>1.0–4.0</td>
<td>2.9</td>
</tr>
</tbody>
</table>

—, Test not performed; ALP, alkaline phosphatase; ALT, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalised ratio.

References
The i-patient or the eyeball patient?

A 44-year-old woman presented to the emergency department complaining of severe central chest pain for 2 weeks. Sequential electrocardiograms and cardiac enzymes were normal; however, an anteroposterior chest X-ray revealed bilateral pulmonary opacities both with air-fluid levels (Fig. 1), and the white cell count was raised at $19.9 \times 10^9$, with 82% neutrophils.

A review of the website-du-jour favoured by trainee physicians offers the following list of likely microorganisms as causative agents of pulmonary abscesses, with the more exotic likely to be found in immunocompromised patients. Most frequently cultured are anaerobes, particularly Peptostreptococcus, Prevotella, Bacteroides (usually not *Bacteroides fragilis*) and Fusobacterium spp., less frequently cultured are non-anaerobes, particularly *Streptococcus milleri* and other microaerophilic streptococci.

Other possibilities include *Staphylococcus aureus*, *Klebsiella pneumoniae*, other Gram-negative bacilli, *Streptococcus pyogenes*, *Burkholderia pseudomallei*, *Haemophilus influenzae* type b, Legionella, Nocardia and Actinomyces. Transthoracic needle aspiration is suggested particularly for identification of the microorganism in resistant cases.

However, returning to the patient to clarify some issues, she gave a history of bilateral breast duct excision for duct ectasia confirmed on histology 18 days previously. A review of the lateral chest X-ray shows the larger air-fluid level to be in the breast, not in the lungs (Fig. 2). A computed tomography pulmonary angiogram was performed to exclude postoperative pulmonary emboli, revealing clear lung fields, but a small amount of gas in the right breast (Fig. 3).

There still appears to be a place for the traditional history and examination before investigations, the eyeball patient before the i-patient.

Received 1 May 2012; accepted 24 May 2012.

doi:10.1111/imj.12013

P. J. O. Stride,1,2 T. Wood,3 J. M. Hunter,2 A. L. Reid2 and S. Walsh2

1University of Queensland School of Medicine and Departments of
2Medicine and 3Radiology, Redcliffe Hospital, Brisbane, Queensland, Australia
General correspondence

FDG-PET for investigation of patients with fever of unknown origin

We read with interest the work of Kim et al.1 regarding the use of positron emission tomography (PET) with fluorodeoxyglucose (FDG) combined with computed tomography (CT) for investigation of patients with fever of unknown origin (FUO). We are concerned that the conclusions drawn from the case series do not match the data presented.

It is erroneous to claim that PET/CT contributed to the diagnosis in 65.8%. Fewer than half of the cases in the series underwent the investigation. Additionally, the inherent nature of a retrospective series and the nonsystematic use of PET imaging in this study make it difficult to conclude other than that PET contributed to the diagnosis in about 23% of cases in a selected series. In the cases when PET was not undertaken, it is not known whether the investigation would have provided assistance.

There are certainly cases where PET/CT may aid in making a diagnosis in FUO, but in many of the cases presented here, other investigations with greater specificity would have been required to make the diagnosis and it is not clear how PET/CT assisted. For example, the most common final diagnosis established after PET/CT was tuberculosis. Microbiological examination of patient samples is required to diagnose this disease. Was the site of involvement really occult on baseline evaluation requiring PET/CT to identify it? In the case of Kikuchi disease, the next most common diagnosis, histopathological examination of an excised lymph node is required to confirm the diagnosis. In a patient with prolonged fever and lymphadenopathy, excisional biopsy is required whether or not PET/CT is employed.

Similarly, the article claimed that PET/CT was helpful in establishing diagnoses of haematological and endobronchial malignancy, Crohn disease, haemophagocytic disease and thyroiditis. Bone marrow biopsy, CT chest, colonoscopy, serum ferritin level and thyroid function tests would be more cost-effective and have higher screening value than FDG-PET/CT as second-line components in the approach to the patient with FUO.

For FUO, the diversity of the causes and variations related to locality and patient age preclude the development of universally applicable algorithms to its diagnosis. Appropriate use of new technologies can be of benefit in establishing difficult diagnoses. Certainly, it is helpful to gain an understanding of how PET/CT can assist in the evaluation of FUO, but it is important to understand the limitations of any dataset in drawing conclusions from it.

Received 31 August 2012; accepted 26 September 2012.

doi:10.1111/imj.12009

J. C. Lee1,2 and A. M. Redmond2,3
1Department of Nuclear Medicine, The Prince Charles Hospital, 2School of Medicine, University of Queensland and 3Infectious Diseases Unit, Royal Brisbane and Women’s Hospital, Brisbane, Queensland, Australia

Reference


Reply

We thank Lee et al. for their comments.1 In our study,2 52.1% of all 18 F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) scans were considered clinically helpful, and 65.8% of abnormal scans contributed to the final diagnosis of fever of unknown origin (FUO). A meta-analysis shows that the 62.1% of the FDG-PET/CT findings contributed to obtaining a final diagnosis in cases of FUO.3 We agree that the role of PET/CT could have been overestimated in our study. The relatively high rate of contribution of PET/CT findings to the final diagnosis could have been due to the following reasons. First, as I described in the manuscript, patients in whom the cause of FUO was diagnosed during the first-line work-up were excluded. Although these patients are satisfactory the classic FUO criteria, they were excluded in our study.
Second, PET/CT was performed in a relatively early stage of the clinical course. This was because patients were usually afraid of or refused to undergo invasive procedures such as bone marrow biopsy, liver biopsy, or surgical procedures other than usual cutaneous lymph node biopsies; therefore, we could not decline patients’ requests to undergo PET/CT. Third, we defined PET/CT to be ‘helpful’ if abnormal uptake in 18F-FDG PET/CT images facilitated further invasive diagnostic evaluations such as surgery or biopsy. In light of these considerations, we feel that the value obtained in our study, that is, 65.8%, was not erroneous but valid.

Tuberculosis was the most common cause of FUO in our study. We already knew that simple lymphadenopathy can be diagnosed with biopsy. However, all TB cases in our study were extrapulmonary tuberculosis including 1 colitis, 1 spleen tuberculosis, and 3 mesenteric lymphadenopathy. In these cases, more proof was required to validate the necessity of an invasive procedure like laparoscopic biopsy. Tuberculosis is one of the most important causes of FUO in Korea, and especially in extrapulmonary tuberculosis, it is difficult to diagnose the condition using a conventional investigation methods because of non-specific manifestation.4–6

PET/CT can reveal pathological metabolic foci as well as anatomic localisation. For patients who tend to avoid the invasive procedures such as surgery or bone marrow biopsy, PET/CT can serve as a bridge method that can convince the patient to undergo more aggressive procedures.

Despite recent advances in diagnostic techniques, the differential diagnosis of FUO remains extensive. In patients with FUO, PET/CT can be considered a useful second-line tool that can allow localisation of the focal origin and thereby facilitate targeting for invasive procedures. However, there is no consensus over the cost-effectiveness of PET/CT, and further studies on its cost-effectiveness are needed to address this aspect.

Received 26 September 2012; accepted 4 October 2012.
doi:10.1111/imj.12004

Y. J. Kim, S. I. Kim, K.-W. Hong and M. W. Kang
Division of Infectious Disease, Department of Internal Medicine, Seoul St Mary’s Hospital, The Catholic University of Korea, Seoul, Korea

References

A plea for the use of systematic review methodology when writing guidelines and timely publication of guidelines

We wish to express concern about the timing and title of the recently published position paper by the Stroke Guidelines Expert Working Group.1 Because the paper post-dates the circulation of the 2010 Guidelines by about 2 years, the unwary reader may perceive that this article provides an update to these guidelines. This is certainly not the case because the main purpose of the article was to show how the 2010 guidelines have differed between the 2005 and 2007 stroke guidelines. This also highlights the problem of guideline development for stroke in Australia because there is no systematic or efficient mechanism to ensure timely updates when the evidence changes. A high-quality guideline requires clinical experts to perform thorough systematic reviews to support their recommendations and ensure that the recommendations accurately reflect the journal articles on which they are based.2–5 Evidence is continually changing, so fast-tracking journal submissions to coincide with the release of new guidelines is essential. We demonstrate this need later by alerting readers to some significant advances that have occurred, as these guidelines were produced in the area of stroke treatment2,6,7 as well as differences in interpretation of the data.2–5 There are also other trials results that have been presented at recent
international meetings and are likely soon to find their way into journals. We summarise our position as follows:

3.1a. Assessment of transient ischaemic attack (TIA) – Two recent Australian studies, and several other studies have confirmed the poor predictive value of the ABCD2 score in stratifying stroke risk in an individual TIA patient. These findings have also now been firmly substantiated in a comprehensive meta-analysis. Indeed, inappropriate classification of risk with this score may result in missing urgently modifiable factors such as atrial fibrillation (AF) and carotid stenosis. Therefore, there is no value in using the ABCD2 score as a prognostic tool to guide urgent clinical decision making.

4.1b. IV recombinant tissue plasminogen activator – Given that European Cooperative Acute Stroke Study was conducted in people <80 years of age, the recommendation that ‘therapy should commence in the first few hours but may be used up to 4.5 hours after stroke onset’ should include this age cut-off.

Acute blood pressure (BP) lowering – inclusion of a new recommendation to acute medical management (4) – There is evidence from the Scandinavian Candesartan Acute Stroke Trial that BP lowering in the acute phase of stroke may carry a risk of stroke progression, with no clear evidence of benefit. This may be considered Grade B evidence, and it is therefore advisable to recommend avoiding BP-lowering drugs in the first week of acute stroke unless thrombolysis is considered or excessively high BP is encountered in patients with haemorrhagic stroke.

5.37. BP lowering (secondary prevention) – In light of the earlier discussion, it may be advisable to place a caveat on the current BP lowering recommendation to delay commencement of BP lowering therapy to at least a week after stroke onset.

5.5. Anticoagulation – We are aware of evidence for the use of anticoagulation for AF and mural thrombus. It could be suggested that a Grade A recommendation may not apply in all suspected cardioembolic stroke (i.e. those with no AF or mural thrombus). The evidence for use of anticoagulation for suspected cardioembolic stroke without AF or mural thrombus is more likely to be Grade D. The issue about when anticoagulation can be started is also controversial and does not yet justify the Grade C recommendation stated. Perhaps it should be left to treating physicians to decide on each individual case.

7.11(d): Prevention of depression – The most recent Cochrane update states that there is no evidence to support psychological strategies to prevent depression after stroke. Hence, this Grade B recommendation now no longer applies.

Although, we acknowledge the Stroke Expert Working Group’s efforts in developing the 2010 guidelines, we suggest that readers consider this new evidence, and other recent or soon-to-be-published clinical trial evidence when making decisions about treating their stroke patients. As we have highlighted in our examples some of the recommendations are now outdated. Timing of guideline updates in journals should also coincide better with the release of guideline documents so that readers get the most out of the information while it is current.

Received 26 June 2012; accepted 16 July 2012.

to doi:1111/j.1445-5994.2012.02953.x

T. G. Phan, A. Thrift, D. Cadilhac and V. Srikanth
Department of Medicine, Monash Medical Centre, Stroke and Ageing Research Centre (STARC), Southern Clinical School, Monash University, Melbourne, Victoria, Australia

References


9 Ghia D, Thomas P, Cordato D, Epstein D, Beran RG, Cappelen-Smith C et al. Low positive predictive value of the ABCD(2) score in Emergency Department transient ischaemic attack.

Letters to the Editor

Reply

The National Stroke Foundation (NSF) is responsible for coordinating and publishing the Clinical Guidelines for Stroke Management 20101 that were approved by the National Health and Medical Research Council (NHMRC). We agree with Phan et al.2 that there have been several areas where new evidence has been published since 2010. Any update of recommendations to reflect recent evidence should employ processes that ensure the literature is reviewed in a manner free from bias and individual influence. This requires systematic search processes and critical appraisal. We would warn against making suggestions of change on the basis of a non-systematic process or on the opinion of a few experts. Instead, we must use agreed methods to ensure the integrity of clinical guidelines.

Finally, guidelines are intended as a useful resource, remembering, of course, that guidelines are not a textbook, rather they are a distillation of primary evidence that has been periodically critically appraised and then summarised for the Australian context. While standards and guidelines are a very useful baseline, up-to-date clinical expertise is still an essential part of delivering evidence-based care.

Received 18 September 2012; accepted 23 September 2012. doi:10.1111/imj.12006

L. Wright,1 K. M. Hill,1 J. Bernhardt,2 R. Lindley3 on behalf of the National Stroke Foundation Stroke Guidelines Expert Working Group
1Guidelines Program, National Stroke Foundation, 2Stroke Division, Florey Neuroscience Institutes, Melbourne and La Trobe University, Melbourne, Victoria and 3Discipline of Medicine, University of Sydney, Sydney, New South Wales, Australia

References

5 National Health and Medical Research Council. Procedures and Requirements for
Chest ultrasound in practice: a review of utility in the clinical setting

I wish to congratulate Drs Hew and Heintze for their article and to make one or two corrections, as well as draw the readers’ attention to the international evidence-based recommendations for point-of-care lung ultrasound (US) published earlier this year in *Intensive Care Medicine*.

**Technique.** Most authors (including this writer) recommend that the operator switch off the tissue harmonic imaging (THI) and compounding (known as ‘multibeam’ on some machines). These two ‘filter out’ artefacts and can render lung pathology such as B-lines much less obvious (Figs 1, 2).

**Pneumothorax.** The authors correctly point out that absence of lung sliding is insufficient to rule out pneumothorax using US. In fact, there are four US signs required to accurately diagnose PTX: (i) presence of lung point(s); (ii) absence of lung sliding; (iii) absence of B-lines and (iv) absence of lung pulse.

‘Comet’. This term is no longer in general use for B-lines because of its similarity to the previously described ‘comet tail artefact’ (seen on US below small calcific/crystalline/highly reflective structures). In fact, it is probably a type of ‘ring down’ artefact, observed because of the interaction of US with very small air bubbles trapped in fluid. Other terms such as ‘lung rockets’ are also falling out of favour.

Received 17 September 2012; accepted 29 September 2012.

doi:10.1111/imj.12005

J. Bowra,1,2,3,4

1Emergency Ultrasound Special Skills Program, Sydney Adventist Hospital, 2Emergency Department, Royal North Shore Hospital, 3CCPU Certification Board for the Australian Society for Ultrasound in Medicine and 4Ultrasound Subcommitteee of the Australasian College for Emergency Medicine, Sydney, New South Wales, Australia

**References**


Reply

We thank Dr Bowra\textsuperscript{1} for his helpful interest in our review of chest ultrasound.\textsuperscript{2}

We are indebted to him for correctly extending our remarks regarding pneumothorax diagnosis.

We also agree with his insightful suggestions to increase the sensitivity of ultrasound for important lung artefacts related to the interstitial syndrome. Concerning terminology, the literature currently refers to these artefacts as B-lines or comets; to aid the reader, we have therefore presented both terms in our paper. As the field of lung ultrasound matures as an area of scientific study, there will be no doubt an increasing standardisation of sonographic descriptors.

Lastly, we join with Dr Bohra in commending to interested readers a key consensus statement on lung ultrasound\textsuperscript{3} published this year shortly after our review was accepted. This guideline is another step towards the above-mentioned scientific maturation.

Received 8 October 2012; accepted 9 October 2012.

doi:10.1111/imj.12003

M. Hew\textsuperscript{1,2} and S. Heinze\textsuperscript{1,2}

\textsuperscript{1}University of Melbourne and \textsuperscript{2}Royal Melbourne Hospital, Melbourne, Victoria, Australia

References


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

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

address for editorial correspondence
Editor-in-Chief, Internal Medicine Journal, The Royal Australasian College of Physicians, 145 Macquarie Street, Sydney, NSW 2000, Australia (tel: +61 2 9256 5431; fax: +61 2 9256 5485). For enquiries regarding ScholarOne Manuscripts (formerly known as ManuscriptCentral) submissions please email ManuscriptCentral@racp.edu.au (e.g. IMJ-0000-2012). General enquiries should be directed to Virginia Savickis, the Editorial Office, Internal Medicine Journal, using imj@racp.edu.au

Comments on published papers are welcomed. Authors are offered right of reply (no more than 500 words) at the discretion of the Editor. Given the current pressures on editorial space, however, invited comments are restricted to one reply.

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

Copyright © 2012 Royal Australasian College of Physicians.

For submission instructions, subscription and all other information visit www.blackwellpublishing.com/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 standardize 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)
## Editorials

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The Journal in 2011</td>
<td>J. Szer</td>
</tr>
<tr>
<td>4</td>
<td>Glucose control in critically ill patients</td>
<td>O. Flower and S. Finfer</td>
</tr>
</tbody>
</table>

## Review

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
</table>

## Ethics in Medicine

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Time to bring down the twin towers in poor Aboriginal hospital care: addressing institutional racism and misunderstandings in communication</td>
<td>A. Durey, S. C. Thompson and M. Wood</td>
</tr>
</tbody>
</table>

## Original Articles

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Simple approach to improving vancomycin dosing in intensive care: a standardised loading dose results in earlier therapeutic levels</td>
<td>J. Truong, B. J. Levkerich and A. A. Padiglione</td>
</tr>
<tr>
<td>29</td>
<td>Monocyte chemoattractant protein-1 is associated with silent cerebral infarction in patients on haemodialysis</td>
<td>E. Ichida, F. Anan, T. Miiko, K. Kamada, T. Nono, N. Oohira, T. Saika and H. Yohimatsu</td>
</tr>
<tr>
<td>43</td>
<td>Variability in vitamin D assays impairs clinical assessment of vitamin D status</td>
<td>J. R. Chai, R. M. Leva, E. Banks, A.-L. Penney and A. Small Investigator Group</td>
</tr>
<tr>
<td>51</td>
<td>Managing acute medical admissions: a survey of acute medical services and medical assessment and planning units in New Zealand</td>
<td>C. Providence, J. Gommans and A. Burns</td>
</tr>
<tr>
<td>57</td>
<td>Implementing a web-based oncology protocol system in Australia: evaluation of the first 3 years of operation</td>
<td>I. M. Hamn, R. L. Ward and S.-A. Pearson</td>
</tr>
<tr>
<td>65</td>
<td>An audit of platelet transfusion within the Wellington Cancer Centre</td>
<td>D. C. Bahkum, M. K. P. Karlon and J. M. Carter</td>
</tr>
<tr>
<td>71</td>
<td>Survival in patients with malignancy and venous thromboembolism by tumour subtype and thrombus location</td>
<td>T. Prestidge, S. Lee, P. Harper, L. Young and P. Ockelford</td>
</tr>
</tbody>
</table>

## Brief Communications

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>Transfer from residential aged care to emergency departments: an analysis of patient outcomes</td>
<td>G. Arendts, C. Dickson, K. Hennard and S. Quine</td>
</tr>
<tr>
<td>83</td>
<td>Childhood asthma and GOLD-defined chronic obstructive pulmonary disease</td>
<td>P. Shirtcliffe, S. Marsh, J. Travers, M. Weatherall and R. Beasley</td>
</tr>
</tbody>
</table>

## Images in Medicine

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>Abnormal air collection on plain abdominal X-ray</td>
<td>C.-F. Lai, B. Chua, S.-D. Chung and Y.-S. Peng</td>
</tr>
<tr>
<td>103</td>
<td>Sweet’s syndrome</td>
<td>E. M. Balcells, N. Garcia and A. Mendez Villarreal</td>
</tr>
</tbody>
</table>

## Letters to the Editor

**Clinical-scientific notes**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>Persistent febrile illness with multisystem organ failure associated with clozapine</td>
<td>D. J. Brown, N. L. Lucas and S. Braude</td>
</tr>
<tr>
<td>106</td>
<td>Vitreal deposits in Val71Ala transthyretin amyloidosis</td>
<td>D. Suan, D. R. Booth, J. H. Emsley, J. Downie, P. Farci, D. Gottlieb, G. J. Stewart and M-W. Lin</td>
</tr>
</tbody>
</table>

**General correspondence**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>Rapid iron infusion with iron polymaltose: further improvements may be possible</td>
<td>B. Sambhi, B. Herrmann, A. Barr and M. Wright</td>
</tr>
</tbody>
</table>
Editorial
113 Dabigatran, Product Familiarisation Programmes, who benefits, who shouldn’t get it?
H. Curley and C. Denaro

Clinical Perspectives
116 Advances in gastrointestinal endoscopy
V. Kwan

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

131 Early implementation of antifungal therapy in the management of febrile neutropenia is associated with favourable outcome during induction chemotherapy for acute leukemias
A. Khalafallah, M. Maimold, T. Hannan, S. Arel, J. Staker and A. Supperamohan

137 Clinical utility of molecular and flow cytometric markers in chronic lymphocytic leukemia
M. L. Sohda, R. J. Rossi, R. R. Hall, S. Bailey and P. J. Macardle

146 Insulin resistance and coronary flow velocity reserve in patients with autosomal dominant polycystic kidney disease

154 Smoking cessation post-discharge following nicotine replacement therapy use during an inpatient admission
J. H. Williams and T. E. Jones

Personal Viewpoint
212 Hypothesis. The importance of a histological diagnosis when diagnosing and treating advanced cancer. Famous patient recovery may not have been from metastatic disease
I. E. Haines and R. M. Lowenthal

Images in Medicine
217 Trapped lung
K. Liew and P. Stride

218 A fluffy chest radiograph
S. Faruqi, R. Robertson and M. Thirumaran

Letters to the Editor
Clinical-scientific notes
219 Silver linings: a case study
M. Wicks and J. Tamargo

220 Multimodal treatment of post-tissue plasminogen activator-related intracerebral haemorrhage
D. Varma, C. Chen, M. McDonald and A. Lee

222 Mental health history and disruptive behaviours in the medical setting
R. A. Sansone, S. Faruqi and M. W. Wiederman

224 Fertility is significantly reduced by female genital tuberculosis: a case series
T. R. Schatz and D. P. Eisen

General correspondence
226 Coronary CT angiography for patients with stable chest pain in the Emergency Department; an appraisal of current and emerging evidence
C. Hamilton-Craig, O. C. Raffel, M. Pincus, M. Hansen, R. E. Slaughter and D. L. Walters

228 Reply
I. Scott

229 Prehospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease
R. Wood-Baker, E. H. Walters, L. Blizzard and M. Austin

230 Prehospital oxygen therapy in exacerbations of chronic obstructive pulmonary disease: the practical issues
A. Swain, S. Hoyte and A. O’Brien

231 Reply
R. Beasley, M. Wijesinghe, K. Perrin and M. Weatherall

232 Treatment of refractory neurosarcoïdosis with TNF-inhibitors: what lies ahead?
H. Ahmadzai, M. C. Kiernan, D. Wakefield and P. S. Thomas

Brief Communications
198 Recreational drug use in type 1 diabetes: an invisible accomplice to poor glycaemic control?
P. Lee, J. R. Greenfield, K. Gilbert and L. V. Campbell

202 New HIV diagnosis after occupational exposure screening: the importance of reporting needlestick injuries
L. M. Uyjohn, R. L. Stuart, T. M. Korman and I. J. Woolley

205 Lymphoma, thymoma and the wooden man: stiff-person syndrome post-thymoma excision and non-Hodgkin lymphoma remission
T. Dai and R. McGrath

208 Polypharmacy – we make it worse! A cross-sectional study from an acute admissions unit
T. M. Betteridge, C. M. Fluitan and D. L. Jardine

© 2012 Royal Australasian College of Physicians
Editorial
233 As clear as MUD
D. Gorman and K. J. Petrie

Review
235 Stochastic processes in the aetiopathogenesis of scleroderma
P. J. Roberts-Thomson and J. G. Walker

Clinical Perspectives
242 Management of opioid substitution therapy during medical intervention
B. Murnion

Ethics in Medicine
247 No evidence or no alternative? Taking responsibility for off-label prescribing
N. Ghinea, W. Lipworth, I. Kerridge and R. Day

Original Articles
252 Pharmacokinetics and safety of Intragam 10 NF, the next generation 10% liquid intravenous immunoglobulin, in patients with primary antibody deficiencies
K. Bleasel, R. Heddle, P. Hissaria, R. Stirling, C. Stone and D. Maher

260 Determinants of masked hypertension in hypertensive patients treated in a primary care setting
A. Andalib, S. Akhtari, R. Rigal, G. Curnew, J.-M. Leclerc, M. Vaillancourt and J.-C. Tarde

267 Prevalence and management of HER2/neu-positive early breast cancer in a single institution following availability of adjuvant trastuzumab
A. Chan and S. R. McGregor

274 Radiographic osteoarthritis and pain are independent predictors of knee cartilage loss: a prospective study
J. Saunders, C. Ding, F. Cicuttini and G. Jones

281 Gender, age and ethnic aspects of analgesia in acute abdominal pain: is analgesia even across the groups?

289 Prevalence of Helicobacter pylori positivity in patients undergoing percutaneous coronary intervention
C. Hiew, A. Duggan, T. de Malmanche, R. Hatton, F. Baker, J. Attia and N. Collins

294 Clinical characteristics and treatment delay of cerebral infarction in tuberculous meningitis
J.-J. Sheu, C.-Y. Hsu, R.-Y. Yuan and C.-C. Yang

300 The safety of flexible fibre-optic bronchoscopy and proceduralist-administered sedation: a tertiary referral centre experience
D. Dang, P. C. Robinson, S. Winnicki and H. P. A. Jersmann

306 Hyponatraemia in older people as a sign of adrenal insufficiency: a case-control study
T. Winchester Behr, M. Sonnenblick, G. Nesher and G. Munter

311 Smoking prevalence and perspectives on smoking on campus by employees in Australian teaching hospitals
T. E. Jones and J. Williams

317 Craving control using nicotine replacement therapy in a teaching hospital
T. E. Jones and J. Williams

323 Pneumatosis cystoides intestinalis in scleroderma-related conditions
A. Ballier-Gurman, G. R. Brook, I. Chernich and Y. Braun-Moscovici

Brief Communication
329 Diffuse large cell non-Hodgkin lymphoma with pituitary and bilateral adrenal involvement

Personal Viewpoint
332 From blood transfusion to patient blood management: a new paradigm for patient care and cost assessment of blood transfusion practice
M. F. Leahy and S. A. Mukhtar

Images in Medicine
339 Purtscher's retinopathy associated with acute pancreatitis
D. Benacim, D. Kahajian, K. Kitamura and R. Zsaka

340 Bead-like coronary spasm
S.-S. Tzeng and J.-T. Liou

Letters to the Editor

Clinical-scientific notes
341 Extracorporeal membrane oxygenation with plasma exchange in a patient with alveolar haemorrhage secondary to Wegener's granulomatosis
S. L. Barnes, M. Naughton, J. Douglas and D. Murphy

342 Carcinoid crisis induced by repeated abdominal examination
K. Morrisroe, I.-W. Sim, K. McLachlan and W. J. Inder

344 A 67-year-old man with persistent fever and high titers of serum anti-cardiolipin antibody
J. Zhang, J.-Y. Jiang, X. Zhang and C.-X. Bai

General correspondence
345 Hair-pulling and borderline personality symptomatology among internal medicine outpatients
R. A. Sansone, C. Lam and M. W. Wiederman

E-publication only Brief Communications
(Available online only at: http://www.wileyonlinelibrary.com)
e1 Mortality risk stratification in severely anaemic Jehovah's Witness patients
A. M. Beliaev, R. J. Marshall, W. Smith and J. A. Windsor

e4 Efficacy of rituximab in refractory anti-synthetase syndrome
V. Emuye, P. Hisaria, C.-L. Liew and R. Koszyka

e7 Case of anti-gliomerular basement membrane antibody-induced glomerulonephritis with cytomegalovirus-induced thrombotic microangiopathy

e12 Rituximab-induced interstitial lung disease in a patient with immune thromboocytopenia purpura
N. Child, M. O'Carroll and L. Berkahn

e15 Role for the left atrial appendage occlusion device in managing thromboembolic risk in atrial fibrillation
M. N. Obeyesekere, S. Lockwood, P. Mottram and J. F. Alison

e19 Prevalence of error-prone abbreviations used in medication prescribing for hospitalised patients: multi-hospital evaluation
M. J. Dooley, M. Wiseman and G. Gu
April 2012, Volume 42, Issue 4

Editorial
349 Challenges of an ageing and dispersed population for delivering cancer services in Australia: more than just doctors needed
J. H. Martin, M. Gryzy and P. Bannik

Review
351 Anti-neutrophil cytoplasmic antibody-associated systemic vasculitis: nature or nurture?
P. A. Gately

Current Controversies
360 Access to the kidney transplant waiting list: a time for reflection
B. A. Poulis, A. Bendorf and I. H. Kerridge

Clinical Perspectives
364 How to select the doctors of the future
K. Oates and K. Glouvan

Original Articles
369 Psychologic of earthquake-induced stress cardiomyopathy, myocardial infarction and non-cardiac chest pain

374 Differences in characteristics of men with localised prostate cancer who demonstrate low, intermediate or high prostate-specific antigen velocity

380 Multicentre audit of inpatient management of acute exacerbations of chronic obstructive pulmonary disease: comparison with clinical guidelines
T. J. Perto, V. M. McDonald, P. A. A. Wark and M. J. Helenly

387 Inability of single resting arterial blood gas to predict significant hypoaemia in chronic obstructive pulmonary disease
J. M. Tauge, C. Giel, T. Tauge and C. L. Steinfors

395 A 5-year follow up of patients discharged with non-specific abdominal pain: out of sight, out of mind?
V. M. Rana, O. Spersien, M. de Maya, H. Zimmermann, D. Cadininas, S. G. Mougiakakou and A. K. Esakkutty

401 Immunophenotypic analysis of erythroid dysplasia and its diagnostic application in myeloplastic syndromes
F. Xu, L. Wu, Q. He, Z. Zhang, C. Chang and S. Li

411 Initiating allopluron therapy: do we need to know the patient’s human leucocyte antigen status?

416 Reporting clinical trial information: colorectal cancer trials at Sydney Cancer Centre
W. Chua, L. Horvath, P. Beale and S. J. Clarke

422 Intracranial cause of delirium: computed tomography yield and predictive factors
M. Y. Lai and D. M. Wong Tin Nam

427 Clinical audit of antiphospholipid antibody testing in tertiary practice: towards improved relevance in thrombophilia investigations
E. J. Favaloro, R. Reben, S. Mohammed and J. Knott

434 Diagnostic utility of endobronchial ultrasound-guided transbronchial needle aspiration compared with transbronchial and endobronchial biopsy for suspected sarcoidosis
M. Ping, R. Pearson, A. Havryk, J. Da Costa, C. Chang and A. R. Glanville

439 Angiotensin-converting enzyme gene insertion/deletion polymorphism and essential hypertension in the Chinese population: a meta-analysis including 21 058 participants
Y. Li

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

How I Treat
450 When should iron chelation therapy be considered in patients with myelodysplasia and other bone marrow failure syndromes with iron overload?
R. J. Bird, M. Kenady, C. Forsyth, J. Willwood, M. F. Leahy, J. F. Seymour and L. R. To

Brief Communications
455 Changes in liquid emptying in migraine patients: diagnosed with liquid phase gastric emptying scintigraphy
H. Yalin, E. E. Okuyucu, E. Ucan, T.oman and S. Yilmazer

459 Intravenous immunoglobulins as treatment of severe cutaneous polyarteritis nodosa
I. Marta, R. Miranda, N. Girszon, J.-C. Soubrane, T. Vandhuick and H. Leveque

Personal Viewpoint
463 Utility, or not, of estimates of glomerular filtration rate in modifying drug dosage, with particular reference to enoxaparin
W. R. Adam

A Historical Perspective
466 Cancer and quackery
K. R. Irving

Images in Medicine
468 Unusual lung mass
S. Rajagopala, A. Partapwani, R. Agarwal and K. Gupta

470 Rosai-Dorfman disease
H. R. Osman, M. Mattar, W. Shanky, R. Rashad and E. Helal

Letters to the Editor
474 Timeline errors undermine hypothesis; ‘famous patient’ did have secondary osteogenic sarcoma and tuberculosis
I. Gawler

476 Lack of adherence to scientific principles of objectivity
R. Gawler

478 The importance of a histological diagnosis . . .
R. Anderson

478 Reply: Treatment of refractory neurosarcoidosis with tumour necrosis factor inhibitors – what lies ahead?
J. A. Pera and N. B. Anderson

480 Errata

E-publication only Brief Communications
(Available online only at: http://www.wileyonlinelibrary.com)
e23 Wegener’s granulomatosis: treatment and survival characteristics in a high-prevalence southern hemisphere region
A. R. Khan, P. T. Chapman, L. E. Stamp and J. L. O’Donnell

e27 Coexistence of renal malakoplakia and myelodysplastic syndrome
B. Kayembe, S. Sow, R. Duttmann, G. Oboy, M. Malarme and S. O. Nondal

e30 Primary central nervous system lymphoma masquerading as bilateral vitreous floaters
G. Endo, S. Miranda, T. Vandhuick and H. Leveque

e39 Myocardial infarction and non-cardiac chest pain
H. R. Osman, M. Mattar, W. Shanky, R. Rashad and E. Helal

E-publication only Original Articles
(Available online only at: http://www.wileyonlinelibrary.com)
e38 Descriptive analysis of emergency department oxygen use in acute exacerbation of chronic obstructive pulmonary disease
J. Considine, M. Botti and S. Thomas

e47 Medication compliance in ischaemic stroke patients
C. Johnson, H. Lane, P. A. Barber and A. Charleston

© 2012 Royal Australasian College of Physicians
May 2012, Volume 42, Issue 5

Editorial
481 Iron chelation therapy in myelodysplastic syndromes: we need more evidence, not more guidelines
A. Budler and W. N. Patton

Review
484 Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies
G. Cheng, C. Huang, H. Deng and H. Wang

Original Articles
491 Barriers faced by migrants in accessing healthcare for viral hepatitis infection
M. Guirgis, F. Nusair, Y. M. Bu, K. Yan and A. T. Zekry
497 General practitioners’ knowledge and management of viral hepatitis in the migrant population
M. Guirgis, K. Yan, Y. M. Bu and A. Zekry
505 Staphylococcus aureus bacteraemia at Alice Springs Hospital, Central Australia, 2003–2006
S. Hewagama, T. Spelman and L. J. Emsiedel
513 Leukaemic transformation of Philadelphia chromosome-negative myeloproliferative neoplasms: are Asian patients different?
R. Cherian and G. C. Wong
517 Association between serum cystatin C, monocytes and other inflammatory markers
A. A. Evangelopoulos, N. G. Vallianos, V. Roumziouka, C. Katagomi, E. Batherellou, E. D. Vogiatzakis, M. S. Benos, J. Bariotou, P. C. Argirios and D. B. Papanastasiou
523 Use of biological disease-modifying anti-rheumatic drugs in patients with concurrent rheumatic disease and hepatitis B
L. K. King, A. Lee and A. Anandasamarnayone
531 Platelet activation in patients with the Raynaud phenomenon
L. Polidoro, B. Barahoubi, P. Giorgini, L. Petrazzi, C. Ferri and G. Properzi
536 Diagnostic yield of bronchoscopic sampling in febrile neutropenic patients with pulmonary infiltrate and haematological disorders
A. Seneviratna, M. O’Carroll, C. A. Lewis and D. Milne
541 Relationship between non-alcoholic fatty liver disease and pulmonary function
547 Low-dose ionising radiation from medical imaging in patients hospitalised in internal medicine
L. Martinneau-Beaulieu and L. Lanthier
554 Implantable cardioverter-defibrillators: a long-term view
D. Wilson, B. Shi, S. Handong, N. Lever and P. Lavrent

Position Paper
562 Stroke management: updated recommendations for treatment along the care continuum

Personal Viewpoint
569 Unintended consequences of performance measurement in healthcare: 20 salutary lessons from the English National Health Service
B. Mannion and J. Healthcare

History in Medicine
575 Medicine, art and the death of Franz Liszt
G. MacLaren

Brief Communications
578 Relationship between body composition, peripheral muscle strength and functional exercise capacity in patients with severe chronic obstructive pulmonary disease
581 Utility of atrial temporary pacing as an acute treatment for bradyarrhythmias and tachyarrhythmias in the intensive care setting with preservation of atrioventricular synchrony
B. Jung, B. Everest and A. D. McGeer
585 Progression of antiphospholipid antibody syndrome to catastrophic antiphospholipid antibody syndrome acutely with cessation of antithrombotic therapy
Y. S. Kutikov and D. A. Kandah
591 Proton pump inhibitors and diarrhoea related to Clostridium difficile infection in hospitalised patients: a case-control study
A. D. Leonard, K. M. Ho and I. Flexman

Images in Medicine
595 Transient acute tetraparesis revealing bihemispheric cerebral infarcts
J. M. Ragnarsdottir and O. Godfrey
596 Encrusted cystitis and pyelitis
N. Anagnostou, M. Sedlak and D. L. Gordon

Letters to the Editor
Clinical-scientific notes
597 Obliterative bronchiolitis after rituximab administration: a new manifestation of rituximab-associated pulmonary toxicity
T. Shen and S. Braude
600 A case of portopulmonary hypertension spanning 18 years: successful use of bosentan for progressive disease after two liver transplantations
E. M. T. Lau, G. W. McCaughan and P. J. Heritas
601 Vitamin B12 deficiency causing hyperhomocysteinaemia and cerebral venous sinus thrombosis
A. F. Whyte, D. L. Jones and M. D. Dreyer

E-publication only Original Articles
(Available online only at: http://www.wileyonlinelibrary.com)
e53 Current discharge management of acute coronary syndromes: baseline results from a national quality improvement initiative
A. Wei, L. R. Pizer, K. Oliver and A. Thompson
e59 Comparison of prediction equations to estimate glomerular filtration rate in Chinese patients with chronic kidney disease
e68 Initiation and duration of proton pump inhibitors in the Australian veteran population
S. V. Gaidhane, E. E. Boughhead and J. M. Mackson
e74 STOP Fracture study: Southern Health Osteoporotic Fracture Screening Project
H. J. Troole, D. A. Renouf, I. A. Jayasuriya and D. Barrie
e80 A pilot study to investigate the scope for an inpatient smoking cessation programme
J. George, S. Taylor, H. Hong, S. Leung and J. Nguyen
e84 Potentially avoidable surgery in inflammatory bowel disease: what proportion of patients come to resection without optimal preoperative therapy? A guidelines-based audit
June 2012, Volume 42, Issue 6

Editorial
605 Productivity gain a triumph for clinician leadership
D. German and M. Horn

Review
607 Towards a vaccine for chronic obstructive pulmonary disease
R. L. Clancy

Clinical Perspectives
614 Clinical aspects of adult syphilis
P. J. Read and B. Donovan

Original Articles
620 Increasing productivity, reducing cost and improving quality in elective surgery in New Zealand: the Wāneta District Health Board joint arthroplasty pilot
J. Coffin, B. Brinded, D. Armstrong, L. Butler, P. Rowe and T. Ashton

627 Mediastinal staging of non-small-cell lung cancer among Australasian thoracic physicians: clinical practice and constraints on minimally invasive techniques
E. J. Dohsche, D. P. Steinfort, L. R. Irving and M. Hew

634 Sleep, blood pressure and obesity in 22,389 New Zealanders

641 Body mass index, sexual difficulties and sexual satisfaction among people in regular heterosexual relationships: a population-based study

651 Detection of patients presenting with adverse drug events in the emergency department

658 Evaluation of iron deficiency anaemia in tertiary hospital settings: room for improvement?
G. Khadok, I. A. Scott and K. Klein

665 Oral drug challenges in non-steroidal anti-inflammatory drug-induced urticaria, angioedema and anaphylaxis
T. Chasaloff, H. Hisara, M. Wiese, R. Heddle, P. Kette and W. B. Smith

672 Anti-glomerular basement membrane disease in Auckland

673 Risk factors for 30-day readmission in general medical patients admitted from the emergency department: a single centre study
C.-C. Shu, Y.-L. Lin, N.-C. Hsu and W.-J. Ko

683 Anaemia is highly prevalent among unselected internal medicine inpatients and is associated with increased mortality, earlier readmission and more prolonged hospital stay: an observational retrospective cohort study

691 Temporal trend of cadmium exposure in the United States population suggests gender differences
P. M. Ferrari, A. Sturmke, A. Natachka, S. D'Alonzo and G. Gamburo

Position Paper
698 Prevention of venous thromboembolism in patients admitted to Australian hospitals: summary of National Health and Medical Research Council clinical practice guideline
N. Wickham, A. S. Gallus, B. N. J. Walters and A. Wilson on behalf of the NHMRC VTE Prevention Guideline Adaptation Committee

Brief Communications
709 Successful catheter ablation of incessant atrial tachycardia in pregnancy using three-dimensional electroanatomical mapping with minimal radiation
H. Wu, L.-H. Ling, G. Lee and P. M. Kirby

712 Severe refractory hyponatraemia in severe pulmonary embolism: a surrogate marker of severe right ventricular dysfunction and indication for thrombolysis
S. Brando and J. Mortens-Nielsen

715 Implementation of standardised surveillance for Clostridium difficile infections in Australia: initial report from the Victorian Healthcare Associated Infection Surveillance System
A. L. Bull, L. J. Worth and M. J. Richards

719 Point-prevalence study of inappropriate antibiotic use at a tertiary Australian hospital
P. R. Ingram, J. M. Sext, C. A. Budgen and R. Murray

Personal Viewpoint
722 Health workforce changes and the roles of information technology associated with these changes
"The Times They Are A-Changin" * (Bob Dylan, 1964)
T. Hamann and P. Brooks

Images in Medicine
727 Ischaemic colitis mimicking ascending colon cancer

Letters to the Editor

Clinical-scientific notes
729 Human T-lymphotropic virus seroconversion associated with pooled human intravenous immunoglobulin therapy
M. Hunter, M. Kirman and J. Fisz

730 Hazards of potassium and multiple sources of sodium in causing osmotic demyelination
M. Kingston and S. Bhuta

732 Cefepime: a rare cause of encephalopathy
A. McNally, A. Pithie and D. Jardine

General Correspondence
734 Plasmapheresis in systemic lupus erythematosus with thrombotic microangiopathy
R. Ramachandran, Y. Sakhuja, V. Jha, H. S. Kohli and M. Bathi

734 Physicians and the indigenous patient
J. E. Thompson and J. N. Jones

735 Unilateral conjunctival icterus and no ‘glass eye’
B. J. Ng, D. Alexander and G. M. Robinson

736 Erratum

E-publication only Original Articles
(Available online only at: http://www.wileyonlinelibrary.com)

e102 Preliminary evaluation of the prevalence of falls, pain and urinary incontinence in remote living Indigenous Australians over the age of 45 years

e107 Comparison of empirical continuous positive airway pressure (CPAP) treatment versus initial portable sleep monitoring followed by CPAP treatment for patients with suspected obstructive sleep apnoea
K. W. Tu, W. C. Chan, F. Q. Chan, J. Ng, A. Tong, S. Ng, R. L. Choo and D. S. Hui

e115 A variant in microRNA-196a2 is not associated with susceptibility to and progression of colorectal cancer in Chinese

e120 Prevalence of risk factors for foot ulceration in patients with end-stage renal disease on haemodialysis
M. Kaminski, N. Frescos and S. Tucker
841 Presentation and outcome of idiopathic thrombocytopenic purpura in a single Australian centre
P. T.-J. Chai, J. E. A. Gordon, M. Harvey and B. H. Chong

Images in Medicine
845 Anomalous origin of the three coronary arteries
A. Turkutan

Letters to the Editor
Clinical-scientific notes
846 Local experience with the novel human anti-CD20 antibody, ofatumumab, as salvage treatment for patients with heavily pretreated chronic lymphocytic leukaemia

848 Pseudo-acute kidney injury with recurrent ascites due to intraperitoneal urine leakage
M. H. Wong, S. K. Lim, K. L. Ng and K. P. Ng

General correspondence
849 The dangers of oxygen therapy
Q. Zhang, N. Mehdi and P. S. Thomas

850 Early career medical research in Australia: looking to the future
H. Eyre and M. Stuart

E-publication only Original Articles
(Available online only at: http://www.wileyonlinelibrary.com)
e145 Quality of life: a potentially useful measure to indicate subclinical flares in Crohn disease
B. J. A. Cámara, P. Juillerat, V. Pittet, A. M. Schoepfer, S. Bégé, R. van Kaaal and the Swiss Inflammatory Bowel Disease Cohort Study Group

e151 Use of antipsychotic medications in patients with Parkinson’s disease at Auckland City Hospital
K. Bloomfield, L. MacDonald, G. Finsane, B. Snow and R. Roxburgh

e157 Comparison of the bacterial isolates and antibiotic resistance patterns of elderly nursing home and general community patients
C. Xia, D. McD. Taylor, B. P. Howden and P. G. P. Charlie

e165 Performance of comorbidity indices in measuring outcomes after acute myocardial infarction in Australian indigenous and non-indigenous patients
J. R. Condon, J. You and J. McDonnell

Editorial
737 Putting professionalism and delivery of value-added healthcare at the heart of physician training and continuing professional development

Review
742 Sleep disturbance in menopause
D. Anestatunga, J. Goldin and M. Hickey

Original Articles
748 Intensive care unit experience of haemopoietic stem cell transplant patients
S. Agarwal, S. O’Donoghue, J. Gowansman, G. Kennedy, H. Randlek and R. Root

755 Influenza-associated bacterial pathogens in patients with 2009 influenza A (H1N1) infection: impact of community-associated methicillin-resistant Staphylococcus aureus in Queensland, Australia
Y. Hayashi, V. L. Vida, H. Baba, G. R. Nimm, L. Davis and D. L. Paterson

760 Fracture risk after thiazide-associated hyponatraemia

765 Single centre experience with pegylated interferon and ribavirin for hepatitis C: looking back before moving forward
K. Muller, A. Rodgers, R. Wudell, Y. Wudell, R. Wudell, D. J. Gordon and A. Wigg

772 Gastro-oesophageal reflux and respiratory symptoms in Basselton adults: the effects of bodyweight and sleep apnoea
S. A. Muthrman, M. W. Kozman, M. L. Dovit, D. J. Cullen, M. Hunter, J. Hui, A. W. Mark and A. L. James

780 Medical oncology clinics through videoconferencing: an acceptable telehealth model for rural patients and health workers
S. Sabesan, K. Motosu and I. Mare

786 Investigating the adverse respiratory effects of beta-blocker treatment: six years of prospective longitudinal data in a cohort with cardiac disease
B. Cochrane, S. Quinn, H. Walters and I. Young

794 Preliminary analysis of the cost-effectiveness of the National Bowel Cancer Screening Program: demonstrating the potential value of comprehensive real world data

801 General practitioners’ knowledge of and attitudes to inflammatory bowel disease
M. Tan, B. H. Holloway, K. Lange and J. M. Andrews

808 Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis
M. P. Puac, A. Herbert, N. A. Grima, A. Pipinas and M. F. O’Rourke

816 Negotiating hope with chronic obstructive pulmonary disease patients: a qualitative study of patients and healthcare professionals
J. Philip, M. Gold, C. Brand, J. Douglas, B. Miller and V. Sundaranan

Personal Viewpoint
822 The 2010 Royal Australasian College of Physicians’ policy statement ‘Circumcision of infant males’ is not evidence based

Brief Communications
828 Australian resident doctors want more palliative medicine education: a survey of attitudes and perceived needs
J. Weil, S. Gold, S. McIver, L. Rotstein and J. Philip

Dietary treatment of hypoglycaemia: should the Australian recommendation be increased?
S. Vindeliz, B. Marsh, J. Sherriff, S. Dhulowl and K. Stanton

Diagnostic value of 18F-FDG PET/CT in patients with fever of unknown origin
Y. J. Kim, S. I. Kim, K.-W. Hong and M. W. Kang

Common peroneal neuropathy and cancer
N. G. Simon and M. C. Kiernan
Editorial
853 The crisis in availability of donor organs: time to move beyond the rhetoric
P. A. Komesaroff

Review
856 Chest ultrasound in practice: a review of utility in the clinical setting
M. Hew and S. Heinze

Original Articles
866 Explaining failure through success: a critical analysis of reduction in road and stroke deaths as an explanation for Australia’s low deceased organ donation rates
A. Bendorf, I. H. Kerridge, P. J. Kelly, B. Pussell and X. Guasch
874 Congenital heart disease-associated pulmonary arterial hypertension: preliminary results from a novel registry
880 Hepatitis B status in migrants and refugees: increasing health burden in Western Australia
887 Dialysis in public and private hospitals in Queensland
N. A. Gray, H. Dent and S. P. McDonald
894 Prospective randomised trial of endobronchial ultrasound-guide sheath versus computed tomography-guided percutaneous core biopsies for peripheral lung lesions
D. I. Fielding, C. Chia, P. Nguyen, F. Bashirzadeh, J. Hundloe, I. G. Brown and K. Stenos
901 Essential, but at what risk? A prospective study on central venous access in patients with haematological malignancies
907 Effects of methylprednisolone in patients with narcotic bowel syndrome: a pilot observational study
P. R. Gibson and G. Morrison
913 Low positive predictive value of the ABCD² score in emergency department transient ischaemic attack diagnoses: the South Western Sydney Transient Ischaemic Attack Study
918 Factors influencing career decisions in internal medicine
C. Macdonald and T. Coward
924 Predicting failure to return to work
R. Mills
928 Natural history of severe eosinophilia with uncertain aetiology and proposals on a practical approach to its management
A. L. Ang, R. X. Wong, Q. Y. Zhuang and Y. C. Linn
933 Prevalence and determinants of QT interval prolongation in medical inpatients
M. Pasquier, O. Pantet, O. Hugh, E. Pruvot, T. Buclin, G. Waeber and D. Aujsky

Brief Communications
940 Coccidioidomycosis in returned Australian travellers
S. Subedi, J. Brown, M. Caffery, M. Bint and D. Sowden
944 Case of syndrome of headache with neurological deficits and cerebrospinal fluid lymphocytosis (HANLD) with focal slowing on electroencephalogram
R. K. T. Tsang, J. C. Boong and H. M. Dewey
948 Oral administration of arsenic trioxide in the treatment of acute promyelocytic leukaemia and accelerated phase chronic myeloid leukaemia: an Australian single-centre study
F. Firkin

Letters to the Editor
Clinical-scientific notes
952 Late presentation of familial Mediterranean fever associated with P369S/R408Q variant in the MEFV gene
L. M. Hamann, J. Ward, R. Ebringer and C. F. McDonald
954 Importance of screening for renal disease among the human immunodeficiency virus-infected patient population
D. M. Gracey, M. Fernandes, J. Ziegler, C. P. White and F. J. Peat
955 Prolonged adefovir therapy associated Fanconi syndrome and interstitial nephritis in hepatitis B

General correspondence
957 ‘The association between time to disposition plan in the emergency department and in-hospital mortality of general medical patients’
P. Heerinckx
958 Reply
959 The Dasorin Liaison method has not underestimated serum 25-OH-vitamin D levels or misclassified patients with vitamin D deficiency in the Australian population
G. Ward, D. Langguth and L. Price
960 Variability in vitamin D assays impairs clinical assessment of vitamin D status
Z. X. Lu and K. A. Sikaris
961 Reply: High variability in the measurement of vitamin D levels is the key clinical issue

© 2012 Royal Australasian College of Physicians

© 2012 Royal Australasian College of Physicians
Editorials
963 Still casting its long shadow: rheumatic heart disease in Australia and New Zealand
C. McLintock

966 Should law have a role in end-of-life care?
B. White, L. Willmott, M. Parker, C. Cartwright and G. Williams

Review
968 Hydroxychloroquine in lupus: emerging evidence supporting multiple beneficial effects
C. T ang, T. Godfrey, R. Stawell and M. Nikpour

Original Articles
978 Rheumatic heart disease in pregnancy: cardiac and obstetric outcomes
J. B. Sartain, N. L. Anderson, J. J. Barry, P. T. Boyd and P. W. Howat

984 Rapid death after admission to palliative care
E. D. Paratz and E. Flynn

990 Spin density projection-assisted R2 magnetic resonance imaging of the liver in the management of body iron stores in patients receiving multiple red blood cell transfusions: an audit and retrospective study in South Australia
G. C. Brown, W. N. Patton, H. E. Tipp, D. J. Taylor and T. G. St Pierre

997 Systematic review of the prevalence of gout and hyperuricaemia in Australia
P. C. Robinson, W. J. Taylor and T. R. Merriman

1008 Cord blood transplantation in Western Australia

1014 Retinal vascular caliber and metabolic syndrome in a Chinese population

1023 Seizure management at Auckland City Hospital Emergency Department between July and December 2009: time for a change?
I. Rosemergy, P. Bergin, P. Jones and E. Walker

1029 Diagnosis of tuberculous lymphadenitis using fine needle aspiration biopsy
J. Knox, G. Lane, J. S. J. Wong, P. G. Trevan and H. Karunajeewa

Personal Viewpoints
1037 Dying at 23 with 1p36 deletion syndrome: Laura’s family story
P. A. Tandy

1040 Referral to specialist palliative care
A. Broom, E. Kirby and P. Good

Brief Communications
1043 Secondary amyloidosis in Indigenous Australians
C. L. Corbett and P. D. Lawton

1046 Prognostic factors in the elderly: a profile and outcomes study of a community palliative care service
M. Chapman, B. Le, A. Gorelik and J. Schwarz

1050 How can we improve junior doctor prescribing?
L. Gartan and W. W. Yeo

1053 Palliative care for patients with chronic obstructive pulmonary disease: exploring the landscape
J. Philip, A. Lowe, M. Gold, C. Brand, B. Miller, J. Douglas and V. Sundaranan

1057 Mesiotemporal changes on magnetic resonance imaging in neurosyphilis
R. R. Sanderson and R. C. Chan

Letters to the Editor

Clinical-scientific notes
1063 Pancytopenia due to severe folate deficiency
N. Bhatnagar, A. Wechalekar and C. McNamara

1065 Nontyphoidal Salmonella prosthetic valve endocarditis
P. Clohsey and J. Stanley

General correspondence
1066 Our experience with anti-neutrophil cytoplasmic antibody-associated systemic vasculitis
A. Gujadhur, L. McMahon and S. Holt

1066 Anti-neutrophil cytoplasmic antibody-associated systemic vasculitis: nature or nurture?
P. A. Gatenby

Book Review
1067 Infectious Diseases: A Clinical Approach, 3rd edition
D. J. Sexton
What is the therapeutic target level of 25-hydroxyvitamin D in osteoporosis and how accurately can we measure it?

P. Glendenning and R. L. Prince

Telerheumatology: an idea whose time has come

L. J. Roberts, E. G. LaMont, I. Lim, S. Sabesan and C. Barrett

Meta-analysis of amiodarone versus beta-blocker as a prophylactic therapy against atrial fibrillation following cardiac surgery


Rural Victorian Telestroke project

K. J. Nagao, A. Koschel, H. M. Haines, L. E. Bolitho and B. Yan

Patterns of inflammatory activation associated with precipitants of acute coronary syndromes: a case-crossover study

D. P. Chen, S. Mattusch, C. Horfall, C. Astley, J. C. Vail and M. X. Joseph

How do we manage venous thromboembolism in pregnancy? A retrospective review of the practice of diagnosing and managing pregnancy-related venous thromboembolism at two major hospitals in Australia and New Zealand


Homozygous FCGR3A-158V alleles predispose to late onset neutropenia after CHOP-R for diffuse large B-cell lymphoma


Gastroenterology training in Australia: a perspective from the coal face


Effect of oxygen versus adaptive pressure support servo-ventilation in patients with central sleep apnoea–Cheyne Stokes respiration and congestive heart failure

A. J. Campbell, K. Ferrer and A. M. Neill

Vitamin D deficiency in Tasmania: a whole of life perspective

L. A. P. van der Mei, D. Duve, T. Winterberg, E. Blizzard and G. Jones

Antibiotic use and misuse in residential aged care facilities

R. L. Stuart, E. Bellaard-Smith, R. Brown, L. Wright, S. Vandergnaaf and E. E. Gillespie

Medical student education: what it costs and how it is funded

K. Goulston, K. Oates, S. Shinfield and B. Robinson

Stereotactic radiosurgery for treatment of Cushing disease: an Australian experience

L. Wein, M. Dally and L. A. Bach

Spontaneous tension pneumothorax: what is it and does it exist?

G. Simpson, S. Vincent and J. Ferns

Cowden syndrome: presenting as advanced breast cancer in a young woman with macrocephaly

H. Winter and A. McEwen

Renal infarction in hypereosinophilic syndrome

A. Smith and S. L. Fernandis

Benign-appearing skin manifestation of a life-threatening condition

H. L. Try

Clarithromycin for community-acquired pneumonia: beware drug interactions

T. Bayles, E. Tong, S. Choo and A. C. Cheng

Angiotensin-converting enzyme 2 polymorphisms and cardiovascular risk

J. A. Grace, L. M. Burrell and S. K. Patel

Ionising radiation: a necessary evil?

J. C. Lee and W. W. B. Chik

Reply

D. Martinou-Boaslu and L. Lanthier
Editorial
1171 Centralising care for cardiac arrest survivors in Australia
M. J. O’Leary

Current Controversies
1173 Do we need cardiac arrest centres in Australia?
D. Stub, S. Bernard, K. Smith, J. E. Bray, P. Cameron, S. I. Duffy and D. M. Kaye

Clinical Perspectives
1179 Leukaemias into the 21st century: part 1: the acute leukaemias

Original Articles
1187 Blastocystis subtypes in symptomatic and asymptomatic family members and pets and response to therapy
1195 Spontaneous conversion of first onset atrial fibrillation
S. Lindberg, S. Hansen and T. Nielsen
1199 Associations between serum total bilirubin levels and functional dependence in the elderly
1207 Method for identifying eligible individuals for a prevalence survey in the absence of a disease register or population register
1213 Comparison of recommendations for radiotherapy from two contemporaneous thoracic multidisciplinary meeting formats: co-located and video conference
G. Stevens, J. Loh, J. Kolbe, W. Stevens and C. Elder
G. Duke, A. Barker, J. Santamaria and M. Graco
1224 Access to anticancer drugs: many evidence-based treatments are off-label and unfunded by the Pharmaceutical Benefits Scheme
1229 Positive spillover effects of prescribing requirements: increased cardiac testing in patients treated with trastuzumab for HER2+ metastatic breast cancer
1235 Myelodysplastic syndrome in New Zealand and Australia
E. J. Rodger and I. M. Morison

How I Treat
1243 How we use recombinant activated Factor VII in patients with haemophilia A or B complicated by inhibitors

Brief Communications
1251 Nutritional status of long-term patients in the acute care setting
1255 Conflict of interest: will it ever end?
S. L. Carnay
1257 SPECT ventilation perfusion scanning with the addition of low-dose CT for the investigation of suspected pulmonary embolism

Letters to the Editor
1261 Healthcare burden of in-hospital gout
G. Lee and L. Roberts
1264 Increased mortality risk in congestive heart failure patients with comorbid sleep apnoea: 10-year follow up
J. P. Bakker, A. J. Campbell and A. M. Neill

Clinical-scientific notes
1268 A fatal case of ‘magic mushroom’ ingestion in a heart transplant recipient
T. H. Lim, C. A. Vaynshch and P. N. Bogerek
1269 Disseminated herpes simplex virus infection following epidermal growth factor tyrosine kinase inhibitor therapy for non-small-cell lung carcinoma
B. W. Teh and L. J. Worsh
1270 A dangerous combination: Fabry disease and factor V Leiden
M. Niemann and F. Weidemann

General correspondence
1272 Antibiotic treatment may exacerbate clozapine induced renal failure
J. D. Kanofsky, M. E. Woesner, A. Z. Harris, J. P. Kelleher, K. Gittens and E. Jerschina
1273 Reducing polypharmacy Don Quixote style
P. Regal
1273 Do shorter emergency department stays increase in-hospital mortality?
A. Cumming
1274 Reply
B. Mina, P. A. Cameron, P. Archer, M. Bailey, P. Pedlage, G. Mele, D. V. Smit and H. Newnham
1275 Guidelines on guidelines – the impact of the Web
A. Thomson
1276 Correcting Morris et al. with respect to anaesthesia for neonatal circumcision
B. Paix
1277 Reply
A. Dilley and B. J. Morris
1278 Evidence-based policy: circumcision of infant males
D. Treher
1279 Reply
1280 ‘Circumcision of infant males’ must warn doctors of possible criminal assault charges
G. Hill, G. J. Boyle and J. V. Geisheker
1281 Legal arguments opposing infant male circumcision are flawed
B. Bates and B. J. Morris
1282 Male circumcision
G. Simpson
1283 ‘The giant waves of Osborn in brain death’
G. Nikolic
1285 Reply
H. R. Omar
1286 Evidence-based policy: circumcision of infant males
D. Forbes
1287 Reply
1288 ‘Circumcision of infant males’ must warn doctors of possible criminal assault charges
G. Hill, G. J. Boyle and J. V. Geisheker
1289 Legal arguments opposing infant male circumcision are flawed
B. Bates and B. J. Morris
1290 Male circumcision
G. Simpson
1291 The giant waves of Osborn in brain death
G. Nikolic
1292 Reply
H. R. Omar
Editorial
1285 Is there a role for coercive treatment in the management of addiction in Australia?
M. Lloyd-Jones

Clinical Perspectives
1287 Probiotics in luminal gastroenterology: the current state of play
J. M. Andrews and M. Tan

Original Articles
1292 Evaluation of an Australian chest pain assessment unit
A. Sonigra, J. Lawlor and L. Roberts
1297 Cisplatin plus etoposide versus other platin-based regimens for patients with extensive small-cell lung cancer: a systematic review and meta-analysis of randomised, controlled trials
L. Jiang, K.-H. Yang, Q.-L. Guan, D.-H. Mi and J. Wang
1300 Prevalence of food allergy in Taiwan: a questionnaire-based survey
1310 Does a ‘code stroke’ rapid access protocol decrease door-to-needle time for thrombolysis?
Y. J. Tai, L. Weir, P. Hand, S. Davis and B. Yau
1314 Obesity does not affect sodium picosulphate bowel preparation
R. C. Fok, I. R. Turner, W. C. Yeh and R. L. Levy
1317 Relationships between HMG-CoA reductase inhibitors (statin) use and strength, balance and falls in older people
W. Haerer, K. Tikhare, H. Bartlett, S. R. Lord and J. Rowland
1323 Awareness regarding venous thromboembolism among internal medicine practitioners in Mexico: a national cross-sectional study
A. Mejia-Cruz, G. Castro Martinez, M. A. Herrera Corneja, G. Lizana-Carrizo, F. Espinosa-Larraga and J. Garcia-Chavez
1327 SPAST mutations in Australian patients with hereditary spastic paraplegia
H. Vandebroek, N. P. Kerr, C. Liang and C. M. Sue

Brief Communications
1337 Changes in serum phosphate during treatment of diabetic ketoacidosis: predictive significance of severity of acidosis on presentation
Z. Shen and S. Chan
1351 Ironic case of hepatic dysfunction following the global withdrawal of sitaxentan
G. W. Don, F. Joseph, D. S. Celemajer and T. J. Corte
1355 Leukaemia cuts in chronic lymphocytic leukaemia following varicella zoster virus reactivation
G. Hapgood, E. Mooney, H. V. Dinh, D. Gin, C. McLean and S. B. Ting
1358 Successful treatment of macrophage activation syndrome complicating adult Still disease with anakinra
N. K. Loh, M. Lucas, S. Fernandez and D. Prentice

Letters to the Editor

Clinical-scientific notes
1363 Rapid recovery of renal function after pulse steroid therapy in a human immunodeficiency virus-infected patient with glomerulonephritis
D. Gracey, R. Garcia, W. Britton and P. McKenzie
1365 Drug reaction with eosinophilia and systemic symptoms associated with H1N1 vaccination
N. Hewitt, M. Levinson and G. Stephenson
1367 The i-patient or the eyeball patient?

General correspondence
1368 FDG-PET for investigation of patients with fever of unknown origin
J. C. Lee and A. M. Redmond
1369 Reply
Y. J. Kim, S. I. Kim, K.-W. Hong and M. W. Kang
1370 A plea for the use of systematic review methodology when writing guidelines and timely publication of guidelines
T. G. Pham, A. Thrift, D. Cadilhac and V. Srikanth
1371 Reply
L. Wright, K. M. Hill, J. Bernhardt, R. Lindley on behalf of the National Stroke Foundation Stroke
1372 Chest ultrasound in practice: a review of utility in the clinical setting
J. Bowra
1373 Reply
M. Hew and S. Heinze

Volume 42 contents
Developing World Access to Leading Research

This journal is available free or at very low cost within institutions in the world’s poorest countries as part of the Research4Life initiative.

Research4Life is a public-private partnership in support of the UN Millennium Development Goals. It provides access to current international peer-reviewed research so that researchers, policy-makers and practitioners in developing countries can find local solutions to local health, environmental, social, economic, agricultural and food issues.

www.research4life.org
Probiotics in luminal gastroenterology

Obesity and sodium picosulphate bowel preparation

SPAST mutations in hereditary spastic paraplegia

“Code Stroke” rapid access protocol for thrombolysis

HMG-CoA reductase inhibitors and falls in older people

Leukaemia cutis in chronic lymphocytic leukaemia and varicella zoster virus