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EDITORIALS

AFOEM’s coming of age
Niki Ellis, Inaugural President, AFOEM, 1992–1994

When the Australasian Faculty of Occupational and Environmental Medicine (AFOEM) went up before the National Specialist Qualification Advisory Committee (NSQAC) seeking status for occupational physicians as consultants in 1996, Ian Gardner, then-president, recalls standing before the chair, the daunting Professor Priscilla Kincaid Smith, as she said ‘occupational medicine has achieved consultant status with indecent haste’. Looking from the outside, this could be true. The time taken for the professionalisation of surgeons from their position as barbers is counted in centuries not decades.1

For most of the 11 of the total of 15 past, current and incoming presidents who gathered in Auckland to celebrate the 20th anniversary of AFOEM on Saturday, 17 May 2014, it is a professional lifetime. From an oral history point of view, we are lucky only one has died, but he was an important one, David Ferguson, the grandfather of occupational medicine in Australia. He was respectfully and fondly acknowledged on many occasions over the days of the scientific meeting.

David Douglas, the first president of the Australasian College of Occupational Medicine, reminded us of the history of our professionalisation. David graduated in 1962 and began his career as a procedural general practitioner in Far North Queensland. In the late 60s, a big alumina refinery came to town and his career in occupational medicine began. When he moved to England, he became a Fellow of the Faculty of Occupational Medicine (FOM) in the Royal College of Physicians. On returning to Australia, he found that there were like-minded people who had taken note of the establishment of the FOM in the UK. The Australian Society of Occupational Medicine had existed since September 1969,2 but now the aim was to achieve recognition as a specialty. As David tells it, the effort was led by Bill Cooper, described by Kevin MacDonald in his own profile in the Australian Medical Association in May 2011 as follows. ‘I was fortunate to be invited to join General Motors Holden in the mid 1970s where I was lucky to be mentored by one of Australia’s pioneering and progressive Occupational Physicians, Dr William (Bill) Cooper, until his retirement in 1981. I stayed there until my retirement in 2004. We looked after a workforce of over 10 000 people, often 3 shifts, 7 days a week, in two states, along with expatriate families in Europe, Asia and the USA and those on assignment in Australia’.

A steering committee was established, chaired for the first meeting on 10 April 1981 by Dean Southgate, after whom the annual prize for the graduating Fellow with the highest aggregate mark for the written and practical examinations is named. David Douglas took over as chair at the end of that meeting. A Memorandum of Incorporation of the Australasian College of Occupational Medicine (ACOM) was signed on 17 March 1982 by Alex Allan, John Bisby, Bill Cooper, Hugh Denchey, David Douglas, David Ferguson, ‘Copper’ Guthrie, Noel Humphrey, Jim Milne, Jim Preston and Fred Rainsford.

However, for many people, the early decades of ACOM are associated with Elaine Siggins, the long-standing executive officer. Elaine wrote to me: ‘My involvement started in mid-1982 when Peter Clark (via his secretary) talked me into organising the Australian and New Zealand Society of Occupational Medicine (ANZSOM) meeting to be held in September 1983 at the Wentworth (now Sofitel) in Melbourne. A couple of weeks after the meeting Peter invited me to lunch, David Douglas and John Bisby also attended. The purpose (unknown to me) was to try and talk me into organising the inaugural meeting for the formation of ACOM. So began my connection with occupational medicine . . . To have been around in the early days and seen the establishment of the College and development of the training programme is something I will always feel proud of. I still get a kick when I see the names of those . . . in senior roles in the Faculty or elsewhere and . . . remember when they started on this path. Takes me back to the exam days and how nerve racking it was for some’.

An Interim Council was established, with David Douglas as president, Alex Allan as vice-president, Jim Milne as hon. secretary, Hugh Denchey as treasurer and David Ferguson as censor in chief. The first elected Council met on 22 June 1983.

A wonderful inauguration of ACOM was held in Clunies Ross House in Parkville, Melbourne, on 29 March 1984, followed by a dinner at the Windsor Hotel. I have a vivid memory of the room packed with hundreds of people, of flags and military uniforms, in those days around 30% of all occupational physicians in Australia were employed by the Australian Department of Defence, of the Governor General arriving in his black car, and most of all of the sense of excitement and occasion. I was in the first cohort of trainees, and undertook the first exams after doing the Master’s of Public Health...
(Occupational Medicine) at Sydney University. David Ferguson asked me to provide a trainee perspective at the ceremony, and when I did I made a joke at his expense. Those lucky enough to know him would agree that he was one of nature’s gentlemen. I got a laugh describing the very important Masters of Public Health as the finishing school for occupational physicians. He was not impressed. The Council minutes on 28 March 1984 noted gifts presented to ACOM on its inauguration were: silver salver from the FOM in London, a visitor’s book from the Australian Occupational Health Nursing Association, and a gavel from the ANZSOM.

The top priority was to have the ACOM qualification accepted as specialist qualification. The application process began in 1985, and specialist status was granted early in 1986 after the development of exit examinations as required by NASQAC. However, ACOM was not allowed consultant status with regard to access to Medical Benefits Schedule (MBS). After a dogged campaign running over a decade, consultant status was approved in 1996, but again without access to specialty remuneration through the MBS. This was finally approved by the Minister on 17 April 1998.¹

The minutes of the Council meeting on 25 November 1987 show that Bill Glass was present as an observer. The process to become the Australasian College of Occupational Medicine had begun.

The idea that we might move ACOM into the Royal Australasian College of Physicians (RACP) appeared on the Council table suddenly, and for me without warning even though I was president at the time, in 1990. I represented a generational change and chairing a group that included the leaders of the founding generation: David Douglas, John Bisby, Peter Clark as I recall was at times challenging. On this day, after I had opened the meeting, they, totally ignoring me and the agenda, said they wanted to discuss this. It turned out ACOM was pushing at an open door. Under the visionary leadership of President John Chalmers, the RACP executive had recognised that drawing in smaller specialty groups whose work aligned with that of physicians would bring mutual benefits in terms of efficiency and expertise. That is not to say it was a stroll in the park. It took considerable work and finesse over the next few years to take both the membership of the RACP and ACOM with us. ACOM was formally welcomed into the RACP at the College ceremony in Hobart in 1994.

I took advantage of the plethora of past presidents in Auckland to seek views on what were the important highlights of our history. There was a strong consensus on several themes:

- Joining the RACP – almost everyone I spoke to cited this; because it was ‘acceptance by our peers’, or because of the leverage we have gained in developing our Faculty from ‘the big C college’. And there was a view that we had only scratched the surface – exploration of joint training has barely begun.
- The development of the training programme – led by the then-censor in chief, later to be president, Ann Long, we were ahead of our time in developing competencies; the only other group to do so at the time was the obstetricians and gynaecologists. Since then, David Goddard has led work to put flesh on the competency bones, although a new trainee representative on the Council tells me trainees want more detail on what is expected of them.
- Influencing work health policy – like most professional bodies, we have always developed policies. These have been used within our practice, and at best by some others with whom we work closely. Then, we really started to learn how to do health advocacy. We had early success working with Craig Patterson, Head of the Health Policy Unit of the RACP, in the mid-1990s, on a forerunner of health benefits of work. This was built upon with the very successful work on the health outcomes of compensable injuries,⁴ which saw us achieve meaningful engagement with a wide range of stakeholders and media interest. More recently, on the back of Dame Carol Black’s work in the UK, our health benefits of work policy⁵ has been jointly signed by workers’ compensation regulators, insurers, industry and unions, and has had a significant influence on public policy.

The landscape in which we practise has changed dramatically in the past 30 years. Gone are the positions in industry for occupational physicians, replaced by contracts, filled increasingly by corporatised occupational health services. Over this time, however, the services we offer have come to be better understood and valued. Industry, courts, workers’ compensation systems, insurers and unions now know that we can advise on how injury or illness will affect work, and work will affect health, and prefer that advice to come from us.

When ACOM was established, it had around 400 members, less than 10 were trainees. Now AFOEM has 390 Fellows and a staggering 105 trainees. As well, we participate in College life. In the recent elections for the College, 31% of AFOEM members exercised their right to vote, compared with the RACP average of 6.5%. We show up to the Annual Scientific Meeting in droves. It seems we are collegiate. Things auger well for the next 20 years.

I acknowledge David Douglas’ significant contribution of information for this article.
Occupational health in New Zealand: where from? where to?

Initiatives in occupational health in New Zealand over the past 70 years have come from government, occupational health organisations, industry and the university.

But first, what do I mean by occupational health? Ramazzini, who died 300 years ago in 1714, told us quite simply and clearly that occupational health was a clinical discipline concerned with the health of working people, their conditions of work and their environment outside the workplace. In other words, it linked the health status of the individual with both the influences of the work environment and the influences of the environment outside work.

In 1944, 70 years ago, Jack Davidson, one of the medical inspectors of factories in the UK, was invited to New Zealand by the Department of Health to report on the hygiene, working conditions and health needs of the worker. His report ‘Industrial Hygiene in New Zealand’1 was damning.

The outcome was a new Factory Act, specific regulations and the appointment of Tom Garland2 in 1947 as director of a new Division of Occupational Health in the Department of Health. He moved quickly to establish a regional system of specialist industrial medical officers working with industrial nurses, a training course for industrial nurses, and industrial clinics based at the major waterfronts and in dense regions of small workplaces. He had recognised the predominance of the small workplace in New Zealand industry, and that it was underserviced in terms of health and safety resources. He made the point that:

It cannot be too often stressed that treatment of industrial casualties is not the primary objective of an occupational health service. The primary objective is to alter conditions and to alter practices and habits so that work becomes healthier and safer.

In 1956, Tom Garland resigned and returned to the UK. His heritage was allowed to decline just at a time when the New Zealand industry was growing.

However, there were two post-Garland initiatives. The first was in 1960, when Francis King, one of the original regional industrial medical officers based in Auckland, was asked to visit overseas and report on occupational health issues. The result was his report on occupational health in 1960,3 in which he advocated the importance of establishing a Central Institute of Occupational Health. This concept was too much for the government, which compromised with a Central Industrial Hygiene Laboratory.

The second, in 1964, was an amendment to the Social Security Act 1964 (part 2), which allowed the Department of Health through the Social Security Fund to subsidise the salary paid by industry to industrial medical officers. This initiative was developed by John Copplestone,4 another of the original industrial medical officers. The result was an upsurge in the appointment of doctors, almost all general practitioners, to private industry. I was fortunate to return to New Zealand in 1959 from postgraduate study in public health and industrial health at the London School of Hygiene and Tropical Medicine, and follow Francis King in Auckland. After a 3-month mentoring period, his advice was that I go out visiting factories each day with his two industrial nurses, Margaret Heller and Ida Booth. There could not have been a better apprenticeship.

By now, as a result of the industrial doctor subsidy scheme, the initiative had moved from government to private industry, with larger companies establishing in-house industrial health clinics, nurse-based, with visiting industrial medical officers. It was now time to offer some organisation and some training to this new discipline beginning to emerge in New Zealand and even earlier in Australia.

In 1968, industrial doctors in Melbourne and in Sydney met in Canberra and made a decision to form the Australian Society of Occupational Medicine (ASOM), with the first annual meeting in Canberra the
following year. In 1970, Des Hall and I attended the second meeting.

Des was a general practitioner who had come into industrial medicine from the clinical approach, whereas I had come from the public health approach, and we both recognised the importance of working closely with the full-time industrial nurse, and were both fortunate to be employed by general managers of companies who had a firm commitment to the health, safety and welfare of the workforce. They saw no contradiction between a healthy workforce and productivity.

In 1970, David Ferguson (the ASOM secretary) visited Auckland to meet with, by now, several New Zealand members. By the third annual meeting of ASOM in Sydney in 1971, membership had reached 200. Keith Brown took over from David Ferguson as secretary, and Darryl O’Donnell followed Bill Nelson as president, and at the Melbourne meeting in 1972 a decision was made to change the name to the Australian and New Zealand Society of Occupational Medicine (ANZSOM).

In 1974, Darryl O’Donnell, now immediate past president, met with New Zealand members of ANZSOM at Waipuna Lodge in Auckland, where it was decided to form a New Zealand Branch. This took effect in Nelson in June 1975, when Des Hall was elected secretary and I president. A letter from David Ferguson confirmed the New Zealand branch should host the Federal ANZSOM meeting in 1977. This was duly held in Rotorua as a combined meeting of ANZSOM and the New Zealand Occupational Health Nurses Association, which had been established at a meeting in Tokoroa in 1971.

The New Zealand branch of ANZSOM has continued to play the dominant organisational role in New Zealand for doctors practising occupational medicine, whether part-time or full-time, or with postgraduate qualifications or without. Its mandate was established at the first meeting in Nelson where it was required to focus on three issues: social, educative and medico-political.

The social side of activities has always been a success as has the educative, with carefully planned conference agendas and guest speakers, on occasions from overseas. The contribution to medico-political issues tended to be more a feature of earlier years.

In 1982, the educative role of ANZSOM took an important step forward when it held discussions with the Department of Health and the Otago Medical School to revise the curriculum of the Diploma in Industrial Health. This was done in order to reflect more clearly the fact that most practitioners of occupational health were general practitioners with no training in the discipline of occupational health.

The first course took place in 1983 with six candidates, all from New Zealand. Over the next 10 years, a total of 70 candidates enrolled and completed the course, with 29 continuing on to specialist status. Apart from New Zealand, candidates came from Malaysia, Australia, Papua New Guinea and Hungary. An attempt to offer the course more widely to doctors in developing countries attracted a number from Africa, but suddenly collapsed when the then Labour Government decided to charge exorbitant cost recovery fees to overseas candidates. Greed had replaced helping one’s neighbour!

However, nothing stays the same, and in time our Australian colleagues realised the need for a specialist qualification and organisation, and in 1984 the Australian College of Occupational Medicine was established with an examination leading to Fellowship. The organising skills and commitment of Elaine Siggins were pivotal to its success. The College became Australasian in 1989 and finally the Faculty in 1993, with a subsequent name change from occupational to occupational and environmental medicine.

The question now needs to be asked: has all this development resulted in the better practice of occupational medicine? Des Gorman raised his concerns in an earlier editorial in this Journal 10 years ago.7 Today, 10 years later, the same question needs to be asked.

Are we, as occupational physicians, making a difference to the burden of occupational disease in the workplace? Does our current practice even take us into the workplace on a regular basis? Are we engaging with industry and the trade unions in seeking to work in unison to develop the World Health Organisation’s concept of a healthy workplace?8 Certainly, the Faculty has endorsed Dame Carol Black’s ‘Working for a Healthier Tomorrow’9 with the position statement, ‘Realising the Health Benefits of Work’.9

Yet when one reads the earlier 2009 Guidance Statement of the American College of Occupational and Environmental Medicine, ‘Healthy Workforce/Healthy Economy’,10 one senses a more direct link between a healthy workforce and a healthy economy with benefits to both parties, as well as a more focused function for the occupational physician. As the Guidance Statement notes:

Fiscal soundness can be advanced through strategic investment in the health and productivity of the working age population and through a new preventive-based paradigm centred in the workplace.

I note the words ‘centred in the workplace’. The future for our speciality, as I see it, is the need for our members to get out from behind their desks and the comfort of the consulting room, to climb down from their pedestals and to re-enter the hazardous and less comfortable conditions of the workplace. It is there where we can...
establish an ongoing dialogue with management and the trade unions.

This is not a new idea; in fact, this is how occupational medicine was practised when ANZSOM began, and of course well before that, overseas. Darryl O’Donnell, in his 1973 presidential address to a meeting in Rotorua, expressed such views with considerable force.

More recently, at an ANZSOM meeting in Wellington in 2011, Ron Loeppke, as the overseas guest speaker, re-emphasised that occupational health to be effective and create positive change must be practised in the workplace, where it needs to respond not only to work caused or related health issues but also chronic diseases and lifestyle health issues which are brought by the worker into the workplace.

There is little point in calling on Ramazzini’s name without practising what he practised. Failure to respond to these challenges that confront us will see our replacement by others who are more aware of this reality, its urgency and relevance.

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Current concepts in the management of prosthetic joint infection

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Key words: prosthetic-related infection, arthroplasty, review, anti-bacterial agent, debridement, biofilms.

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Abstract

Prosthetic joint infection (PJI) is a serious complication of arthroplasty that is associated with significant mortality, morbidity and costs. PJI is difficult to cure because causative bacteria form and persist in biofilm adherent to the prosthesis surface. PJI can be classified into early, delayed or late according to the time of onset after insertion of the prosthesis, and this classification can help determine pathogenesis and appropriate management. Traditional treatment has been with prolonged intravenous antibiotics and prosthesis exchange, which has been successful in treating infection but is technically difficult and has high rates of associated morbidity. On the basis of in vitro and animal studies, interest has turned to the use of antimicrobials that are particularly active against biofilm-associated bacteria. Recent clinical evidence shows success in more than 77% of early PJI with surgical debridement, retention of prosthesis and the use of rifampicin-based combinations for staphylococcal PJI. Fluoroquinolones are preferred for Gram-negative PJI. Optimal antimicrobial treatment duration and the management of polymicrobial, enterococcal, fungal and culture-negative infections are still yet to be defined but will become more clear as the results of current research comes to hand.

Introduction

The number of cases of prosthetic joint infection (PJI) seen in Australia continues to rise. Although rates of PJI are stable, occurring in around 1–2% of hip or knee arthroplasties, the number of joint replacements performed is steadily increasing, with over 82,000 knee or hip joint arthroplasties in the year 2012, a 55.4% increase compared with 2003.1 When PJI occurs it can be devastating. Treatment involves further extensive surgery and prolonged antibiotics. Mortality rates have been reported at between 1% and 2.7%, and additional costs of treatment are greater than $50,000.2

Advances in understanding of the pathogenesis, agreement on clinical classification, improved selection of surgical treatment approaches and the use of antibiotics with specific activity against prosthetic infections have recently led to improved outcomes for patients with PJI.3 We review these advances with special emphasis on the antimicrobial therapy for different organisms causing PJI.

Pathogenesis

Infections involving prosthetic material are difficult to treat because the causative bacteria form and exist in biofilm that is adherent to the prosthesis surface. There are many purported mechanisms by which biofilm protects bacteria from effective eradication, including antimicrobial inactivation and importantly, the differentiation of some bacteria in to a low-growth state that makes them more resistant to immune defences and the action of many antimicrobials.4 The formation and maturation of bacterial biofilm is time dependent, with biofilms established for more than 77% of early PJI with surgical debridement, retention of prosthesis and the use of rifampicin-based combinations for staphylococcal PJI. Fluoroquinolones are preferred for Gram-negative PJI. Optimal antimicrobial treatment duration and the management of polymicrobial, enterococcal, fungal and culture-negative infections are still yet to be defined but will become more clear as the results of current research comes to hand.

Microbiology of PJI

The spectrum of microorganisms causing PJI is wide; however, Staphylococcus aureus and coagulate-negative...
Staphylococci (CNS) are the most commonly isolated organisms, occurring in approximately 50%. In Australia, methicillin-resistant staphylococcal infections are common (45% of cases). Gram-negative bacilli, streptococci and enterococci form significant minorities. Polymicrobial infections, often involving staphylococci, gram-negative bacilli and enterococci occur frequently and tend to involve hip PJI more than knee. An organism is not isolated (culture-negative) in 2–10% of cases, mainly where antibiotics have been given prior to culture specimens being obtained. Shoulder arthroplasty infections are more likely to be caused by indolent organisms, such as Propionibacterium acnes and CNS.

Classification

One classification system for PJI can be seen in Table 1. It classifies according to the time of onset of symptoms after the insertion of prosthesis and can be helpful in determining pathogenesis, likely organisms and the appropriate treatment approach.

Surgical management

The traditional surgical treatment of PJI involves prosthesis exchange. This can be achieved by either 1-stage exchange, involving re-implanting a new prosthesis directly after the infected prosthesis is removed or 2-stage exchange, usually involving insertion of an antibiotic-loaded cement spacer after removal of the infected prosthesis and then reinserterion of another prosthesis after a delay of approximately 6 weeks. These approaches have been associated with cure rates of greater than 80%. The disadvantages of prosthesis exchange are that it involves difficult surgery, prolonged periods of immobilization and high rates of complications and morbidity.

Early attempts at treating PJI with antibiotics and debridement and retention (DAR) of the original implant in situ resulted in poor outcomes, with less than 40% of infections treated successfully. As patient selection, surgical techniques and antibiotic therapy have improved, interest has swung back to DAR as it involves less extensive surgery and is better tolerated. Currently, DAR is the most common surgical treatment approach for PJI in Australia. Importantly, outcomes are better with DAR if patients have early infections (<3 months from the time of insertion) and less than 3 weeks of symptoms, where bacterial biofilm is not yet fully established. Some authors have seen better results when DAR is limited to patients with PJI within 1 month of prosthesis insertion; however, this has been in patients who were not treated with biofilm-active antibiotic regimens. Patients in whom DAR is attempted should not have an infection with multi-resistant organisms, should have a stable prosthesis and good overlying soft tissues without a sinus tract. DAR can also be attempted in patients with late, likely haematogenous infections with a short duration of symptoms; however, outcomes are not as good. Debridement should be through open arthrotomy rather than arthroscopy, and the polyethylene liner should be changed. Some studies suggest one debridement operation is optimal; however, planned repeat debridement operations (usually two to three) are often performed in Australia with good results.

For patients with delayed PJI or where DAR has failed, the recommended treatment approach is prosthesis exchange. This is often achieved with two-stage exchange rather than one-stage because of generally better outcomes. Some specialised international centres have reported good outcomes with one-stage exchange particularly for hip PJI using antibiotic-loaded cement in selected patients with sensitive organisms, without systemic sepsis and good local soft tissues. Permanent removal of the prosthesis or amputation can be considered for patients who are unlikely to achieve mobility or a functional joint with exchange surgery.
Surgical treatment decisions are complex and should be made by multidisciplinary teams, involving an experienced orthopaedic surgeon in consultation with, among others, infectious diseases specialists and microbiologists. Although a protocolised approach cannot account for all patient circumstances and treatment clearly must be individualised, some surgical algorithms have been proposed that have shown improved results when adhered to in retrospective validation studies.3,10,23 As a guide, we have presented a simplified surgical approach in Figure 1 based on these algorithms.

Recent advances in medical management

The accumulating clinical and in vitro evidence suggests that the key to the medical treatment of PJI is the use of antimicrobial agents with activity against biofilm-associated microorganisms. This is particularly important where DAR is attempted.

Staphylococcal PJI

In vitro experiments and animal models of foreign-body infections show that rifampicin has superior activity against biofilm-associated staphylococci compared with other anti-staphylococcal antibiotics.24 This has been confirmed clinically in relatively large numbers of patients in multiple cohort studies and one small randomised controlled trial where successful outcomes have been achieved in 77–89% of early staphylococcal PJI treated with DAR and rifampicin-based regimens.8,14–17 One recent large multicentre cohort with a large proportion of delayed or late/haematogenous infections and strict definitions of success only had success in 55% of patients.20 In cohorts where both non-rifampicin and rifampicin-based antibiotic regimens were used, rifampicin regimens have been associated with better outcome;17,20 The best results reported in patients undergoing DAR with intravenous beta-lactam or glycopeptide antibiotic regimens is 71%;10,16 however, most cohorts report success in less than 40% of patients.5

Rifampicin has excellent anti-staphylococcal activity, very good oral bioavailability and penetrates well in to bone.25 Most staphylococcal isolates in Australia are sensitive to rifampicin, whether methicillin sensitive or resistant.26 Doses used for PJI have usually been 300–450 mg orally twice daily; however, the 300 mg twice daily dose may be better tolerated.16 In Australia, rifampicin is not Pharmaceutical Benefits Scheme (PBS) subsidised for the treatment of PJI and so is mainly supplied from hospital pharmacies under guidance from infectious diseases specialists. The most common side effect is nausea, which leads to a change in therapy in approximately 5% of patients.8,16 Rifampicin is a potent inducer of cytochrome P450 enzymes and so interacts with many medications, including warfarin. If rifampicin is used as a single agent resistance emerges rapidly. Due to this it must be used in combination with another antibiotic with proven efficacy in this role and compliance with both antibiotics must be excellent. There is good evidence supporting the use of fluoroquinolones, such as levofloxacin (not marketed in Australia) or ciprofloxacin in combination with rifampicin.15–17,24 Moxifloxacin is a fluoroquinolone available in Australia that has enhanced activity against biofilm-associated staphylococci in vitro27 and is theoretically well suited to combine with rifampicin for PJI; however, given rifampicin induces its metabolism the correct dose of moxifloxacin in this combination is not yet known.28 Moxifloxacin has been used as a single agent with success in a limited number of orthopaedic-device associated infections.27 Although most strains of methicillin-sensitive S. aureus are sensitive to fluoroquinolones, 71% of hospital-associated methicillin-resistant S. aureus isolates across Australia are resistant to fluoroquinolones,26 limiting their utility in this setting. Most methicillin-sensitive and resistant staphylococcal strains in Australia are still sensitive to fusidic acid.26
Fusidic acid has shown clinical efficacy in combination with rifampicin for PJI.\textsuperscript{29} It is subsidised by the Australian PBS for use in combination with another agent (usually rifampicin) for staphylococcal infections. There have been descriptions of fusidic acid interacting with statins and causing rhabdomyolysis.\textsuperscript{29}

Other oral antibiotics that have been used in combination with rifampicin for staphylococcal PJI in smaller numbers of patients with less success or more intolerance are pristinamycin,\textsuperscript{30} trimethoprim/sulfamethoxazole\textsuperscript{31} and minocycline.\textsuperscript{32} There is good in vitro evidence that linezolid can prevent the emergence of rifampicin resistance and some clinical evidence that it can be used as a single agent for PJI where rifampicin cannot be used; however, its use is limited by the development of severe adverse effects, such as peripheral neuropathy, optic neuropathy and cytopenias, especially when used for longer than 4 weeks.\textsuperscript{33,34}

Intravenous anti-staphylococcal beta-lactams or glycopeptides are usually used for short periods at the start of treatment prior to a rifampicin-based regimen. Some recommendations suggest using rifampicin with an intravenous beta-lactam or glycopeptide during this early period.\textsuperscript{19} While intravenous antistaphylococcal beta-lactams, such as flucloxacillin may be able to prevent rifampicin resistance, it has been shown that glycopeptides don’t.\textsuperscript{35} Due to the serious consequences of induced rifampicin-resistance we recommend that at all times it be used in combination with other oral antibiotics with proven efficacy in preventing resistance as described above.

**Gram-negative bacilli PJI**

*In vitro* and clinical data again point to the advantages of extended courses of oral fluoroquinolones, especially ciprofloxacin, over other antibiotics, such as beta-lactams and aminoglycosides for eradicating gram-negative bacilli PJI treated with DAR.\textsuperscript{36–38} Primary resistance to ciprofloxacin in gram-negative organisms in Australia is rare; however, rates are increasing.\textsuperscript{29} Concurrent intravenous beta-lactams at the start of the oral ciprofloxacin course have been used in described regimens, and longer durations of concurrent treatment may be important for Pseudomonas and Acinetobacter infections where the development of ciprofloxacin resistance can emerge during treatment.\textsuperscript{3,37}

**Enterococcal and streptococcal PJI**

There are limited data guiding optimal treatment for enterococcal and streptococcal PJI. For susceptible isolates, outcomes are reasonable with intravenous beta-lactams although only limited information is available for patients treated with DAR.\textsuperscript{40,41} For enterococci, adding synergistic aminoglycosides to penicillins or vancomycin may not add to efficacy but does add to toxicity.\textsuperscript{40} Synergistic ceftriaxone has been given with penicillin with success in some patients.\textsuperscript{42} For continuing oral treatment of penicillin-resistant enterococci after intravenous vancomycin, linezolid or pristinamycin have been used\textsuperscript{10,13} and clindamycin has been used for streptococci.\textsuperscript{43} Combinations of fluoroquinolones, rifampicin and linezolid have good activity against enterococcal biofilms in vitro,\textsuperscript{39} but there are no reports of treatment outcomes in humans.

**Fungal PJI**

Candida species are the most commonly reported causes of fungal PJI.\textsuperscript{44} Most cases of fungal PJI have been treated with two-stage prosthesis exchange and combinations of amphotericin and azoles. *In vitro* evidence shows good activity of echinocandins and liposomal amphotericin against biofilm-associated Candida.\textsuperscript{45}

**Culture-negative PJI**

If a PJI has been rendered culture-negative due to antibiotic therapy given prior to microbiological sampling, then a treatment regimen with a similar spectrum of activity to the previously used antibiotic can be used. Some patients treated with DAR have been cured after treatment with mainly intravenous beta-lactam antibiotic regimens.\textsuperscript{46} Broad-spectrum treatment regimens with rifampicin, fusidic acid and ciprofloxacin have led to good outcomes for infection treatment but are difficult to tolerate.\textsuperscript{47}

**Duration of treatment**

For staphylococci and most gram-negative bacilli, successful regimens where oral biofilm-active antimicrobials are available have used initial intravenous therapy for 2 weeks or less before changing to oral;\textsuperscript{5,15,16} however, some authors and current Australian guidelines have recommended up to 6 weeks of intravenous therapy regardless.\textsuperscript{15,48} For organisms where oral biofilm-active agents are not available, at least 4–6 weeks of intravenous therapy is advised. The optimal duration of oral antibiotic therapy for early PJI treated with DAR is not known. Most cohorts reporting good outcomes have used oral antibiotic regimens of at least 3–6 months.\textsuperscript{15,16} Some recommend 3 months treatment for hip PJI and 6 months for knee PJI.

A summary of options for the antibiotic treatment of PJI treated with DAR and curative intent, based on the above discussion, can be seen in Table 2.
Venous lipopeptide antimicrobial that has good making treatment much easier. Daptomycin is an intra-
cally, the bacterial biofilm has been removed surgically efficacy against biofilm-associated staphylococci, including most methicillin-resistant strains. In one trial it was superior to intravenous beta-lactam or glycopeptide antibi-
tics at a dose of 6 or 8 mg/kg for treatment of PJI managed by two-stage exchange. Its exact role is currently unclear because of the potential for emergence of resistance when it is used alone, cross-resistance with vancomycin and the serious side effect of rhabdomyolysis. Relapses of PJI treated with prosthesis exchange are likely related to residual biofilm in bone or on retained bone cement so we recommend oral biofilm-active antibiotic regimens as for DAR for these patients also. Outcomes using these antibiotics were good in one study.

The antibiotic treatment for one-stage exchange, given it involves insertion of the prosthesis into an infected field and the potential for biofilm formation, is with biofilm-active antibiotics.

**Prosthesis exchange**

Cure rates of more than 80–90% have been achieved with various different antibiotics regimens, including 4–6 weeks of an appropriate intravenous beta-lactam antibiotic for PJI treated with two-stage exchange. Theoretically, the bacterial biofilm has been removed surgically making treatment much easier. Daptomycin is an intra-
venous lipopeptide antimicrobial that has good in vitro efficacy against biofilm-associated staphylococci, including most methicillin-resistant strains. In one trial it was superior to intravenous beta-lactam or glycopeptide antibi-
tics at a dose of 6 or 8 mg/kg for treatment of PJI managed by two-stage exchange. Its exact role is currently unclear because of the potential for emergence of resistance when it is used alone, cross-resistance with vancomycin and the serious side effect of rhabdomyolysis. Relapses of PJI treated with prosthesis exchange are likely related to residual biofilm in bone or on retained bone cement so we recommend oral biofilm-active antibiotic regimens as for DAR for these patients also. Outcomes using these antibiotics were good in one study.

The antibiotic treatment for one-stage exchange, given it involves insertion of the prosthesis into an infected field and the potential for biofilm formation, is with biofilm-active antibiotics.

**Long-term antibiotic suppression**

For patients with a delayed infection and significant comorbidities at too high a risk to undergo exchange surgery, long-term antibiotic suppression with or without initial DAR can be attempted, aiming to suppress rather than cure infection. In these patients, antibiotic selection depends on sensitivities of the infecting organism as well as long-term tolerability more than activity against biofilm-associated organisms.

**Table 2** Antibiotic options for prosthetic joint infection treated with debridement and retention

<table>
<thead>
<tr>
<th>Organism</th>
<th>Initial intravenous treatment</th>
<th>Continuing oral antibiotic regimen</th>
<th>Alternative oral antibiotic regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococci</td>
<td>Flucloxacin 2 g iv 6 hourly OR vancomycin iv to achieve trough levels 15–20 mg/L x 2 weeks</td>
<td>Rifampicin 300 mg po twice daily AND one of: pristinamycin 500–1000 mg po three times a day OR trimethoprim/sulfamethoxazole 160/800 mg po twice daily OR minocycline 100 mg po twice daily OR linezolid 600 mg po twice daily x 3–6 months</td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>Broad-spectrum intravenous beta-lactam e.g. ceftriaxone 2 g 24 hourly or meropenem 1 g 8 hourly x 2–4 weeks†</td>
<td>Ciprofloxacin 500–750 mg po twice daily§ x 3–6 months</td>
<td>Amoxicillin/clavulanic acid 875/125 mg po twice daily OR trimethoprim/sulfamethoxazole 160/800 mg po twice daily x 3–6 months</td>
</tr>
<tr>
<td>Enterococci</td>
<td>Benzylpenicillin 1.8–2.4 g 4–6 hourly† OR vancomycin iv to achieve trough levels 15–20 mg/L x 4–6 weeks</td>
<td>Amoxicillin 1000 mg po three times a day x 3–6 months</td>
<td>Pristinamycin 500–1000 mg po three times a day OR linezolid† 600 mg po twice daily x 3–6 months</td>
</tr>
<tr>
<td>Streptococci</td>
<td>Benzylpenicillin 1.8–2.4 g 4–6 hourly OR ceftriaxone 2 24 hourly OR vancomycin iv to achieve trough levels 15–20 mg/L x 4–6 weeks</td>
<td>Amoxicillin 1000 mg po three times a day x 3–6 months</td>
<td>Rifampicin 300 mg po twice daily OR moxifloxacin 400 mg po daily OR clindamycin 450–600 mg po three times a day x 3–6 months</td>
</tr>
</tbody>
</table>

Choice dependant on antimicrobial sensitivity testing and preferred agents are listed first. Doses given are for patients with normal renal function. †Duration of linezolid use likely to be limited to 4–6 weeks due to toxicity. §If ciprofloxacin resistant then intravenous antibiotic duration should be extended for longer than indicated duration. ¶Benzylpenicillin is the preferred agent so if penicillin allergy exists consider desensitisation.

**Future considerations**

Large controlled trials are not currently available to inform management decisions for patients with PJI, with most evidence still largely from retrospective cohort or non-controlled studies. Recently, the Infectious Diseases Society of America published guidelines and an International Consensus Meeting published a consensus document regarding the diagnosis and management of PJI; however, both acknowledged that in many areas their recommendations were based on expert opinion given the lack of data. Important information is still lacking in the areas of antibiotic treatment duration, pharmacokinetics of antibiotics used for PJI and the optimal treatment of polymicrobial, enterococcal, fungal and culture-negative infections. Outcomes other than infection eradication need to be assessed, such as function and complications. A recent survey of infectious diseases physicians conducted by the Australasian Society for Infectious Diseases identified PJI management as the top research priority. Based on this, a multi-centre prospective observational study is being established in Australia and New Zealand to describe further and refine PJI...
management in the local setting. Other similar studies are underway internationally, including a limited number of randomised controlled trials.

Conclusions

Advances in management strategies for patients with PJI, particularly the improved selection of patients that can be treated with DAR and the use of biofilm-active antibiotics have recently seen better outcomes. Management is complex and should involve close collaboration of all involved medical professionals and include orthopaedic and infectious diseases specialists experienced in treating PJI. As results from current research come to hand, patient outcomes from this serious complication are likely to improve further.

References

ETHICS IN MEDICINE

Dilemmas in the compassionate supply of investigational cancer drugs

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Abstract
In Australia, patients who want to access medicines that are not yet approved have only two options: to enrol in a clinical trial if they are eligible, or obtain their medicine through ‘compassionate supply’, which is provided at the discretion of the manufacturer. In this article, we explore ethical issues associated with the provision of oncology medicines that are still in development, either prior to regulatory approval or government reimbursement.

Introduction
The possibility of developing cancer is a terrifying prospect for most people. It is unsurprising, therefore, that media reports relating to ‘breakthroughs’ in the fight against the disease invariably capture the attention of the Australian public.

Stories of promising early clinical trial data presented in the media – as well as at conferences, in medical journals and through the Internet – may also prompt interest from patients, their relatives and their doctors to gain access to new agents without the need to wait years for their regulatory approval.

Patients desiring access to medicines that are not yet approved generally have only two options: to enrol in a clinical trial if they are eligible (although this does not, of course, guarantee allocation to the new experimental treatment) or to ask the manufacturer to supply the medicine on ‘compassionate’ grounds. The recent story of Nick Auden illustrates what happens when both of these options fail.

Nick Auden was an Australian patient and young father who died in 2013 from advanced metastatic melanoma. He and his family attempted, unsuccessfully, to gain access to two ‘promising’ new therapies currently under development – nivolumab (Bristol-Myers-Squibb, NY, USA) and lambrolizumab (Merck, NJ, USA). While not approved by any international regulatory bodies, these two drugs had shown promise in phase I clinical trials, and at the time of Auden’s approach to the two companies patients were being enrolled into phase II and III studies.

Advanced metastatic melanoma has a very poor prognosis, with an overall 5-year survival being 10–20%.1 Conventional therapies, such as surgery, radiotherapy, cytokines and established chemotherapeutic agents (such as dacarbazine, temozolomide, paclitaxel, cisplatin), offer little more than short-term palliative benefits for many
patients. For this reason, enormous excitement has surrounded the emergence of newer targeted therapies (vemurafenib and ipilimumab) as early studies have suggested a clinical benefit with relative increases in average patient survival of 63% and 36% respectively.\(^2\)\(^1\)

However, because neither nivolumab or lambrolizumab was approved by the Therapeutic Goods Administration (TGA), and because he was not eligible to participate in phase II or III studies, Auden, his family and other high-profile advocates pleaded for ‘compassionate access’ from the companies developing these two medicines. The two companies, however, refused his requests, despite his case gaining international media coverage and a petition signed by many thousands of supporters.

The public disquiet surrounding this case, and many others like it, illustrate several ethical, legal, commercial and sociopolitical challenges associated with compassionate access to cancer medicines, particularly those still in clinical development. In this article, we describe features of compassionate access processes in Australia, highlight their limitations and suggest the kinds of changes that might be required to ensure more appropriate and equitable access to prescription medicines.

**Compassionate access to cancer medicines in Australia**

The most common mechanism for patients to access currently unapproved or approved but unfunded treatments is through patient access programmes (PAP) – also referred to as ‘compassionate use’, ‘named patient’ or ‘expanded access’ programmes. These programmes, run by pharmaceutical companies, make drugs available (often, but not always, for free\(^4\)) to patients within a structured company-administered framework. Inclusion criteria are usually similar to, but less rigorous than, those of a clinical trial, and tend to be closely aligned to the indication being sought by the company for their new product.

Companies usually decide to institute PAP following the emergence of phase III clinical trial data (i.e. data on efficacy and safety in patients with the relevant indication), and after an assessment of whether existing data are likely to support the eventual commercial launch of the new drug. In Australia, the ability to prescribe non-approved treatments is legislated for through the Australian Therapeutics Good Administration Category A Special Access Scheme. This provides clinicians with the authority to prescribe non-approved treatments in the setting of a life-threatening condition.

Outside of formal PAP, patients can approach companies with individual requests for supply of a desired medicine. They can also purchase the medicine themselves, either locally if it is available, or from another country where the treatment has regulatory approval. Companies may or may not help patients afford these medicines, which are often expensive, through various kinds of co-payment or cost-sharing arrangements. Some hospitals also have high-cost drug and therapeutics committees, which may agree to supply cancer medicines that are not approved by the TGA and/or not funded on the Pharmaceutical Benefits Scheme.

**Companies’ obligations**

As is evident in Nick Auden’s case, companies are under no obligation to respond positively to requests for compassionate access. This is despite attempts made overseas to change this situation. In 2007, a group in the US called the Abigail Alliance argued that both the US Food and Drugs Administration (FDA) and pharmaceutical companies had an obligation to provide early access to life-saving medicines.\(^3\)

The Abigail Alliance claimed, on libertarian grounds, that if a terminally ill patient had a fundamental right to refuse life-sustaining treatment, knowing that they would die as a consequence of that choice (a statute ruling from previous US cases), a corollary had to be that terminally ill patients should have the right to access any treatment that may extend or improve the quality of their lives, including those still in development. In rejecting this proposal, the FDA countered that such access would undermine the entire clinical research process, and thus have a ‘devastating’ impact on the interest of future patients.\(^6\) Following the failure of the Abigail Alliance’s case, at the current time, patients like Nick Auden have no option but to continue to lobby for compassionate access to medicines – leaving pharmaceutical companies to make their own decisions about whether or not they are able to help.

At present, each pharmaceutical company independently determines when to allow compassionate access to its products, who should receive such access and for how long. As Auden’s and other previous cases that led to the Abigail Alliance’s actions have illustrated, decisions relating to ad hoc requests can be highly controversial, leaving some patients feeling that they have been abandoned for unjustifiable reasons. This, in turn, raises the question of how decisions about compassionate supply should be made and how compassionate access programmes should be designed and overseen.

**Ethical considerations and tensions in the provision of compassionate access**

There are several tensions inherent in the provision of compassionate access to cancer medicines, resulting from...
a complex interplay among medical need, evidence, ethics, medical law and commercial interest.

The first of these is the tension between providing benefit to patients without causing harm to them, to those supporting them, to the health system or to the research enterprise. Although robust clinical research and regulatory processes take time and delay access to medicines, they have evolved for good reason, and history has demonstrated that significant harms may arise where medications are inadequately researched or regulated – such as what occurred with rofecoxib for arthritis and thalidomide for ‘morning sickness’. Notwithstanding that ‘risk/benefit’ considerations may be considerably different for patients with imminently life-threatening illnesses, as compared with patients with, say, morning sickness or arthritis, potential harms still need to be considered. In this regard, it is noteworthy that several cancer and HIV medicines that have been the source of initial excitement have subsequently failed to live up to their promise – even for people in desperate situations. These include, for example, cytokines for renal carcinoma, anti-angiogenic therapies for breast cancer and some earlier anti-retroviral drugs used in the treatment of AIDS. In the context of life-threatening illness, we also need to bear in mind that effective palliation may be foregone if patients are led to believe that an expensive new treatment is their ‘only hope’. This lost opportunity is a real harm that needs to be factored into any risk – benefit calculation.

Second, because resources are limited (even for companies, as will be discussed later), decisions have to be made about who should be privileged in terms of compassionate access. This inevitably creates a tension between allocating resources efficiently, so that the greatest amount of good is done for the greatest number of patients, and allocating resources in such a way that no particular individual or group is disadvantaged.

Third, as was evident in the Abigail Alliance debate, there is a tension between clinical care, which focuses on the needs of current patients, and research, which is primarily concerned about the future, and ultimately many more patients. If enough patients receive supply of a medication outside of the clinical trial setting, then opportunities are lost to gather crucial data on safety and efficacy. Trials might also be impacted if compassionate access makes it difficult for manufacturers to supply enough medicines needed for research.

Fourth, there are tensions between the needs of patients (both current and future) and the need for pharmaceutical companies to ensure early and maximal commercial returns. Pharmaceutical companies are businesses, and compassionate supply of their medicines may or may not be aligned with their longer term commercial interests.

On the one hand, as critics of industry have argued, companies may use compassionate access schemes as marketing tools designed to familiarise prescribers with their products, to create demand among patients and consumer for access and continued supply of these medicines, and to generate support from patients and clinicians for submissions to regulatory and funding bodies.

On the other hand, compassionate supply may work against the commercial interests of companies, costing them money and diminishing community advocacy for third-party (government or insurance company) funding as a means to access, thus reducing long-term revenues for manufacturers.

So with these tensions in mind, what might be a scientifically, ethically, politically and commercially sound approach to early access to potentially life-saving medicines?

The future of compassionate access programmes

The first thing for those considering compassionate supply or designing compassionate access programmes is to acknowledge that there is no simple solution to any of the tensions described above, and it is therefore unlikely that a satisfactory ‘one size fits all’ process will ever be defined. Indeed, as described above, numerous models exist for PAP, and there is significant heterogeneity between these.

In all cases, therefore, engagement between companies and other stakeholders who may be impacted, such as clinicians, patients and regulators, should occur to ensure that values are made explicit, that all interests are considered, and that trade-offs are acknowledged and managed. In technically complicated and value-laden processes such as these, it may be important to establish an appropriate forum that brings together representatives of industry, consumers, government, health providers, insurers, physicians, researchers and ethicists to develop a framework for PAP, and where resources are available to review and advise on specific programmes. While it is beyond the scope of this article to consider the details of how such a forum should be established and run, it could draw on frameworks for policymaking such as ‘accountability for reasonableness’ as this emphasises inclusive, transparent, accountable processes rather than on pre-refined rules of allocation.

Second, properly informed consent should always be obtained – particularly when the treatment has not yet been approved by a regulatory agency. Patients requesting compassionate access are highly vulnerable and may feel a genuine sense of desperation, but they still need to
understand the risks of bypassing research and regulatory processes, and the decision has to be theirs and not their family’s or their doctor’s.

Once access has been granted and consent obtained, patients need to be carefully monitored for adverse events. In this regard, it is noteworthy that, while, as discussed above, some PAP requires approval by health authorities prior to opening within hospitals under their jurisdiction, these programmes rarely go through a human research ethics committee (HREC) review process. Indeed, data collection is often kept to a minimum in order to avoid the need for such review. The explicit justification for this is that the need for review may delay patient access to, and clinician experience of, a new product. Implicitly, reluctance to collect data and submit it for review may be in conflict with the commercial interests of a company wishing to launch a new product as quickly as possible. Whatever the reason for bypassing review, the absence of sufficient oversight by HREC may place patients at greater risk than those enrolled in clinical trials if a treatment is very early in its development, and also limit the extent to which PAP can be used as alternative sources of data about safety and efficacy. Because of this, it is important that appropriate safeguards are in place to protect the interests of the most vulnerable of patients.

In terms of forward planning, it is important for any company to consider the possibility that they might never achieve either regulatory approval or reimbursement, and to ask themselves what this would mean for the future of patients enrolled in a PAP. One option simply would be to apply a ‘rule’ that the PAP runs for a limited time, as is the case with patient familiarisation processes (PFP). Under the rules of Medicines Australia’s Code of Conduct, PFP may run for only 6 months. However, while the application of such a rule to PAP provides transparency, clarity and consistency, it may not adequately account the many complex factors that underpin decisions to provide compassionate access.

A different approach, however, could take the form of single-arm phase IV studies. These would have the benefit of generating useful additional evidence relating to safety, quality of life or other response-related end-points. They may also help generate evidence for outcomes that are difficult to demonstrate through randomised controlled trials due, for example, to confounding caused by crossover or post-study exposure to study treatments.¹⁵ Indeed, compared with evidence generated within ‘artificial’ parameters of a randomised clinical trial, such activity may also be more reflective of the clinical effectiveness of a new treatment within a local and, because of less stringent inclusion criteria, a more diverse patient population. Such studies would, however, be reliant on good biobank and patient registry infrastructure, and would need to be managed very carefully so as not to compete with patient recruitment to clinical trials.

One other issue that needs to be considered is that pharmaceutical companies are only one ‘player’ in this complex field. While the focus of our discussion has been on medicines that have not yet received regulatory approval, compassionate access programmes exist in part because governments and/or private insurers may choose not to fund even those medicines that have been shown to be safe and effective (but may not be cost effective) – such as trastuzumab (Herceptin) for metastatic breast cancer. This raises a whole suite of issues about the organisation and priorities of the public and private health systems that are beyond the scope of this article. But it is important to bear in mind that ensuring access to life-saving medicines is a shared responsibility that falls to many different stakeholders, each of whom is driven by a complex set of moral and sociopolitical concerns.

**Conclusion**

Despite some media reports to the contrary, decisions about compassionate supply of cancer medicines that are still to be approved is not a simple matter of helping, or not helping, an individual in need. Rather, they involve highly complex decisions that raise many ethical, regulatory, commercial, scientific and clinical tensions, all of which need to be considered and balanced.

Importantly, the potential risk that PAP may undermine or circumvent carefully structured processes for drug approval needs to be managed. This is because history provides us with several examples of drugs that initially appeared promising, but which were later found to be unsafe or of less clinical value than initially believed. In the context of cancer and other life-threatening illnesses where patients may be desperate for help and clinicians may feel enormous pressure to use whatever experimental treatments are available, it cannot be forgotten that appropriate palliative care may be a more suitable option for some patients than access to treatments that may well prove to be ineffective and/or unsafe. For these reasons, the interests of both present and future patients need to be carefully considered, with decisions made in ways that are systematic, transparent, accountable, explicit about values, respectful of patient autonomy and inclusive of all stakeholder perspectives.
References


Association of better iron status biomarkers and coronary artery disease risk

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Key words
iron, coronary artery disease, receiver operating characteristic analysis.

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Abstract

Background: Epidemiological evidence concerning the role of body iron in coronary artery disease (CAD) is inconsistent, which is largely explained by the lack of relatively ideal estimations of body iron stores.

Aim: The aim of the present study was to attempt to explore the ideal iron indicator that has the best effect on disease risk for further studies related to iron overload metabolism research worldwide.

Methods: A case–control study was conducted with 258 CAD cases and 282 healthy controls. The association of serum iron (SI) parameters, including SI, total iron-binding capacity (TIBC), serum ferritin (SF) and serum transferrin receptor (sTfR), and CAD risk, was evaluated with receiver operating characteristic analysis. The areas under the receiver operating characteristic curve (AUC) were compared with each other to indicate the one showing the strongest association with CAD risk.

Results: The AUC (95% confidence interval) were 0.73 (0.69–0.77), 0.74 (0.69–0.78), 0.53 (0.48–0.58) and 0.61 (0.56–0.66) for SI, TIBC, SF and sTfR respectively. After comparing the AUC with each other, the combination of SI and TIBC (AUC (95% confidence interval): 0.86 (0.83–0.90)) was superior to other examined iron parameters or the combination of iron indicators (P < 0.05).

Conclusions: The present study indicated that the combination of SI and TIBC may have the best effect on CAD risk. Further studies are warranted to verify this preliminary result.

Introduction

Iron is a transition metal that could cause organ dysfunction through the production of reactive oxygen species,1 and it has been suggested to be involved in many harmful biological processes and diseases in the human body.2,3 Hereditary haemochromatosis results in excess iron accumulation in the body and a variety of ensuing clinical manifestations involving liver cirrhosis, diabetes and cardiovascular disease.4 The possible relationship between body iron and cardiovascular disease has been of considerable interest since the early 1980s, when a study reported by Sullivan5 proposed that excess body iron stores were important new cardiovascular risk factors.

Supporting evidence comes from in vitro lipid peroxidation studies6,7 and from cholesterol-fed iron-overload animal models.4 Therefore, the ‘iron hypothesis’ is more plausible and appealing.

To date, extensive debates have been generated from epidemiological studies and clinical trials.9–11 In these, elevated body iron stores have been associated with increased risk of coronary artery disease (CAD) in some12 but not in all studies.13,14 A prospective study conducted in Finland15 suggested that a high level of stored iron, assessed by elevated serum ferritin (SF) concentrations, was a risk factor for cardiovascular disease, while another study that evaluated iron status by serum iron (SI) failed to indicate a correlation between iron stores and CAD risk.16 The inconsistency in the epidemiological studies may be largely explained by the different biochemical markers of the estimations of body iron stores. SF is a sensitive indicator of iron stores,17 although its main limitation is that chronic infection or inflammation elevates the concentration two to three times higher than values
representing iron stores. Total iron-binding capacity (TIBC) measures the ability of plasma proteins to bind iron and reflects the fraction of transferring-free places to bound iron, and it was suggested to be a reliable predictor of accumulation of free iron in the vessel wall. SI, as an indicator of organic iron, is linked positively to the incidence of atherosclerosis in several studies. Thus, identifying a better combination of SI indicators to estimate the iron status could be important in clarifying the association between body iron stores and CAD risk.

So far, a good deal of SI indicators, such as SI, SF, serum transferrin receptor (sTfR) and TIBC, were used in the present publications to assess the relation of body iron store to some kind of disease risk, such as CAD. Among the above parameters, almost no one could independently reflect the body iron levels for various weaknesses. Thus, in this study, we attempt to explore the ideal iron indicator or combination of iron indicators that has the best effect on CAD risk for future studies related to iron overload metabolism research worldwide.

**Methods**

**Study design**

A total of 258 newly diagnosed CAD patients and 282 healthy controls was included in the present hospital-based case–control study. All the CAD patients were recruited from the Department of Cardiology, Qilu Hospital, Shandong University. The diagnosis of CAD patients was defined according to the World Health Organization criteria and described briefly below: more than 50% of stenosis in at least one major coronary artery determined by percutaneous coronary angiography; symptoms, electrocardiographic changes and elevation of cardiac enzymes for myocardial infarction; and symptoms and electrocardiographic changes for arrhythmias and angina pectoris. The 282 controls were recruited from the healthy persons examined in the Physical Examination Center at Qilu Hospital. All subjects were asked to fill out a questionnaire regarding their lifestyle. This study was reviewed and approved by the Ethics Review Committee of Shandong University, and all subjects provided informed consent.

**Laboratory analysis methods**

The blood samples were obtained from the remnants of the venous blood for the subject’s laboratory tests and were stored at −80°C. All the SI parameters, including SI, SF, TIBC and sTfR, were measured by enzyme-linked immunosorbent assay method using a commercial kit (Blue Gene, Shanghai, China). Serum triglyceride (TG) and total cholesterol (TC) were measured by enzymic colorimetric method on a Hitachi 717S automatic biochemical analyser (Tokyo, Japan).

**Statistical analysis**

Pearson’s Chi-squared test was performed to compare the distribution of categorical variables between cases and controls. One-way analysis of variance was used to test the differences of means between cases and controls for continuous variables. The variables of smoking, alcohol intake, hypertension and diabetes were utilised as dichotomous variables. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or a history of hypertension. The variables of age, TG (mmol/L), TC (mmol/L), body mass index (BMI, kg/m²) and 8-iso-prostaglandin F2α (8-iso-PGF2α, an indicator for oxidative stress) were treated as continuous variables.

The areas under the receiver operating characteristic (ROC) curves (AUC) and 95% confidence intervals (CI) were calculated with logistic regression analysis for each iron parameter and the combination of iron indicators. The AUC is a summary measure of ROC analysis, which means that a higher AUC indicates a better predictive model. Analyses were adjusted for age, sex, smoking, alcohol, hypertension, BMI, TC, TG and 8-iso-PGF2α. Putative confounders were adjusted by the backward selection stepwise multiple logistic regression models taking 0.05 as the significant level. The AUC was also compared with each other using a method suggested by Cleves.

All statistical analyses were performed with Stata version 12 (Stata Corporation, College Station, Texas, USA). All reported probabilities (P-values) were two-sided, with P < 0.05 considered statistically significant.

**Results**

**Subject demographic and clinical characteristics**

Baseline characteristics of the case–control study are listed in Table 1. Specifically, cases were of older age (P < 0.05) and had a higher proportion of smokers (P < 0.05) and hypertension prevalence (P < 0.05). The mean level of the iron parameters were significantly different (P < 0.05) between cases and controls except for SF.

**The AUC of the iron indicators**

In the univariate analysis, the AUC (95% CI) were 0.73 (0.69–0.77), 0.74 (0.69–0.78), 0.53 (0.48–0.58) and 0.61
The AUC of the combinations of iron indicators

In the univariate analysis, the AUC (95% CI) were 0.86 (0.83–0.90), 0.73 (0.68–0.77), 0.77 (0.73–0.81), 0.62 (0.57–0.66), 0.75 (0.71–0.79) and 0.75 (0.71–0.79) for SI + TIBC, SI + SF, SI + sTfR, SF + sTfR, TIBC + SF and TIBC + sTfR respectively (Table 3). After adjusting for age, sex, smoking, alcohol, hypertension, BMI, TC, TG and 8-iso-PGF2α, the AUC (95% CI) were 0.89 (0.86–0.92), 0.90 (0.87–0.93), 0.88 (0.85–0.91) and 0.88 (0.86–0.91) for SI, TIBC, SF and sTfR respectively (Table 2).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Univariate model AUC (95% CI)</th>
<th>P</th>
<th>Multivariate-adjusted† P AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI + TIBC</td>
<td>0.86 (0.83–0.90)</td>
<td>0.001</td>
<td>0.92 (0.90–0.95)</td>
</tr>
<tr>
<td>SI</td>
<td>0.73 (0.68–0.77)</td>
<td>&lt;0.001</td>
<td>0.89 (0.86–0.92)</td>
</tr>
<tr>
<td>TIBC</td>
<td>0.74 (0.69–0.78)</td>
<td>&lt;0.001</td>
<td>0.90 (0.87–0.93)</td>
</tr>
<tr>
<td>SF</td>
<td>0.53 (0.48–0.58)</td>
<td>&lt;0.001</td>
<td>0.88 (0.85–0.91)</td>
</tr>
<tr>
<td>sTfR</td>
<td>0.61 (0.56–0.66)</td>
<td>&lt;0.001</td>
<td>0.88 (0.86–0.91)</td>
</tr>
</tbody>
</table>

P, the P-value for statistical significance of the difference between the combination of SI + TIBC and each of other iron parameters. †Adjusted for sex, age, smoking, alcohol, hypertension, BMI (body mass index), TC (total cholesterol), TG (triglycerides) and 8-iso-PGF2α (8-iso-prostaglandin F2α). AUC, areas under the receiver operating characteristic curves; CI, confidence interval; SF, serum ferritin; SI, serum iron; sTfR, serum transferrin receptor; TIBC, total iron-binding capacity.

PGF2α, the AUC (95% CI) were 0.92 (0.90–0.95), 0.88 (0.86–0.92), 0.90 (0.87–0.92), 0.88 (0.85–0.91), 0.90 (0.88–0.93) and 0.90 (0.88–0.93) for those combined iron indicators mentioned above respectively (Table 3; Fig. 1).

Comparison of the AUC of iron parameters or combination of iron indicators

The statistical comparison of the AUC indicated that the combination of SI and TIBC showed the strongest association with CAD risk among other iron parameters or the other combinations of iron indicators (P < 0.05) both in univariate and multivariate models (Tables 2, 3). Thus, based on the above results, the combination of SI and TIBC was suggested to be the strongest iron indicator correlated to CAD risk.
Discussion

This case–control study with SI, TIBC, SF, stTfR and combinations of iron indicators as surrogates for body iron status was conducted to seek to identify a powerful iron indicator with the highest risk of CAD. Results suggested that the combination of SI and TIBC, with the biggest AUC both in univariate and multivariate models, has the best effect on CAD risk.

A solid body of basic and clinical evidence supported an important role of iron in promoting atherosclerosis and vascular accidents. In the process of atherosclerosis, iron could catalyse the formation of free radicals and thus enhance peroxidation of lipoproteins. Besides, biochemical markers of body iron stores can be used as an early investigative tool for assessing the oxidative stress in coronary heart disease. Plenty of evidence indicated that excess free iron was an important factor in promoting the generation of potentially tissue-damaging free radicals, particularly hydroxyl ions. Moreover, studies have also demonstrated that iron may act as a nitric oxide scavenger and thus induce endothelial cell dysfunction. A recent systematic review and meta-analysis of iron and cancer risk also assessed the association of total iron, dietary iron, haem iron and biomarkers of iron status and cancer risk, and it suggested a positive association between haem iron intake and cancer risk.

The most accurate and reliable measure of body iron stores was a histological evaluation of iron deposits in a bone marrow biopsy specimen. However, this measure is not feasible for use in large-scale epidemiological studies; thus, other less invasive measures of iron stores should be generally practicable. To date, studies conducted in this field often used different and sometimes inappropriate estimations of body iron stores, which make them difficult to detect the true association between body iron and CAD risk. Therefore, exploring the appropriate body iron markers associated strongly with CAD risk is of particular importance and necessity. Among the body iron parameters, TIBC was suggested to be a reliable predictor of accumulation of free iron in the vessel wall; TIBC, as an indicator of organic iron, was linked positively to the incidence of atherosclerosis in several studies. On the other hand, SF, an acute-phase protein that was prone to be increased by myocardial damage and inflammation, was of limited value related to CAD risk. Our result (AUC: 0.53 (0.48–0.58)) also demonstrated this issue, which is similar to the study (AUC: 0.68 (0.57–0.78)) conducted by Dominguez-Rodriguez et al.36 Besides, stTfR was mostly used as a marker of body iron stores to assess its effect on anaemia; few researches have studied the relation between stTfR and CAD risk.

ROC analysis plays a fundamental role in clinical practice. Recently, the methodology has been adapted to some clinical areas, such as laboratory testing, epidemiology and radiology. Furthermore, the AUC, a recommended index of the accuracy of ROC analysis, is a summary measure of ROC analysis. AUC equals to 0.5 when the ROC curve corresponds to random chance and 1.0 for perfect accuracy. Thus, the bigger its value, the stronger the association with the disease risk. In our study, the AUC (95% CI) of the combination of SI and TIBC was 0.86 (0.83–0.90) in univariate model, which was significantly higher than that of other iron parameters or combination of iron indicators (P < 0.05).

The limitations in this study should be considered. This was only a hospital-based case–control study, and selected bias might exist and could distort the association. Moreover, the iron indicators measured in this study only represented the status of body iron store at the time of disease diagnosis, so a causal link between body iron store and CAD risk could not be confirmed directly.

Conclusion

Despite these limitations, our results suggested that the combination of SI and TIBC has a stronger correlation than other evaluated iron parameters between body iron store and CAD risk. Further prospective studies are needed to validate these preliminary findings.

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Effect of a patient-directed discharge letter on patient understanding of their hospitalisation

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Key words
discharge letter, understanding, hospitalisation.

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Abstract

Background/Aim: Poor patient understanding of their diagnosis and treatment plan can adversely impact clinical outcome following hospital discharge. Discharge summaries are primarily written for the doctor rather than the patient. We determined patient understanding of the reasons for hospitalisation, in-hospital tests, treatments and post-discharge recommendations, and whether a brief patient-directed discharge letter (PADDLE) delivered during a brief discussion prior to discharge would improve understanding.

Methods: A prospective randomised controlled trial was conducted, including 67 hospitalised patients. After a baseline questionnaire, patients were randomised to receive the PADDLE letter or usual care. Those receiving the letter had an immediate follow-up questionnaire. Patient understanding was compared with a summary letter written by the treating clinician, using a 5-point Likert scale ranging from none to full understanding. A questionnaire was administered at 3 and 6 months.

Results: At baseline, patients had almost full understanding (median score 4) of reasons for hospitalisation and treatments. However, despite high self-appraisal, patients objectively had very little understanding of tests performed and post-discharge recommendations (median 2). Those receiving the letter had an immediate increase to almost full understanding (median 4) of tests performed ($P < 0.001$) and to full understanding (median 5) of post-discharge recommendations. This increase did not persist at 3 or 6 months.

Conclusions: A simple patient-directed letter delivered during a brief discussion improves patient understanding of their hospitalisation and post-discharge recommendations, which is otherwise limited. Further evaluation of this brief and well-received intervention is indicated, with the goal of improving patient understanding, satisfaction and clinical outcomes.

Introduction

The transition of hospitalised patients into the community is an important phase where lack of understanding of the hospitalisation and the post-discharge plans could adversely affect patient outcome. Currently, the discharge letter, while provided to the patient, is addressed primarily to the community physician and is often unhelpful to the patient because of the medical terminology and focus of the content not matching the patient’s level of knowledge or health literacy.

Poor understanding of diagnoses treated during hospitalisation and related discharge plans is common among patients. To some extent, this is because information for continuity of care is often missing at the time of discharge. A lack of patient and family education is associated with unplanned hospital readmissions. Bobay et al. also noted that patients with a low score on a ‘readiness for discharge’ scale were more likely to have emergency department visits and readmissions than those with a better score. There is also evidence that effective patient education improves outcomes and that patients themselves desire information that can be read and retrieved later when required. There is, however, a lack of consensus as to the optimal way to ensure patient education needs are met, and to deliver education balancing time efficiency and cost. Challenges in providing a single discharge summary for both patients and their physicians include difficulties in writing letters that

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are useful and comprehensible for patients while sufficiently informative to colleagues. Sandler et al. previously reported that a comprehensive patient discharge booklet improved patient knowledge of their admission and medications, that patients often showed it to family members, and that the patients and their family doctors had a positive response to the booklet. However, no information was provided on the method of delivery or communication used.

The purpose of our study was to determine whether a brief patient-directed discharge letter (PADDLE), delivered during a brief discussion with the treating physician would improve patient understanding at the time of hospital discharge and would be feasible for busy clinicians to administer.

Methods

Participants and selection criteria

Participants were recruited from the cardiology, respiratory and endocrinology wards at a tertiary referral centre, Royal North Shore Hospital in Sydney, Australia. Inclusion criteria were that the participants were medical patients (non-surgical), sufficiently proficient in English that they could read and communicate without interpretation, were independent in their self-care, were to be discharged home and not to other facilities, and had a life expectancy greater than 6 months.

Study design

The following study design was reviewed and approved by the ethics committee prior to commencement of the study. After the participants provided informed consent, they completed a baseline questionnaire on the day of discharge in which they were asked to describe in their own words their understanding of four domains of their admission: (i) the reason for hospitalisation, (ii) the tests performed and their results, (iii) any treatments received and (iv) recommendations for the patient following discharge. The baseline questionnaire also included questions related to their perceived level of understanding and their usual level of concordance with routine medications before this admission. Prior to randomisation, a clinician on the medical team prepared a PADDLE letter (Fig. 1) which summarised their hospitalisation using the four domains. Clinicians were instructed to minimise...
medical jargon as much as possible and to write the letter at a level of comprehensibility appropriate to the participants’ background. No formal training was required for the delivery or completion of the letter; the only pre-requisite was that it was completed by a doctor on the patient’s treating medical team. This allowed observations as to how the letter and delivery would perform if used by various medical teams across the whole hospital.

Participants randomised to control did not receive the letter and were discharged with no change to routine practice. For the intervention group, following completion of the baseline questionnaire, the clinician read the letter to the participant at the bedside, explained its contents and provided the opportunity to ask questions. Writing the letter took 5–10 min, as did the discussion, depending on the complexity of the admission and post-discharge care plan. The post-letter level of understanding was then immediately assessed with a repeat questionnaire. Investigators were blinded to the randomisation except the investigator carrying out the initial questionnaires at the bedside. All participants received the standard discharge letter to give to their family physician.

A research nurse blinded to randomisation administered a 3- and 6-month telephone questionnaire assessing participant recall of their hospitalisation using the four domains. Participants were asked whether they had followed the recommendations given at time of discharge and whether they had any readmissions. The primary outcomes were the immediate effect of the letter on understanding in the intervention group, and the comparison between intervention and control understanding at 3 months. Secondary outcomes included the participants’ subjective assessment of their understanding and satisfaction with hospitalisation, and readmission rate at 3 and 6 months based on whether the readmission was potentially preventable.

Scoring systems

Three scoring systems were used to assess the four individual domains of understanding. First, a ‘point score’ expressed as percentage was assigned based on how many key points in the PADDLE letter were mentioned by the participants. Second, a blinded senior physician assigned a score based on comparing participant responses with the corresponding section in the PADDLE letter using a 1–5 Likert scale (referred to as a scaled score). The scale was the same as the participant self-rating, ranging from 1: no understanding; 2: very little understanding; 3: somewhat understands; 4: almost full understanding; to 5: full understanding. Third, a global score was calculated as the sum of the scaled scores for the four domains (maximum score 20). This score represented a measure of overall understanding of the admission.

Data analysis

Data were analysed using SPSS version 20. Comparisons between groups were conducted using chi-squared for categorical data, Mann–Whitney test for ordinal data and t-test for continuous data and according to the distribution of the data. Comparisons across time in patients’ understanding and knowledge were determined using Wilcoxon signed rank tests and repeated measures analysis of variance for total global knowledge scores. We evaluated age, gender, maximum level of education and complexity of the letter for those that received the PADDLE letter, since these factors may affect the recall of information.

Results

Sixty-seven patients were recruited from cardiology, endocrinology and respiratory wards. The two groups were well matched in baseline characteristics (Table 1). The control group was aged 63.4 ± 17.8 years with 63% males, and the intervention group was aged 62.1 ± 17.6 years with 56% males. The majority had completed at least high school education.

Baseline scores

At baseline, there were no significant differences in the level of understanding between the control or intervention groups using the points score or the scale score. There were also no differences between participants’ self-rated levels of understanding, satisfaction or medication compliance (Table 2).

The median scale score of patient understanding for both groups regarding the reasons for hospitalisation and the treatments received was 4, representing almost full understanding. However, the median for knowledge of tests performed and post-discharge recommendations was 2, representing very little understanding. The median global knowledge score was 3. This subjective assessment contrasted with the median of the participants’ self-assessment of their understanding as having full (5) or almost full understanding (4).

Immediate impact of the PADDLE letter

After receiving the PADDLE letter, the intervention participants increased their scores for all four domains, with understanding of tests performed increasing to almost full...
understanding (median 4, \(P < 0.001\)) and post-discharge recommendations to full understanding (median 5, \(P < 0.001\)) (Table 3). The greatest improvement occurred for recommendations for post discharge (23–80%, \(P < 0.001\)). There was no change in participants’ self-ratings of their satisfaction or level of knowledge, which remained high. Most who received the patient discharge letter rated the letter as ‘very helpful’ (69%) or ‘helpful’ (25%) and no patient rated the letter as ‘unhelpful’. Written feedback included comments, such as ‘Basic language, easy to understand’, ‘Good reflection on why and what I’ve got’ and ‘no big graphs and numbers’.

Although not formally evaluated, the practicality of completing the letter and communicating with the participant were monitored through regular feedback from the doctors who performed this task. As the intervention was usually timed close to the regular discharge schedule, the extra time that the doctors required did not extend significantly beyond the 5–10-min periods required to complete the letter and then speak with the patient. The clinicians considered that completing and administering the PADDLE letter was feasible and acceptable within their daily work load.

Three- and 6-month understanding

At the 3-and-6-month telephone interview, there were no significant differences between the control and intervention groups in the four knowledge domains or for global knowledge (data not shown).

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>Age, mean years (SD)</td>
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<tr>
<td>Male, (n) (%)</td>
</tr>
<tr>
<td>Education ≥ high school (year 12) ((n = 46))</td>
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<tr>
<td>Department</td>
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<tr>
<td>Cardiology</td>
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<tr>
<td>Respiratory</td>
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<tr>
<td>Endocrinology</td>
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<tr>
<td>≥3 comorbidities, (n) (%)</td>
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<tr>
<td>Moderate/high cognitive load letters (%)</td>
</tr>
</tbody>
</table>

SD, standard deviation.

<table>
<thead>
<tr>
<th>Table 2 Baseline comparison of knowledge scores and self-rated scales</th>
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<tr>
<td>Domain</td>
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<tr>
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<tr>
<td>Reasons for Hospitalisation</td>
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<tr>
<td>Points score (%)</td>
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<tr>
<td>Scale score</td>
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<tr>
<td>Tests in Hospital</td>
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<td>Points score (%)</td>
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<tr>
<td>Scale score</td>
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<tr>
<td>Treatments in Hospital</td>
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<td>Points score (%)</td>
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<tr>
<td>Scale score</td>
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<tr>
<td>Recommendations on Discharge</td>
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<tr>
<td>Points score (%)</td>
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<tr>
<td>Scale score</td>
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<tr>
<td>Patient scales, median (range)</td>
</tr>
<tr>
<td>Understanding</td>
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<td>Satisfaction</td>
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<tr>
<td>Medication compliance</td>
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<td>Global knowledge, mean (SD)</td>
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</table>


Readmission rates

The study was not powered to assess differences in readmission rates; however, 21 participants (36%) experienced a readmission within 6 months, with 12 (20%) occurring in the first 3 months. Readmissions were equally distributed between control (20%) and intervention (21%), and did not differ whether they were deemed potentially preventable.

Associations with level of understanding

Baseline understanding correlated with understanding at 3 months (0.47, \(P < .001\)) and 6 months (0.26, \(P = 0.049\)). Age was negatively correlated with understanding at baseline (−0.26, \(P = 0.035\)), 3 months (−0.35, \(P = 0.008\)) and 6 months (−0.54, \(P < 0.001\)). Gender, level of education or cognitive load did not influence the level of understanding. However, at 6 months, the scaled scores were greater in those with <3 than ≥3 comorbidities (12.3 ± 2.8 vs 9.5 ± 2.6, \(P < .001\)). Those who were readmitted within 6 months had worse understanding than those without a readmission (10.0 ± 2.8 vs 11.6 ± 3.1, \(P = .047\)). Independent predictors of global knowledge score at 3 months were age (beta = −0.06, 95% CI −1.06−0.24) and a readmission (beta = −2.43, 95% CI −4.37−−0.49), and at 6 months was age alone (beta = −.09, 95% CI −0.14−0.05).

Discussion

Our study demonstrates that a brief patient-directed discharge letter (PADDLE) discussed with the patient on the day of discharge improved immediate understanding of their hospitalisation and discharge recommendations. The letter and discussion were well received by the participants. Our data also confirmed that patients frequently have poor understanding of the events that occurred during their hospitalisation as well as their post-discharge recommendations, and that they overestimated their level of understanding. The immediate improvement in participants’ understanding was not sustained at 3 and 6 months.

The improvement in immediate understanding following delivery and discussion of the PADDLE letter may be attributed to several observations. Ley et al. have shown that breaking down medical information into useful categories, increased patient recall by 25–50%. Simplifying written communication has also been shown to improve patient comprehension. Also important is the verbal communication of the letter contents and the opportunity for discussion. Through completing and explaining each individual section of the letter, the doctor is prompted to address each area and the patient is afforded the opportunity to ask questions.

A single-page letter format was chosen for this study as it could be easily and inexpensively reproduced. It was also favoured over a multiple-page booklet in keeping with simplifying information for the patient and minimising the time required to complete the letter by a busy clinician.

No formal patient input was sought in designing the PADDLE letter, although feedback was positive, reflected by the ratings of as ‘helpful’ or ‘very helpful’ with praise of the basic language that was easy to understand.

---

**Table 3** Baseline versus immediate post-PADDLE level of understanding (\(n = 32\))

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline</th>
<th>Immediate</th>
<th>(P)-level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range/SD</td>
<td>Median</td>
</tr>
<tr>
<td>Reasons for hospitalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Points score (%)</td>
<td>71</td>
<td>25–100</td>
<td>100</td>
</tr>
<tr>
<td>Scale score</td>
<td>4</td>
<td>2–5</td>
<td>5</td>
</tr>
<tr>
<td>Tests in hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Points score (%)</td>
<td>50</td>
<td>0–100</td>
<td>88</td>
</tr>
<tr>
<td>Scale score</td>
<td>2</td>
<td>1–5</td>
<td>4</td>
</tr>
<tr>
<td>Treatments in hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Points score (%)</td>
<td>50</td>
<td>0–100</td>
<td>100</td>
</tr>
<tr>
<td>Scale score</td>
<td>4</td>
<td>1–5</td>
<td>5</td>
</tr>
<tr>
<td>Recommendations at discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Points score (%)</td>
<td>27</td>
<td>0–100</td>
<td>80</td>
</tr>
<tr>
<td>Scale score</td>
<td>2</td>
<td>1–5</td>
<td>5</td>
</tr>
<tr>
<td>Patient scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Understanding</td>
<td>4</td>
<td>3–5</td>
<td>5</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>5</td>
<td>2–5</td>
<td>5</td>
</tr>
<tr>
<td>Total knowledge score</td>
<td>11.7</td>
<td>2.6</td>
<td>15.5</td>
</tr>
</tbody>
</table>

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Evaluating the components of the discharge letter and discussion that patients most valued would be useful since our study and others indicated a higher patient self-rating of their level of understanding than objective measures, suggesting patients may not appreciate important information regarding their hospitalisation and post-discharge planning.

The failure to see an impact of the letter and discussion at longer-term follow up may be due to several reasons. First, 3 and 6 months after discharge is a long time to retain information that may not have been needed to be recalled or were no longer relevant. Kessels noted that 40–80% of medical information provided by medical practitioners is forgotten immediately, and recollection is often poor and inaccurate, especially if the patient is older or anxious. This short-term retention may be exacerbated if the hospitalisation was brief and the information only relevant for a short period. For example, a discharge recommendation for 7 days of antibiotics may be forgotten once it has been completed. Second, readmissions and outpatient testing during follow up may have resulted in additional and potentially conflicting information being provided to the patients and affected responses at follow up. Indeed a readmission was associated in our study with a lower 6-month level of understanding.

Although our study was not powered to evaluate readmission rates, other studies suggest that interventions that reinforce patient recall of their hospitalisation, especially post-discharge instructions, reduce readmissions. Our study also did not demonstrate a difference in self-rated concordance with medication, instructions or medical knowledge; however, most participants rated themselves highly despite evidence suggesting otherwise.

The letter and brief discussion were well received by the patients. Patient satisfaction plays a role in optimising patient adherence with recommendations and treatment. Patient satisfaction with the hospitalisation tends to reduce with time after discharge.

Future versions of the letter may include less detail on tests and results, and more focus on the post-discharge recommendations as this area will most strongly influence readmission rate. Inclusion of allied health input is increasingly relevant in the context of an ageing population.

**Limitations**

The project was carried out over a limited time period so the final sample size was determined by the eligible patients who agreed to participate in that time. Another limitation is the difficulty in separating factual recall from true understanding. As the initial post-PADDLE interview occurred on the day of discharge, we cannot exclude the possibility that the increase in knowledge was of short duration. Follow up at 1–4 weeks could have provided a greater insight into retention of knowledge that was also relevant to early post-discharge care. Many follow up appointments occur within 4 weeks, which is also when a large proportion of readmissions occur related to the initial admission. The questionnaires and scoring methods were devised for this study and require further evaluation. Data on feasibility were only obtained informally. Finally, the generalisability of our results is limited by the study being conducted at a single site.

**Conclusion**

Our study showed that patients’ understanding of their in-hospital tests and post-discharge recommendations is limited and can be improved by a simple PADDLE delivered during a brief discussion. With hospitalisation trends towards reduced length of stay, older age of patients and greater complexity of admissions, interventions that improve understanding for the patient and their families become increasingly important. Brief interventions, such as our PADDLE intervention, deserve further evaluation and consideration for integrating into routine discharge practice.

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Patient-directed discharge letter

Outcomes of behavioral treatment for idiopathic chronic constipation

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Key words
constipation, behavioral therapy, biofeedback therapy.

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Abstract
Background/Aim: Behavioral therapy is effective in patients with chronic intractable constipation despite standard treatment, but long-term results in unselected patients are unclear. This study investigates the effects of behavioral therapy on symptoms, subjective well-being, and the physical and mental quality of life.

Methods: Patients who had failed standard care for idiopathic chronic constipation underwent behavioral therapy in a specialist clinic. Symptom severity and quality of life were assessed before and after therapy using the ‘Constipation Scoring System’ and the Short-Form 36 questionnaire. The primary outcome was subjective perception of improvement. Secondary outcomes were symptoms of constipation and quality of life scores.

Results: Of 233 consecutive patients with self-reported constipation (median symptom duration 5–10 years, median age 44 years, females 86%), 180 (77%) completed treatment in a median of three (range 1–7) sessions. One hundred and sixty-five patients (71% of all referrals or 92% of those completing treatment) reported subjective improvement. Median bowel frequency improved from once every 2–7 days to 1–3 per day (P=0.05). Pain and bloating improved in more than 80% of patients. The Short-Form 36 physical (P<0.05) and mental (P<0.05) composite scores improved significantly. Patients with a longer duration of symptoms were less likely to complete treatment. Digital evacuation prior to treatment was a predictor of poor outcome.

Conclusion: Behavioral therapy is associated with significant improvement in symptoms of chronic constipation and quality of life. Non-drug therapies that successfully treat patients with functional gut disorders resistant to standard treatment are needed in the mainstream provision of care.

Introduction

Chronic constipation is a common condition in the community, in general practice and in specialist gastroenterological practice. Its prevalence in the community has been measured at 6–30% of adults, in both the West and the East.1,2 Constipation varies in its presentations, with a range of gut and non-specific subjective symptoms.3,4

The aetiology of constipation is complex and multifactorial. Consequently, patients vary in their symptomatology and response to treatment. Risk factors in adults include female gender, low socioeconomic status, and a history of abuse or depression.3 A disturbance of defecatory and colonic function contributes to the symptoms and physiological abnormalities observed in patients with constipation.3

Behavioural therapy, also known as ‘biofeedback’ therapy because it frequently included real-time physiological feedback on pelvic floor function to the patient, trains patients to focus on, and improve, bowel function. It was first shown to be effective in the treatment of constipation in 1987.5–9 Since then, several randomised controlled trials10–12 and systematic reviews12,13 on behavioural therapy have established its superiority over standard laxative therapy for idiopathic constipation,10,12,14,15 with benefit in up to 78% of patients in one meta-analysis.12 In order to prioritise patient selection, studies have also explored potential predictors of success of
behavioural therapy, but results of this approach have been inconsistent.16–18

The current study is a large prospective analysis of the results of behavioural therapy for idiopathic constipation. The study was conducted in a multidisciplinary clinic in patients who had exhausted other standard drug treatment options for constipation. Outcomes were assessed across patients’ biopsychosocial domains as well as the overall improvement in quality of life.

**Methods**

**Patients**

Consecutive patients with chronic constipation referred to a specialist gastroenterology clinic were included in the study. Patients defined themselves as ‘constipated’, a term that encompasses a range of gut and non-gut symptoms.4,19 Patients were referred by general practitioners or gastroenterologists for behavioural treatment, specifically because they had failed standard care.

A detailed medical history on initial consultation identified possible contributing factors to patients’ symptoms, including previous abuse, mental illness, depression, anxiety and eating disorder.20

Whole gut transit time was assessed prior to treatment at the referring doctor’s discretion using a standardised radio-opaque marker technique and a single plain abdominal radiograph.21

Prior to, and immediately after the completion of treatment, patients were assessed using (i) the ‘Constipation Scoring System’ questionnaire,22 which evaluates eight domains of constipation symptomatology including frequency of bowel movements, pain on evacuation, incomplete evacuation, abdominal pain, length of time per attempt at defecation digital or laxative assistance for defecation, unsuccessful attempts at evacuation, and duration of constipation; and (ii) the Short-Form 36 (SF-36) quality of life questionnaire.23

Anorectal function was assessed by the therapist, to include (i) pelvic floor and anal sphincter resting tone, (ii) ability to relax the anal sphincter and pelvic floor muscles, (iii) rectal sensation, and (iv) ability to expel a rectal balloon during simulated defecation.

Simulated defecation was performed with a balloon placed in the rectum while the patient was in the left lateral position. The patient was asked to try and pass the balloon while the catheter tube attached to the balloon was held by the therapist to sense balloon movement. The therapist also palpated the abdominal muscles and observed the straining strategies used by the patient.

If the patient was unable to expel the balloon, gentle traction was supplied to assist. The patient gradually learned how to coordinate an effective defecation pattern, expelling the balloon with minimal effort and without therapist assistance.

Several key elements were assessed and recorded during initial simulated defecation (Table 1). These were the ability to (i) relax puborectalis and maintain relaxation during attempted balloon expulsion, (ii) provide an effective abdominal expulsive effort that could propel the balloon within the rectum, (iii) perform diaphragmatic breathing, and (iv) perceive rectal distension (first sensation threshold 30 mL, desire to defecate sensation threshold 120 mL).

**Table 1  Therapist assessment of simulated defecatory function**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to relax puborectalis</td>
<td>57</td>
</tr>
<tr>
<td>Paradoxical puborectalis contraction on straining</td>
<td>27</td>
</tr>
<tr>
<td>Poor expulsion</td>
<td>71</td>
</tr>
<tr>
<td>Respiratory pattern (‘apical’)</td>
<td>82</td>
</tr>
<tr>
<td>Rectal sensation (decreased)</td>
<td>32</td>
</tr>
</tbody>
</table>

**Therapy protocol**

Treatment was conducted in a specialist multidisciplinary clinic that includes the collaboration of gastroenterologists, a behavioural therapist/physiotherapist, a gut-focused psychologist and a psychiatrist.

The primary goal of behavioural therapy was to establish regular and effective defecation without the use of laxatives or digitation. The methods for achieving this are outlined below.

First, patients were educated about gut anatomy and function. This included discussion about the interaction between the brain and gut. This process continued throughout treatment to assist the patient in understanding the potential importance of past and current physical, psychological and social factors that affect bowel function.

Second, lifestyle modification was implemented in the areas of toileting and eating habits, dietary and fluid intake, stress management, and general exercise. If a patient revealed significant psychosocial factors during a session, or psychological disturbance became more evident, referral for psychological intervention within the therapeutic team was made.

Third, bowel habit training was implemented. This involved a routine of sitting on the toilet when defecation is more likely to occur, and preventing prolonged or repeated straining attempts. It aimed to increase awareness of rectal sensation. Supporting patients to cease anal
digitation and cease laxatives on commencement of training was regarded as essential. Suppositories were used initially, if required, to assist evacuation while patients were learning their new skills, although these were also later withdrawn.

Fourth, patients underwent defecation training. Teaching the patient how to achieve an effective defecation technique was performed using various forms of feedback – verbal, digital and rectal balloon expulsion to coordinate the diaphragm, abdominal, pelvic floor and sphincter muscles. This included pelvic floor and abdominal muscle relaxation training and diaphragmatic breathing exercises to improve muscle function. Repeated rectal balloon inflations were sometimes used to train perception of rectal sensation.

Last, patients were given a home training programme. Each patient was provided with an individualised home training programme requiring daily adherence. Clinical sessions were generally 4 weeks apart, and patients were able to telephone for assistance between appointments.

Follow up

The primary outcome measure was the patient’s subjective view as to whether he/she had benefited from treatment. Patients were asked to rate the outcome of treatment as ‘worse’, ‘no improvement’, ‘mildly improved’ or ‘fully improved’.

Secondary outcome measures included bowel frequency, the need to evacuate digitally, a sense of incomplete evacuation, abdominal pain and bloating, and the use of laxatives.

Clinical variables at baseline were correlated with the treatment outcome.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA). The Mann–Whitney U-test was used for continuous variables, and Chi-squared test was used for categorical variables. Regression analysis was not appropriate due to the small sample size in patients who did not improve with behavioural therapy.

Results

Of 233 patients (median age 44 (range 15–81) years, 86% females) referred for treatment, 180 completed a course of treatment (Fig. 1). Each patient received between one and seven (median 3) sessions of behavioural therapy, every 4 weeks.

Fifty-three patients failed to complete therapy, after a median of one session. Reasons for dropout were cost, loss or lack of motivation, patient dissatisfaction with the speed of response, opting for surgical treatment, and other circumstances such as moving interstate. These patients were also included in analysis to investigate potential contributing factors to failure to complete therapy.

Patient demographics, clinical features and toileting behaviour at baseline

Patients had experienced constipation for a median of 5–10 years (range 1 to more than 20 years), with 40% of patients reporting more than 20 years of symptoms. Two hundred and twenty patients perceived their symptoms as moderate to severe (Table 2).

At baseline, patients had a median bowel frequency of once per 2–7 days and a median stool form score of 2 (firm). A sense of incomplete evacuation was reported in 96% of patients, bloating in 90%, abdominal pain in 67% and digital evacuation in 40%. Laxatives were taken by 73% of patients at the start of treatment.

There was a history of previous or current formal diagnosis and treatment of mental illness in 171 patients: 102 depression, 51 anxiety and 18 eating disorders. Fifty-one
patients (22%) had been treated by a psychiatrist and 26 (11%) had been treated by a psychologist. Twenty-seven patients disclosed a past history of sexual abuse on direct questioning.

A radio-opaque marker transit study was performed in 110 patients. Thirty-one per cent of these demonstrated slow bowel transit.

**Relationship between clinical features and primary outcome measures**

Of the 180 patients who completed behavioural therapy, 24 patients reported mild and 141 full improvement. No patient reported symptom worsening, and 15 reported no change.

Patients with a longer duration of symptoms (median 11–20 years) were significantly less likely to complete therapy, compared with those with a short duration of symptoms (5–10 years) (Table 3).

Age, gender, pretreatment self-rated symptom severity, constipation score, laxative use at the commencement of treatment and individual symptoms of constipation were not associated with treatment outcome (Table 4).

Patients with laxative-related faecal incontinence and the need to digitate were significantly less likely to report full improvement than those without these symptoms (Table 5).

**Secondary outcome measures**

Improvement was noted across all symptom domains listed in the questionnaire by up to 70% of patients. Median bowel frequency after treatment was one to three bowel actions daily.

Symptom improvement correlated with improvement in quality of life, with improved physical and mental composite SF-36 scores. The median physical and mental composite scores improved from 55 and 58 to 75 and 72 respectively.

### Table 2 Bowel function and toileting behaviour

<table>
<thead>
<tr>
<th>Toileting behaviour (n = 233)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitation</td>
<td>34</td>
</tr>
<tr>
<td>Incomplete emptying</td>
<td>96</td>
</tr>
<tr>
<td>Bloating</td>
<td>90</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>84</td>
</tr>
<tr>
<td>Faecal incontinence</td>
<td>23</td>
</tr>
<tr>
<td>Bowel frequency</td>
<td></td>
</tr>
<tr>
<td>&lt;1/week</td>
<td>4</td>
</tr>
<tr>
<td>&lt;3/week</td>
<td>37</td>
</tr>
<tr>
<td>&lt;1/day</td>
<td>26</td>
</tr>
<tr>
<td>1–3/day</td>
<td>17</td>
</tr>
<tr>
<td>&gt;3/day</td>
<td>15</td>
</tr>
</tbody>
</table>

### Table 3 Comparison of patients who did and did not complete treatment (n = 233)

<table>
<thead>
<tr>
<th>Dropout (n = 53)</th>
<th>Completed treatment (n = 180)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median [IQR]</td>
<td>46 [33]</td>
<td>44 [28]</td>
</tr>
<tr>
<td>Total SF-36, median [IQR]</td>
<td>50 [37]</td>
<td>63 [38]</td>
</tr>
<tr>
<td>Female (%)</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>History of abuse (%)</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Diagnosis/treatment of mental illness (%)</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>History of eating disorder (%)</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Pain (%)</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td>Laxatives (%)</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Digitation (%)</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>Incomplete emptying (%)</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>Bloating (%)</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>Faecal incontinence (%)</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>No. sessions, median [IQR]</td>
<td>1 [0.5]</td>
<td>3 [2]</td>
</tr>
<tr>
<td>Slow transit time (%)</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Severity, median [IQR]†</td>
<td>3 [1]</td>
<td>3 [1]</td>
</tr>
<tr>
<td>Duration of symptoms, median [IQR]‡</td>
<td>3 [1]</td>
<td>2 [3]</td>
</tr>
<tr>
<td>Bowel frequency, median [IQR]§</td>
<td>2 [2]</td>
<td>2 [2]</td>
</tr>
</tbody>
</table>

†Severity: 1 = mild; 2 = moderate; 3 = severe. ‡Duration of symptoms: 1 = 1–5 years; 2 = 5–10 years; 3 = 11–20 years; 4 = >20 years. §Bowel frequency: 0 = <1/week; 1 = <3/week; 2 = <1/day; 3 = 1–3/day; 4 = >3/day. IQR, interquartile range; SF-36, Short-Form 36.

### Table 4 Comparison between patients who completed treatment (n = 180)

<table>
<thead>
<tr>
<th>Not improved (n = 15)</th>
<th>Improved (n = 165)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median [IQR]</td>
<td>50 [35]</td>
<td>41 [29]</td>
</tr>
<tr>
<td>Female (%)</td>
<td>73</td>
<td>86</td>
</tr>
<tr>
<td>History of abuse (%)</td>
<td>13.3</td>
<td>14.5</td>
</tr>
<tr>
<td>Diagnosis/treatment of mental illness (%)</td>
<td>60</td>
<td>56.4</td>
</tr>
<tr>
<td>History of eating disorder (%)</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Pain (%)</td>
<td>93</td>
<td>81</td>
</tr>
<tr>
<td>Laxatives (%)</td>
<td>73</td>
<td>59</td>
</tr>
<tr>
<td>Digitation (%)</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>Incomplete emptying (%)</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>Bloating (%)</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>Faecal incontinence with laxatives (%)</td>
<td>47</td>
<td>21</td>
</tr>
<tr>
<td>Slow transit time (%)</td>
<td>53</td>
<td>27</td>
</tr>
<tr>
<td>Severity, median [IQR]†</td>
<td>3 [1]</td>
<td>3 [1]</td>
</tr>
<tr>
<td>Duration of symptoms, median [IQR]‡</td>
<td>4 [2]</td>
<td>2 [3]</td>
</tr>
<tr>
<td>Bowel frequency, median [IQR]§</td>
<td>2 [3]</td>
<td>2 [2]</td>
</tr>
</tbody>
</table>

†Severity: 1 = mild; 2 = moderate; 3 = severe. ‡Duration of symptoms: 1 = 1–5 years; 2 = 5–10 years; 3 = 11–20 years; 4 = >20 years. §Bowel frequency: 0 = <1/week; 1 = <3/week; 2 = <1/day; 3 = 1–3/day; 4 = >3/day. IQR, interquartile range; SF-36, Short-Form 36.
Incomplete emptying and laxative use were still present to some degree in 66% and 42% of patients, respectively, in all patients who completed therapy. This was despite many of these patients reporting overall improvement. Data are shown in Table 6.

### Discussion

This large prospective consecutive cohort study has demonstrated the efficacy of behavioural therapy in treating chronic idiopathic constipation in a real-life clinical setting. The improvement in symptoms and quality of life mirrored those reported in previous randomised controlled trials.7,24,25 Seventy per cent of patients in the current study reported symptomatic improvement, a result at least as good as those reported previously.7,25 In our patient cohort, all symptoms related to constipation were improved by therapy.

The majority of patients who were treated in this multidisciplinary clinic setting reported benefit. This type of care is not widely available; this report establishes the viability of such a service in a specialist setting.

Factors influencing therapy completion and subsequent improvement were assessed. Findings from previous literature have been inconsistent.16,18 Univariate analyses were substituted for logistic regression due to the small number (n < 10) of patients in some groups. In this study, longer duration of symptoms was the only significant predictor of failure to complete therapy.
Patients with longer duration of constipation may be less amenable to behavioural change due to consolidated bowel habits or lack of motivation for therapy. However, some patients with a very long history did benefit from treatment, suggesting that they should not be excluded from receiving treatment.

A history of childhood abuse or an eating disorder has been demonstrated to be poor prognostic predictors. Our data also show that a history of abuse and eating disorder was more common in patients who did not complete the course of treatment, but this was not statistically significant.

This study did not include long-term follow up. However, previous studies from some of our group have demonstrated the long-term durability of therapeutic benefit from this treatment. Anorectal physiological testing in our experience does not add diagnostic, prognostic or therapeutic value to the therapy, and therefore does not form part of our approach. We acknowledge the subjective nature of reported benefit, although this may reflect the most important determinants of success, and standardised questionnaires were used to characterise patients’ condition prospectively. Furthermore, such subjective reports have been shown to correlate with improved measured gut transit, and did correlate with improved measured quality of life in the current study.

This prospective cohort study did not include a comparison group. However, all patients sought treatment due to the failure of standard care. Previous controlled trials have demonstrated superiority over standard care and sham behavioural treatment.

**Conclusion**

Behavioural therapy is an effective and safe treatment that is increasingly utilised as a first-line option for chronic intractable constipation. We have demonstrated its applicability in a multidisciplinary setting in a large group of patients, supporting the provision of such care for patients who have failed standard care.

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Burden of decompensated cirrhosis and ascites on hospital services in a tertiary care facility: time for change?

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Key words
paracentesis, chronic liver disease, spontaneous bacterial peritonitis, hospital readmission, models of care, healthcare cost.

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Abstract

Background: Ascites, the most frequent complication of cirrhosis, is associated with poor prognosis and reduced quality of life. Recurrent hospital admissions are common and often unplanned, resulting in increased use of hospital services.

Aims: To examine use of hospital services by patients with cirrhosis and ascites requiring paracentesis, and to investigate factors associated with early unplanned readmission.

Methods: A retrospective review of the medical chart and clinical databases was performed for patients who underwent paracentesis between October 2011 and October 2012. Clinical parameters at index admission were compared between patients with and without early unplanned hospital readmissions.

Results: The 41 patients requiring paracentesis had 127 hospital admissions, 1164 occupied bed days and 733 medical imaging services. Most admissions (80.3%) were for management of ascites, of which 41.2% were unplanned. Of those eligible, 69.7% were readmitted and 42.4% had an early unplanned readmission. Twelve patients died and nine developed spontaneous bacterial peritonitis. Of those eligible for readmission, more patients died (P = 0.008) and/or developed spontaneous bacterial peritonitis (P = 0.027) if they had an early unplanned readmission during the study period. Markers of liver disease, as well as haemoglobin (P = 0.029), haematocrit (P = 0.024) and previous heavy alcohol use (P = 0.021) at index admission, were associated with early unplanned readmission.

Conclusion: Patients with cirrhosis and ascites comprise a small population who account for substantial use of hospital services. Markers of disease severity may identify patients at increased risk of early readmission. Alternative models of care should be considered to reduce unplanned hospital admissions, healthcare costs and pressure on emergency services.

Introduction

The burden of liver disease is rising, due in part to increasing prevalence of non-alcoholic fatty liver disease, hazardous alcohol consumption, and chronic viral hepatitis B (HBV) and C (HCV). In Australia, liver disease, including fatty liver, affects more than a quarter of the population, and in 2012 the health costs of treating liver disease were estimated to be $432 million. Regardless of aetiology, most of the morbidity and mortality from chronic liver disease (CLD) occur among people with advanced fibrosis or cirrhosis, who are at risk of developing complications of cirrhosis, including ascites, hepatic encephalopathy and variceal haemorrhage.

The morbidity and healthcare costs associated with these complications of cirrhosis are substantial. In the US, cirrhosis is responsible for more than 150 000 hospitalisations, costing in excess of US$4 billion annually. Recurrent hospital admissions among this patient population are common and are associated with higher risk of
subsequent mortality. A recent study from a US academic liver transplant centre found that 37% of patients with decompensated cirrhosis were readmitted within a month of discharge at a cost of over US$20 000 per admission. Risk factors for readmission included liver disease severity and complexity of medical management. Importantly, 22% of hospital readmissions were judged to be possibly preventable, due to failure to titrate appropriately or monitor medications, or to plan ahead for paracentesis.

Ascites is the most frequent complication of cirrhosis and is associated with poor prognosis, reduced quality of life and increased hospital admissions. A significant complication of ascites is spontaneous bacterial peritonitis (SBP), which occurs in approximately 1.5–3.5% of outpatients and 10% of inpatients, and is the most common infection in patients with decompensated cirrhosis. Published guidelines and quality indicators describe effective acute interventions for management of patients hospitalised with ascites. However, after hospital discharge, patients receive episodic outpatient care and risk subsequent complications, including reaccumulation of ascites, fluid or electrolyte imbalance, and renal impairment, which may result in readmission. In other common chronic diseases such as congestive heart failure and chronic obstructive pulmonary disease, risk factors for early readmission have been identified, and institution of chronic disease management has led to a reduction in disease-related admissions and cost savings. In contrast, little information is available regarding factors that predict hospital readmission in Australian patients with ascites.

The main aim of this study was to investigate the use of hospital services at a single tertiary hepatology centre over a 12-month period by patients requiring paracentesis for ascites due to decompensated cirrhosis. The second aim was to determine clinical parameters that may help identify and coordinate care for patients with early unplanned readmissions and higher care needs.

Methods

Patients and clinical data

A retrospective cohort investigation was conducted at Princess Alexandra Hospital, a tertiary care facility containing a dedicated gastroenterology and hepatology department, and the referral centre for the statewide liver transplant service. The study protocol was approved by Metro South Hospital and Health Services Human Research Ethics Committee. Informed consent was waived as the study data were anonymised and involved no risk to patients’ rights or welfare.

Patients with CLD who underwent abdominal paracentesis at Princess Alexandra Hospital between October 2011 and October 2012 were included in the study. Patients were identified if an ascitic fluid sample related to cirrhosis was recorded on the Queensland Pathology database during the study period. Further paracenteses were identified for these patients on review of their medical record. The first hospital admission and first paracentesis performed during the 12-month period are referred to as the ‘index admission’ and ‘index paracentesis’ respectively. Admissions or paracenteses were defined as ‘planned’ if they were arranged admissions and ‘unplanned’ if they were not scheduled. Early unplanned readmissions were defined as unplanned readmissions that occurred within 1 month of a previous admission. Deaths were identified from the medical record and hospital-based corporate information system.

Patient medical records were reviewed to obtain for each paracentesis: demographic details, previously diagnosed liver disease and other medical conditions, medications, and history of tobacco and alcohol use. Current alcohol use was stratified according to whether the patient consumed less than or greater than recommended weekly allowance of alcohol (140 g/week for women, 210 g/week for men), which is the threshold when liver injury is likely to occur (based on epidemiological data). Previous heavy alcohol use was defined as ≥350 g/week for women and ≥420 g/week for men, for >6 months. Results from ascitic fluid analysis and routine haematological and biochemical tests performed at each paracentesis were recorded. SBP was defined as an ascitic fluid polymorphonuclear count >250/mm³. Standard biochemical and serological assays, liver imaging, and histological assessment of a liver biopsy (if performed) were used to confirm diagnosis of liver disease and cirrhosis. The severity of liver disease was evaluated using the Child-Turcotte-Pugh (CTP) classification, Model for End-Stage Liver Disease (MELD) score and the United Kingdom Model for End-Stage Liver Disease score. Comorbidity was graded using the Charlson comorbidity index and cirrhosis-specific comorbidity scoring system.

The outpatients’ scheduling information management system and the hospital radiology database were searched to identify use of outpatient and radiology services during the 12-month period. Endoscopic reports were obtained from the hospital endoscopy database for all procedures completed during the year.

Statistical analysis

Conventional descriptive statistics were used to describe the demographic and clinical characteristics for the whole cohort. The Mann–Whitney U-test was used to test for
significant differences in MELD and CTP score between those who had undergone paracenteses prior to commencement of the study and patients who experienced their first paracentesis during the study period. Survival analysis of time to readmission was completed using the Kaplan–Meier method with the event being readmission.

The second aim was to examine potential variation between those patients with and without an early unplanned readmission. Continuous variables that were not normally distributed or had heterogeneity were examined using the Mann–Whitney U-test. Categorical variables were examined using the Fisher’s exact test. The per month rate for the total number of paracenteses, number of admissions and the total length of hospital stay were calculated for each patient by adjusting for the period of time during the study period that the patient could potentially be readmitted following the index admission. Patients were not eligible for readmission once they died or had a liver transplant.

Results

Patient characteristics at index paracentesis

A total of 41 individual patients with portal hypertension and ascites requiring paracentesis were admitted over the 12-month period. The demographic and clinical data for these patients are displayed in Table 1. The primary cause of portal hypertension was alcohol-related liver disease in 18 patients, chronic HCV in 13, chronic HBV and hepatocellular cancer in 1, and other in 9. Previous harmful alcohol consumption was also a cofactor in 6 of the 13 patients with chronic HCV. The median MELD score was 17 (interquartile range (IQR): 13–21) and the median CTP score was 10 (IQR: 9–12). There was no difference in median MELD (P = 0.77) or CTP (P = 0.48) score between the 19 patients who had undergone paracenteses prior to commencement of the study and the 22 patients who experienced their first paracentesis during the study period.

Medical comorbidities were also present in this patient cohort, as detailed in Table 1. All patients were taking medications at index presentation, with a median number of medications per patient of 6 (IQR: 2–8). Furthermore, prescriptions for medications to manage complications of cirrhosis (e.g. propranolol, lactulose and diuretics) increased over the study period, as did the use of proton pump inhibitors. Diuretic therapy was eventually prescribed to 36 (87.8%) patients during the study period, but importantly was ceased at least once for 13 patients due to acute kidney injury (n = 11) and/or hyponatraemia (n = 9).
Hospital admissions and occupied bed days

During the 12-month study period, the 41 patients had a total of 127 hospital admissions. One hundred and two (80.3%) of these admissions were for the management of ascites, of which 60 (58.8%) were planned and 42 (41.2%) unplanned.

Overall, there was a total of 1164 occupied bed days comprising 41 outpatient days (day procedure unit) and 1123 inpatient days. Of the inpatient days, 832 (74%) were attributed to admissions for management of ascites. Median (IQR) length of inpatient stay for admissions for management of ascites was 6 (3–11) days, compared with 11 (5–27) days for admissions for another reason (e.g. gastrointestinal bleed, infection, falls). Seven patients died and one patient had a liver transplant during their index admission, thus were not eligible for readmission. Twenty-three (69.7%) patients were readmitted during the study period, of whom 14 (42.4%) had unplanned readmissions within a month of discharge. The median (95% confidence interval (CI)) time to readmission for the 33 patients eligible for readmission was 68 (5.9–130.1) days following discharge from the index admission, as demonstrated in Figure 1. Patients were censored if they died or received a liver transplant, since this affected their likelihood of readmission. The probability (95% CI) of readmission at 1 month was 0.4 (0.2–0.6), and at 3 months, when patients with decompensated liver disease are usually scheduled for review in outpatient clinic, was 0.6 (0.4–0.8).

Outpatient care and medical imaging use

During the study period, the patients had a total of 328 outpatient appointments: 274 (83.5%) were related to liver disease (e.g. appointments scheduled with hepatology, hepatobiliary surgery, liver transplant clinic, liver dietician). Furthermore, there were 343 ‘chart reviews’ (patient care-related events without the patient present) (e.g. to follow-up laboratory tests and medical imaging, and to advise about medication dosages), although the majority (98.8%) of these were for patients who had received or were being assessed for a liver transplant. Twenty-six patients had 34 endoscopic procedures performed during the study period.

The patients received 733 medical imaging services over the 12-month period: abdominal ultrasounds \((n = 180)\), computed tomography scan \((n = 67)\), magnetic resonance imaging \((n = 8)\), radiographs \((n = 418)\), bone mineral densitometry \((n = 11)\) and other radiological services (e.g. interventional procedures or other ultrasounds) \((n = 49)\). Five hundred and thirteen (70.0%) of these were performed on patients who presented with an unplanned admission.

Paracenteses

The 41 patients received a total of 206 paracenteses (median 4, IQR: 2–9). During unplanned admissions, only 25.0% of initial paracenteses occurred in a liver-related ward, with 38.3% occurring in the emergency department. In contrast, during planned admissions, 97% of paracenteses were performed in a liver-related ward, with none occurring in the emergency department.

Greater than half the paracenteses \((n = 124, 60.2\%)\) were performed for therapeutic purposes, with a mean (standard deviation) volume of 7.5 L (± 4.0 L) fluid removed during each procedure. Eighty-two (39.8%) paracenteses were performed for diagnostic purposes, usually to exclude the presence or monitor treatment of SBP. Paracentesis occurred within 24 h for 84.3% \((n = 107)\) of admissions, and in 90.3% \((n = 186)\) of procedures an ascitic fluid cell count and differential was performed. During the 12-month period, SBP was confirmed in 22 paracenteses for 9 patients during 10 hospital admissions. For all of the cases, antibiotics were commenced within 24 h of SBP diagnosis. However, 9 of the 10 admissions had a negative ascitic fluid culture on initial paracentesis, 6 of which had antimicrobials detected in the ascitic fluid.

Factors associated with early unplanned readmission

The second aim was addressed by comparing clinical parameters at the index paracentesis for 33 patients with
(n = 14) or without (n = 19) early unplanned readmissions (eight patients excluded due to death (n = 7) or liver transplantation (n = 1) during the index admission). Comparisons between the ‘No early unplanned readmission’ and ‘Early unplanned readmission’ groups are shown for demographic data and comorbidities (Table 1), laboratory studies and medications at index admission (Table 2), and care needs (Table 3).

Haemoglobin (P = 0.029), haematocrit (P = 0.024), MELD score (P = 0.030), previous heavy alcohol (P = 0.021) and hepatic encephalopathy (P = 0.037) were significantly different between the two groups. Furthermore, five (35.7%) patients who had an early unplanned readmission died, compared with none in the ‘No early unplanned readmission’ group (P = 0.008), and six developed SBP in the ‘Early unplanned readmission’ group, compared with one in the other group (P = 0.027).

In comparison with ‘No early unplanned readmission’, ‘Early unplanned readmission’ patients had higher care needs, with a greater number of admissions per month (P = 0.001), total length of hospital stay per month (P = 0.001)}

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Laboratory studies, severity of liver disease scores and medication use at index admission for ‘No early unplanned readmission’ and ‘Early unplanned readmission’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical parameter</td>
<td>‘No early unplanned readmission’ (n = 19)</td>
</tr>
<tr>
<td>Serum sodium, median (IQR) (mmol/L)</td>
<td>136.0 (131.0–139.0)</td>
</tr>
<tr>
<td>Serum urea, median (IQR) (mmol/L)</td>
<td>4.7 (3.1–7.2)</td>
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<tr>
<td>Serum eGFR, median (IQR) (mL/min)</td>
<td>90.0 (69.8–90.0)</td>
</tr>
<tr>
<td>Serum bilirubin, median (IQR) (μmol/L)</td>
<td>37.5 (18.8–71.5)</td>
</tr>
<tr>
<td>Haemoglobin, median (IQR) (g/L)</td>
<td>125.0 (102.0–134.0)</td>
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<tr>
<td>Haematocrit, median (IQR)§</td>
<td>0.38 (0.31–0.40)</td>
</tr>
<tr>
<td>Mean cell volume, median (IQR) (fL)</td>
<td>96.0 (89.0–101.0)</td>
</tr>
<tr>
<td>C-reactive protein, median (IQR)‡ (mg/L)</td>
<td>13.0 (6.5–30.0)</td>
</tr>
<tr>
<td>Ascitic fluid total protein, median (IQR)† (g/L)</td>
<td>14.5 (5.0–18.8)</td>
</tr>
<tr>
<td>CTP score† (IQR)</td>
<td>9.0 (8.0–11.0)</td>
</tr>
<tr>
<td>MELD score† (IQR)</td>
<td>14.5 (10.8–18.3)</td>
</tr>
<tr>
<td>UKELD score† (IQR)</td>
<td>56.0 (50.5–58.3)</td>
</tr>
<tr>
<td>Number of medications, median (IQR)</td>
<td>4.0 (2.0–6.0)</td>
</tr>
<tr>
<td>Diuretic use, n (%)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Proton pump inhibitor use, n (%)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Propranolol use, n (%)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>SBP prophylaxis, n (%)</td>
<td>1 (5.3)</td>
</tr>
</tbody>
</table>

†‘No early unplanned readmission’ (n = 18). ‡‘No early unplanned readmission’ (n = 17) and ‘Early unplanned readmission’ (n = 13). §‘Early unplanned readmission’ (n = 13). CTP, Child-Turcotte-Pugh; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; SBP, spontaneous bacterial peritonitis; UKELD, United Kingdom Model for End-Stage Liver Disease.

<table>
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<tr>
<th>Table 3</th>
<th>Use of hospital services for ‘No early unplanned readmission’ and ‘Early unplanned readmission’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical parameter</td>
<td>‘No early unplanned readmission’ (n = 19)</td>
</tr>
<tr>
<td>Length of index admission hospital stay (days)</td>
<td>6.0 (3.0–11.0)</td>
</tr>
<tr>
<td>Total length of hospital stay during the study (days)</td>
<td>10.0 (6.0–26.0)</td>
</tr>
<tr>
<td>Total length of hospital stay per month (days)</td>
<td>1.5 (0.8–3.9)</td>
</tr>
<tr>
<td>Number of admissions per month</td>
<td>0.2 (0.1–0.5)</td>
</tr>
<tr>
<td>Number of paracenteses during the study period</td>
<td>2.0 (1.0–6.0)</td>
</tr>
<tr>
<td>Number of paracenteses per month</td>
<td>0.4 (0.1–0.7)</td>
</tr>
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</table>
Discussion

Although CLD is not currently a national health priority area, there is increasing concern about the growing impact of liver disease on the health of Australians and the healthcare system. This study was undertaken to examine the use of hospital services by patients with cirrhosis and ascites, and to identify factors that may help detect those at risk of early readmission and with higher care needs. The present study indicated that decompensated CLD is associated with very high use of hospital services, with a number of admissions unplanned.

CLD has a substantial latency period, during which affected individuals remain relatively asymptomatic despite progressive hepatic fibrosis and development of cirrhosis. Ascites is usually the first sign that cirrhosis has progressed to a decompensated phase. The median survival time of patients with decompensated cirrhosis is around 2 years, and not unexpectedly around one quarter of our cohort died during the study. Over a 12-month period, patients in this study had frequent and prolonged hospital admissions, illustrating the high morbidity, mortality and resource utilisation of this patient population.

These findings are consistent with previous reports that medical care for decompensated cirrhosis and ascites is complex, and patients with CLD often have comorbidities that increase the burden of illness and use of healthcare resources. As evidenced by this study, patients are often prescribed multiple medications, many of which require dosage adjustments or titration based on clinical response, side-effects or laboratory follow up. A recent study demonstrated that the number of medications on discharge was a risk factor for hospital readmission among patients with decompensated cirrhosis. Although the precise reason for this was not established, it is likely contributed to by frequent dosage adjustments and potential compliance issues related to factors such as depression and hepatic encephalopathy, which were common in this patient cohort. Our data suggest that comorbidities, such as prior heavy or current alcohol consumption and diabetes, may also contribute to early readmission. Diabetes and alcohol-related liver disease have previously been identified as risk factors for frequent readmissions in patients with cirrhosis. It has been suggested that diabetes is a risk factor for hepatic encephalopathy, a factor more prevalent in our patients with early readmission. The role of alcohol use in early re-hospitalisation emphasises the importance of assessing alcohol histories and prompt referral to alcohol and drug treatment services.

This study demonstrated that patients with early unplanned readmissions experienced more hospital admissions, with longer hospital stays. Deterioration in liver or renal function or development of SBP may identify a subgroup of patients requiring more intensive follow up and implementation of prophylactic interventions. MELD, a validated score that predicts survival in CLD patients, has been reported to predict early readmission following hospital discharge. MELD is based on three objective, quantitative variables: serum bilirubin, international normalised ratio of the prothrombin time and serum creatinine. In the current study, patients with early unplanned readmission had higher MELD scores compared with subjects with no early readmission. There was also a significant difference for both haematocrit and haemoglobin levels between the two groups, which may be due to haemodynamic abnormalities in advanced cirrhosis or result from other complications of decompensated cirrhosis.

The majority of hospital readmissions during the study period were for management of ascites. Determining the specific factors contributing to readmission for ascites (e.g. poor efficacy or non-compliance with medical therapy, progression of liver disease or medication side-effects) was beyond the scope of the current study and should be a focus of future research. It has been speculated that one quarter of hospital readmissions may be prevented by better patient understanding of their medication regimen or more intensive outpatient monitoring. Unfortunately, a recent Australian pilot study involving intensive CLD patient monitoring after discharge did not show a reduction in occupied bed days or other secondary end-points of hospital use. The findings did, however, suggest an improved approach to hospital use, with an increase in planned admissions and increased attendance rate at outpatient care. Prospectively, this may lead to better management and compliance with medications, and reduce the use of emergency and radiological services. Improved coordination of patient care and specialist involvement should provide a more efficient, less resource intensive approach to management of ascites, resulting in better patient outcomes and cost savings.

This study likely reflects the patients and practices in other Australian tertiary care hepatology centres, but may not represent centres with less specialised services. The study was limited to one calendar year, with 41 patients recruited during this period; thus, only simple univariate statistical analyses were possible. In addition, statistical significance may have not been achieved for some clinical parameters due to the cohort size and because six of the patients received a liver transplant during the study period, all of whom had improved outcomes.
Conclusion

Patients with cirrhosis and ascites comprise a relatively small population who account for a substantial use of hospital services, due to frequent admissions that are often unplanned. Management of these patients is complex, and markers of disease severity may help identify patients who are at increased risk of poorer outcomes. The present study supports the need to consider alternative or adjunct models of care for this patient cohort to determine whether more intensive patient monitoring and coordination of patient care will reduce unplanned hospital admissions and result in reduced healthcare costs and pressure on emergency services.

References

Management and outcomes of single subsegmental pulmonary embolus: a retrospective audit at North Shore Hospital, New Zealand

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Key words
pulmonary embolism, venous thromboembolism, multidetector computed tomography, diagnosis, therapy.

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Abstract

Background: It is unknown whether filling defects in subsegmental arteries on multidetector computed tomography pulmonary angiography correlate with clinically relevant subsegmental pulmonary embolism (PE) on pulmonary angiography. Current guidelines do not differentiate between PE in segmental and subsegmental vessels, and many patients receive at least 3 months anticoagulation. The strategy employed at North Shore Hospital in haemodynamically stable patients with single subsegmental PE is to perform bilateral lower leg compression ultrasound (CUS). Anticoagulation is withheld if CUS is negative; a bilateral CUS is repeated in 7–10 days.

Aim: The aim of this retrospective audit was to ensure our current management strategy is safe.

Methods: All diagnoses of single subsegmental PE between June 2005 and June 2013 were included. The primary outcome was the rate of venous thromboembolism (VTE) recurrence within 3 months of single subsegmental PE diagnosis. Secondary outcomes were rates of major/minor bleeding and all-cause mortality.

Results: Thirty-two patients were included – 20 were treated with anticoagulation; 12 were managed with observation/serial bilateral lower limb CUS. None of the patients in either group had VTE recurrence by 3 months. No bleeding episodes were observed in the observation group; there was a 10% major bleeding rate (n = 2) in the treatment group. One death occurred in each group, neither of which was attributed to VTE.

Conclusion: Withholding anticoagulation in patients with single subsegmental PE and negative serial bilateral CUS appears to be a safe and effective management strategy, with a low risk of VTE recurrence.

Funding: None.
Conflict of interest: None.
**Introduction**

Venous thromboembolism (VTE), which comprises pulmonary embolism (PE) and deep vein thrombosis (DVT), is responsible for significant morbidity and mortality. Approximately 10% of PE are rapidly fatal, and approximately one quarter of surviving patients die within 1 year.\(^1\) The introduction of multiple-detector computed tomography pulmonary angiography (CTPA) has improved the sensitivity of diagnosis of PE by allowing visualisation down to the fifth- and sixth-order pulmonary arteries, thereby increasing rates of diagnosis of subsegmental PE.\(^2\) A recent systematic review suggests a rate of subsegmental PE diagnosis by multidetector CTPA of 9.4% compared with 4.6% by single-detector CTPA.\(^3\) In the past, these would have been undiagnosed and untreated.

Pooled data from two studies showed that none of 30 patients with subsegmental PE on CTPA left untreated experienced a thromboembolic event during the 3-month follow-up period.\(^4\) A subsequent review reported that over 60 patients diagnosed with subsegmental PE on CTPA, who were DVT negative by ultrasound, have been managed without anticoagulation and reported in the literature, with a rate of recurrent symptomatic VTE of 0% during the 3-month follow-up period (95% confidence interval (CI) 0–7.4%).\(^5\)

Single subsegmental PE at North Shore Hospital is usually managed with bilateral lower limb ultrasound. If this is negative for DVT and the patient is haemodynamically stable, with adequate pulmonary reserve, then anticoagulation is withheld and the bilateral lower limb ultrasound is repeated in 7–10 days. If the repeat scan is negative, then anticoagulation is withheld and patients are followed up for at least 3 months. To establish whether this was a safe and effective strategy, we carried out a retrospective audit of all patients with single subsegmental PE presenting to our catchment area.

**Methods**

**Study population**

All patients diagnosed with single subsegmental PE presenting to our catchment area from June 2005 to June 2013 who had completed 3 months of follow up were included in this retrospective analysis. We did not test for major thrombophilia; however, these patients were not specifically excluded. Similarly, a history of prior VTE was not an exclusion. However, those patients with known active or recent malignancy, and patients receiving chemotherapy, were excluded. Demographic data were collected, including age, sex, ethnicity and provoking factors.

**Definitions**

Subsegmental PE was identified as the location of the largest defect at the subsegmental level on a multidetector CT, allowing a satisfactory visualisation of all pulmonary arteries at the segmental level or higher. Isolated subsegmental defects were classified as either single (one subsegmental vessel involved) or multiple (two or more subsegmental vessels involved).

Bleeding was classified as major and minor according to the International Society of Thrombosis and Haemostasis definitions.\(^6\)

**Study end-points**

The primary outcome was the rate of VTE recurrence (DVT, PE, other thromboembolism) within 3 months of diagnosis of single subsegmental PE. Secondary outcomes were rates of major and minor bleeding, and all-cause mortality.

**Statistical analysis**

Descriptive statistics were used to summarise baseline variables and results. Ninety-five per cent CI were calculated for the study end-points using exact confidence limits in SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Study population**

Sixty-one patients were identified from our VTE database. On review of data, eight patients were excluded as they were found to have segmental rather than single subsegmental PE; one was lost to follow up. This left a total of 52 subsegmental PE, of which 17 were multiple and 35 single subsegmental PE. The latter were used in our retrospective analysis. Of the 35 patients with single subsegmental PE, 20 patients received anticoagulation, whereas 15 patients were managed with observation and serial compression ultrasound (CUS), as per our treatment algorithm. Within the observation group, three patients were removed following a retrospective review of imaging as two had multiple subsegmental PE and one had more proximal PE. This left 12 patients within the observation group, giving a total study population of 32.

Baseline demographics are summarised in Table 1. In the anticoagulation group, 15 (75%) received anticoagulation for up to 3 months. Six (30%) of those receiving anticoagulation had concomitant DVT, of which five were distal and one was proximal. Two of these
patients had DVT diagnosed on their first CUS, and subsequently did not have a second scan. The remaining four were diagnosed on the second CUS. However, 10 patients in the treatment group with negative first ultrasound scans did not have a second CUS, and 1 patient had no CUS at all. No patients in the observation group had a diagnosis of concomitant DVT, at presentation or on follow up; however, it should be noted that three of these patients did not have a second CUS.

VTE recurrence

Study outcomes are summarised in Table 2. There were no VTE recurrences by 3 months in either group.

Bleeding

There were two episodes of major bleeding in the anticoagulation group (10%; gastrointestinal bleeding in both) and no episodes of major bleeding in the observation group. Anticoagulation was ceased in both patients, with no VTE recurrences documented at 3 months in either patient. No episodes of minor bleeding were observed in either group.

Mortality

One patient died in each group, one due to lung cancer (anticoagulation group) and one due to infective exacerbation of chronic obstructive pulmonary disease (COPD) (observation group). The latter patient was readmitted within 3 weeks of single subsegmental PE diagnosis, with worsening dyspnoea on a background of severe COPD. A repeat CTPA showed the previously documented PE (unchanged) and changes in keeping with infection. This patient was commenced on Clexane but died in the community a few days after discharge. It is very unlikely that this death was due to the single subsegmental PE.

Multiple subsegmental PE outcomes

On review of our data, incidental note was made of 8 patients (within the initial pool of 52 patients) with multiple subsegmental PE and negative CUS who were also observed without anticoagulation. As for those with single subsegmental PE, none of these patients suffered a VTE recurrence within 3 months of diagnosis.

Discussion

Limitations of our study include the small patient numbers and likely assignment bias in the two groups. Due to the small numbers of patients, the 95% CI are quite wide, so that there is an overlap between the two groups. However, non-significance does not necessarily mean there is no statistical difference between the two groups. Despite this, our results are consistent with published data, with a rate of VTE recurrence at 3 months in the observation group of 0%. This lends weight to the published body of evidence demonstrating that patients with isolated single subsegmental PE and negative bilateral lower limb CUS are at low risk of VTE recurrence. The overall rate of concomitant DVT in this study was 18.8% (6 patients in treatment group/total of 32 patients in study); all of these patients were treated with anticoagulation. A bilateral lower limb CUS, therefore, plays an important role in management decisions when managing those with single subsegmental PE, as this identifies a subset of patients with single subsegmental PE who are at higher risk for VTE recurrence and clearly need treatment with anticoagulation.

Interobserver agreement at the subsegmental level is noted in the literature as being poor; therefore, a second review (non-blinded) was undertaken of the observation

<table>
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<tr>
<th>Table 1</th>
<th>Baseline patient characteristics</th>
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<tr>
<td>Characteristics</td>
<td>Anticoagulation group, n (%)</td>
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<tr>
<td></td>
<td>(n = 20)</td>
</tr>
<tr>
<td>Male</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>69.1</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Maori/Pacific island</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
</tr>
<tr>
<td>Provoking factors</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Immobility</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Post-surgery</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Concomitant deep vein thrombosis</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>VTE recurrence and bleeding/mortality outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anticoagulation group, n (%)</td>
</tr>
<tr>
<td></td>
<td>(n = 20)</td>
</tr>
<tr>
<td>VTE recurrence within 3 months</td>
<td>0 (0) [0–17%]</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2 (10) [1–32%]</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1 (5) [0–25%]</td>
</tr>
<tr>
<td>VTE-related mortality</td>
<td>0 (0) [0–17%]</td>
</tr>
</tbody>
</table>

CI, confidence interval; VTE, venous thromboembolism.
group. This revealed that two patients in fact had multiple subsegmental PE, while one had more proximal PE. None of these patients had concomitant DVT, and although they were managed without anticoagulation (according to their initial diagnosis), they were removed from our initial group of 15 patients.

The importance of single subsegmental PE continues to be debated in the literature. There is a high rate of interobserver variability in CTPA showing subsegmental PE, with one study showing that consensus readings altered interpretations for 30% of such patients, whereas per-embolus interpretations were altered for 37% of all subsegmental emboli. Similarly, in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, there was a lack of consensus of interpretation of subsegmental PE diagnosis in one-third of cases. This brings us to two important points.

First, in accordance with this, the PIOPED study showed that 17% of those with a low-probability ventilation-perfusion (VQ) scan had subsegmental PE on CTPA compared with only 1% of patients with high-probability VQ scans, with a rate of 6% overall. It is, therefore, likely that many patients with subsegmental PE on VQ scan are left untreated, yet the 3-month thromboembolic risk is similar by either strategy. Several prospective management cohort studies have shown that patients with low to intermediate VQ scan results can safely be managed without anticoagulation when the results are combined with pretest probability and CUS, with a risk of recurrent VTE of 0.5% (95% CI 0.1–2.9%).

Second, because of the high interobserver variability within the literature, consideration should be given to a second (radiologist) review of the CTPA in those with a diagnosis of single subsegmental PE, particularly in cases where the diagnosis is indeterminate or probable. This would avoid inappropriate withholding, or anticoagulation, of those found to have either more proximal PE or not to have a PE at all.

The risks of committing a patient to anticoagulation should not be underestimated. There is a risk of major bleeding on anticoagulation estimated at 0.25–3% per year, with bleeding more likely to occur early in the course of anticoagulation. Our findings are consistent with this, with a rate of major bleeding of 10% in the treatment group. It is acknowledged that the higher rate of bleeding on anticoagulation in our study than seen in the literature is likely due to small patient numbers.

Overall, the risk–benefit ratio appears to be in favour of withholding anticoagulation in patients with single subsegmental PE and negative serial bilateral lower limb CUS, as the risk of bleeding outweighs the risk of VTE recurrence. Whether the same management strategy can be extrapolated to those with multiple subsegmental PE is uncertain, as this was not the focus of our study. However, there were no recurrences in the six with multiple subsegmental PE managed with this strategy, suggesting that this may also be safe.

It is interesting that no patients in the observation group had a DVT on the repeat bilateral lower limb CUS, suggesting that the repeat CUS may not be necessary. However, numbers are small and no firm conclusions can be drawn.

Conclusion

Withholding anticoagulation in patients with single subsegmental PE and negative bilateral serial lower limb CUS appears to be a safe and effective management strategy, with a low risk of VTE recurrence. These findings are currently being investigated in a prospective cohort study of withholding anticoagulant treatment in patients with single subsegmental PE who have negative results on serial CUS for DVT (NCT01455818), which will better help to inform us on the safety of this management strategy.

References

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**Introduction of an interdisciplinary heart team-based transcatheter aortic valve implantation programme: short and mid-term outcomes**

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**Key words**

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**Abstract**

**Background:** Transcatheter aortic valve implantation (TAVI) has been developed to treat symptomatic aortic stenosis in patients deemed too high risk for open-heart surgery. To address this complex population, an interdisciplinary heart team approach was proposed.

**Aim:** Present the short- and mid-term outcomes of the first 100 patients in the Royal Prince Alfred Hospital multidisciplinary TAVI programme.

**Methods:** Single-centre registry. Baseline and procedural data were prospectively recorded. Outcomes were recorded according to Valve Academic Research Consortium – version 2 guidelines.

**Results:** All patients underwent a comprehensive interdisciplinary pre-procedural evaluation. Sixty-eight transfemoral and 32 transapical implantations were performed. Mean age was 82 (±8.9) years old with an average logistic EuroSCORE of 33. Although 13 procedures had major complications, there was no intraprocedural mortality. During the first month, 9% of patients were re-admitted due to heart failure and 13% had a permanent pacemaker implanted. A 3% 30-day and 8% follow-up (mean 17 months) mortalities were recorded. While no significant differences in the rate of complications were found between the first and second half of the experience, all cases of mortality within 30 days (n = 3) occurred in the initial half. Sustained haemodynamic results were obtained with TAVI (immediate mean aortic valve gradient reduction from 47 to 9 mmHg; 1-year echocardiographic gradient 9.9 mmHg, with no moderate or severe aortic regurgitation).

**Conclusion:** Excellent results can be achieved with TAVI in very high-risk patients at an Australian institution. A comprehensive evaluation based on a heart team can overcome most of the difficulties imposed by this challenging population.
**Introduction**

Transcatheter aortic valve implantation (TAVI) has been developed to treat severe symptomatic aortic stenosis in patients deemed high risk for open-heart surgery. Since its clinical introduction in 2002, an appreciable amount of experience has been gained, leading to progressive improvements in safety and procedural efficacy. However, as with any new intervention, there exists a great variability between different centres in terms of patient selection and the results achieved by the procedure. Whereas a single high-volume Israeli centre reported a 30-day mortality as low as 2.3%, the multicentre European experience has reported a much higher 15% 30-day mortality, although both studies recruited patients with similar levels of risk. Likewise, the Ibero-American registry reported 1220 patients with an average EuroSCORE of 17.8%, markedly lower than the 27.8% in the Australia-New Zealand registry.

A significant learning curve has been reported for TAVI with considerable reduction in adverse clinical events, including mortality, with increasing procedural experience. As more sites seek to initiate TAVI programmes, there is concern that the learning curve associated with the procedure may predispose to suboptimal clinical outcomes. Moreover, in order to improve clinical decision making and procedural outcomes of these challenging patients, interdisciplinary heart teams have been recommended.

The aim of this study was to present the short and midterm outcomes of the first 100 patients in the Royal Prince Alfred Hospital (RPAH) TAVI programme, with a special emphasis on the value of a multidisciplinary approach.

**Methods**

**Patient selection**

Between the beginning of our TAVI programme in June 2009 and July 2013, 100 consecutive implantations were performed and formed the study cohort. Data regarding baseline patient characteristics (age, gender, comorbidities, symptomatic status, previous medical history), cardiac and pulmonary function, basic laboratory tests, intraoperative outcomes, echocardiography results and clinical follow up were prospectively recorded. Local ethics committee approval was obtained.

**Procedural aspects**

TAVI were performed either by the transfemoral (TF) or transapical (TA) approaches using one of the two currently available devices: the Edwards SAPIEN transcatheter heart valve (Edwards Lifesciences, Irvine, CA, USA) and the Medtronic CoreValve Revalving system (Medtronic, Minneapolis, MN, USA). A combined team comprised of interventional cardiologists and cardiothoracic surgeons performed all implantations. Additionally, the patients were prepared as per open-heart surgery, with general anaesthesia, full haemodynamic monitoring (arterial line, central venous access with pulmonary artery catheter) and trans-oesophageal echocardiography. When deemed necessary, vascular surgeons were also included in the procedure and a primed extracorporeal membrane oxygenation (ECMO) circuit was available for use if needed.

The procedure was performed following the current technical recommendations, explained in detail elsewhere.

**End-points definitions**

Events were prospectively recorded as per Valve Academic Research Consortium version 2 (VARC2) criteria. Echocardiographic follow up was made according to the treating physician preference and all patients had at least one exam prior to discharge, one during the first 6 months and one echocardiogram yearly thereafter. Clinical follow up was made by the treating physician as well as at least one member of the TAVI team. Composite end-points were also defined by VARC2 and included device success and early safety (at 30 days postoperation).

**Statistical analysis**

Continuous variables were reported as mean ± standard deviation (SD) and categorical variables as number (percentage). In order to determine if there was an early phase of poorer performance, the cohort was divided into an early group (n = 50) and late group (n = 50). Differences in the means of continuous variables (e.g. age) were tested through the use of an independent samples t-test or nonparametric test for non-normally distributed data, while proportional differences in categorical variables (e.g. patient did or did not have a life-threatening bleed) were tested through the use of Fisher’s exact test. Statistical analysis was performed with SPSS 22 software (IBM, Armonk, NY, USA).

**Results**

**TAVI multidisciplinary team**

As described previously, our TAVI team is comprised of two interventional cardiologists, a non-invasive cardiologist, two cardiothoracic surgeons, a clinical nurse...
consultant, a respiratory physician, a cardiac radiologist, a cardiac anaesthetist and a geriatrician. Criteria for inclusion into the TAVI programme included interdisciplinary consensus that a patient is high risk for surgical aortic valve replacement, defined as a logistic EuroSCORE > 15% and/or the presence of other complicating factors not represented in classical risk scores, such as frailty, porcelain aorta, liver disease or hostile chest. Pre-procedural evaluation includes at least a comprehensive echocardiographic analysis, a coronary, aortic and ilio-femoral angiography, a cardiac and aortic computed tomography (CT) scan, spirometry, carotid ultrasonography and any other required evaluation depending on the patient’s comorbidities. Multimodality imaging of aortic valve anatomy, incorporating echocardiographic analysis, calibrated angiography and three-dimensional (3D) CT aortography (in the second half of our experience), was used to determine anatomic suitability for TAVI and for procedural planning (Fig. 1). Peripheral vascular anatomy was routinely assessed by a combination of calibrated angiography and 3D CT angiography, principally to determine suitability for TF arterial access. Once the patient is considered suitable for TAVI, the case is presented again at the meeting and all the procedural aspects of that individual implantation are discussed in order to foresee any possible complications and plan suitable bailout strategies.

Patient characteristics

A total of 100 patients underwent TAVI at RPAH during the period from June 2009 to June 2013. Of these, 68 were TF and 32 TA implantations. Regardless of the mode of vascular access, all TAVI were performed by at least one interventional cardiologist and one cardiothoracic surgeon. Mean age was 82 (±8.9) years old and 37% of patients were female. Patients included in our TAVI programme were all very high risk for open surgery, as demonstrated by a mean logistic EuroSCORE of 33. When the cohort was divided and analysed into the first and second 50 patients, there were no major differences in the baseline patient characteristics and the logistic EuroSCOREs were comparable between groups (31.4 vs 34.8, \(P = 0.45\)). Table 1 shows the baseline patient characteristics for the total population and for TF and TA groups.

**Table 1** TAVI baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Transfemoral</th>
<th>Transapical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>82.6 ± 8.9</td>
<td>83.1 ± 10.0</td>
<td>81.6 ± 5.8</td>
</tr>
<tr>
<td>Male</td>
<td>63 (63)</td>
<td>42 (62)</td>
<td>21 (66)</td>
</tr>
<tr>
<td>Body mass index (mean ± SD)</td>
<td>26.2 ± 5.0</td>
<td>26.8 ± 5.0</td>
<td>25.3 ± 5.0</td>
</tr>
<tr>
<td>NYHA class III and IV</td>
<td>87 (87)</td>
<td>57 (84)</td>
<td>30 (94)</td>
</tr>
<tr>
<td>Moderate-severe lung disease</td>
<td>12 (12)</td>
<td>5 (7)</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>31 (31)</td>
<td>16 (24)</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>39 (39)</td>
<td>28 (41)</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>29 (29)</td>
<td>21 (31)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Previous valve surgery</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Previous balloon aortic valvuloplasty</td>
<td>48 (48)</td>
<td>34 (50)</td>
<td>14 (44)</td>
</tr>
<tr>
<td>Previous permanent pacemaker</td>
<td>15 (13)</td>
<td>11 (16)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>28 (28)</td>
<td>14 (21)</td>
<td>14 (44)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>30 (30)</td>
<td>15 (22)</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Renal insufficiency *</td>
<td>44 (44)</td>
<td>29 (43)</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Patients on dialysis</td>
<td>5 (5)</td>
<td>1 (1)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>34 (34)</td>
<td>25 (37)</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Logistic EuroSCORE</td>
<td>33.1 ± 22.6</td>
<td>27.9 ± 17.7</td>
<td>44.3 ± 27.6</td>
</tr>
</tbody>
</table>

Figures presented as \(n\) (%), median (range) as appropriate. \(\*\)Defined as creatinine > 110 μmol/L. CABG, coronary artery bypass graft; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.
Procedural outcomes

All but two TAVI were performed using balloon-expandable Edwards SAPIEN transcatheter heart valves. The Medtronic CoreValve was used in the other two cases, one due to anatomic characteristics (valve-in-valve implantation into a small diameter bioprosthetic valve) that favoured the self-expanding CoreValve system. The Edwards SAPIEN XT transcatheter heart valve on a Novoflex delivery system was introduced from the case number 21 onwards. The main advantage is its lower profile resulting in a smaller minimum ilio-femoral vessel diameter requirement, thereby favouring the TF approach. Nine out of 20 cases performed with the former SAPIEN system were TA (45%), whereas only 23 of the following 78 cases performed with the XT system were TA implantations (29%).

Elective haemodynamic support using ECMO was used in eight cases. Moreover, in three additional patients ECMO was emergently instituted as a rescue for life-threatening complications. There was no intraprocedural mortality in our series. Table 2 reports the main procedural aspects and intraoperative outcomes of the TAVI patients for the whole cohort, TF and TA procedures, and the first and second half of our experience. Immediately after valve implantation, paraavalvular aortic regurgitation (AR) was assessed by a combination of transoesophageal echocardiography, angiography and invasive haemodynamics. In case moderate or severe aortic AR was found – depending on the mechanism – balloon post-dilation (for valve malapposition) or valve-in-valve deployment (for valve malpositioning) were performed. This allowed for only 6% moderate AR and 0% severe AR after TAVI. The mean aortic valve gradient was significantly reduced after the implantation, from an average of 47 mmHg to 9 mmHg 1 month after the procedure (Fig. 2).

30-day outcomes

There were three mortalities during the first 30 days after the procedure: two due to cardiac causes and one due to acute adrenal insufficiency after inadvertent suspension of chronic steroid therapy when admitted to another hospital. They all occurred within the first 50 cases of our experience. The most common events during the first month were re-admission due to heart failure and the need for a permanent pacemaker after the procedure (9% and 13% respectively). On the other hand, the incidence of new myocardial infarction (MI) or stroke was low (2% each). Table 3 reports the short-term results after the implantation. Early safety outcome (as per VARC2 criteria) is a measure of a 30-day uncomplicated course after TAVI and was achieved by 86% of patients. Hospital length of stay (HLOS) was 6.1 (±8.3) days for the whole cohort and 4.7 (±8.4) days for the TF patients.
Late follow-up outcomes

The cumulative mortality of our series during an average follow up of 17.1 (SD 10.5) months was 8%. The estimated 1-year mortality was 7%. The five additional deaths after the first month were due to cardiac causes in three and non-cardiac in two (died after surgery for oesophageal cancer and for peripheral vascular disease). Two of the cardiac deaths were sudden death in patients with previous TA access. After the first 30 days, there were two patients with new strokes, two with MI and three patients with newly diagnosed cancer. The prosthetic valve gradient and degree of AR up to 1 year after the procedure are shown in Figure 2. No episodes of valve thrombosis or endocarditis were recorded.

Discussion

This single-hospital series of our first 100 cases undergoing TAVI demonstrates that high rates of procedural success and low complication rates are achievable in a high-risk elderly patient cohort when using a multidisciplinary approach. Although this was an extremely high-risk population, with a mean logistic EuroSCORE of 33%, the clinical and technical success were comparable with most current series.14,15

Patient selection and pre-procedural management

During interdisciplinary evaluation, patients were offered TAVI if they fit within the eligibility ‘sweet spot’ of (i) meeting high-risk criteria for surgical aortic valve replacement; (ii) fulfilling anatomical suitability criteria for TAVI and (iii) were deemed highly likely to derive significant functional and prognostic benefit from the procedure. Using this heart team approach, the patients selected had similar scores to other current registries such as SOURCE ANZ.7 However, in contrast to some programmes (e.g. partner cohorts), patients with comorbidities (e.g. oxygen-dependent chronic airways limitation, metastatic malignancy, etc.) that would preclude significant functional or prognostic improvement from TAVI were not offered the procedure.

In addition, an essential part of this heart team approach is to re-assess and optimise management of the patient’s comorbidities and treatments. As shown here, almost one third of patients had a history of MI and 39% of previous bypass surgery. Previous series have shown that up to 75% of patients have documented coronary artery disease.16 We treated with angioplasty all significant stenoses prior to TAVI, frequently using a fractional flow reserve-guided approach that has been shown to recognise accurately haemodynamically significant stenoses and reduce future events.17 By the similar means, clinically indicated carotid and peripheral stenoses were addressed before TAVI. This may have contributed to the low rates of strokes and MI showed in our series. Pre-TAVI coronary artery intervention is, however, still a matter of debate, and ongoing studies will seek to clarify further the role of pre-TAVI coronary intervention (ACTIVATION trial, ISRCTN registry number 75836930).

Balloon aortic valvuloplasty (BAV) as a bridge to TAVI

Figure 2 TAVI (transfemoral and transapical combined) echocardiographic data pre-TAVI, 0–3 months post-TAVI, and 1 year post-TAVI. (A) Mean aortic gradient. (B) Aortic valve area. (C) Paravalvular regurgitation. ■, Severe; ■, moderate; ■, mild; ■, none/trace.
was also commonly performed (48%). Recent experience has shown that BAV is associated with low complications in this setting (1% mortality in stable patients without severely depressed ejection fraction), is useful to categorise patients without a clear-cut indication for TAVI (e.g. symptoms not solely due to aortic stenosis) and is associated with a significant clinical improvement prior to the decision for TAVI being made.18

Intraprocedural and acute management

Although 13% of procedures had a major complication, some of them with more than one simultaneously, none of the patients died during the implantation procedure. Serious complications such as aortic annulus rupture and acute pericardial tamponade were managed by the combined efforts of the procedural heart team. In Germany, a detailed experience of 412 patients showed a 1% incidence of aortic annulus rupture, 5.6% of valve malpositioning, 2.5% of tamponade and 10% of major vascular complications.19 These numbers are very similar to our series, underscoring the complexity of the procedure and the importance of being prepared to deal promptly with these untoward events. In the German experience,19 1.2% of patients received emergency cardiopulmonary bypass. Femoral veno-arterial ECMO was used more frequently in our experience (11% of patients), the difference mainly due to an 8% use of elective ECMO (and only 3% of emergent use). Reasons to provide this support during the TAVI were biventricular heart failure that did not respond sufficiently to inotropes, unrevascularisable coronary artery disease or refractory pulmonary hypertension with poor right ventricular function.

The excellent haemodynamic results obtained with this technology are well-recognised.20 As expected, we found a marked reduction in the aortic valve gradient after the procedure. Importantly, this was accompanied by a very low percentage of significant paravalvular AR, which has been shown to impact the late prognosis negatively.21 Proper sizing of the valve, with multimodal assessment of the aortic root and ascending aorta with CT scan, echo-cardiography and aortography is a critical step to minimise prosthesis mismatch and residual AR.22 In case of moderate or severe AR due to valve malapposition, balloon post-dilatation, weighing the benefits of reducing AR and the greater risk of stroke,23 is a useful tool to improve the immediate result.

<table>
<thead>
<tr>
<th>Table 3 TAVI 30-day postoperative outcomes</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>n = 100</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>All-cause</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Peri-procedural (&lt;72 h)</td>
</tr>
<tr>
<td>Neurological injury</td>
</tr>
<tr>
<td>Disabling</td>
</tr>
<tr>
<td>Non-disabling</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
</tr>
<tr>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>Acute renal failure‡</td>
</tr>
<tr>
<td>New renal replacement therapy</td>
</tr>
<tr>
<td>Vascular complications</td>
</tr>
<tr>
<td>Major</td>
</tr>
<tr>
<td>Minor</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Life-threatening</td>
</tr>
<tr>
<td>Major</td>
</tr>
<tr>
<td>Minor</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Need for PPM</td>
</tr>
<tr>
<td>HLOS (days)</td>
</tr>
<tr>
<td>Early safety†</td>
</tr>
</tbody>
</table>

Figures presented as n (%) and mean ± standard deviation as appropriate. †Defined according to VARC2 criteria. ‡VARC2 acute kidney injury stages 2–3. AF, atrial fibrillation; HLOS, hospital length of stay; PPM, permanent pacemaker; TAVI, transcatheter aortic valve implantation; VARC2, Valve Academic Research Consortium version 2.
Although 11% of patients had VARC2 criteria stage 2 or 3 renal dysfunction after the procedure, this did not impact the short-term mortality and no patient requiring temporary renal support required long-term haemodialysis. In contrast, this follow up might have translated into a rate of pacemaker implantation after the TAVI (13%) higher than the 6.5% previously reported for the Edwards SAPIEN valve.24 The short HLOS is encouraging as these fragile patients might benefit from an early discharge. In a previously published experience of surgical aortic valve replacement in elderly patients at RPAH, the HLOS was 12.5 days,25 markedly longer than the TAVI experience.

The role of experience

Although the importance of experience has been demonstrated by Webb et al., there were no significant differences neither in intraprocedural outcomes nor in acute complications between the first and the second 50 patients of our series. However, three patients died within the 30-day period in the first half compared with zero in the second half of the experience, and there was a nonsignificant trend to more permanent pacemaker implantations in the second 50 patients. We believe this highlights how a new TAVI programme can be successfully initiated on the experience of existing high-volume centres, learning from their achievements and complications in order to avoid a long learning curve. Furthermore, the systematic implementation of a comprehensive training programme that incorporates electronic learning resources, simulators, didactic teaching, case observation and case proctoring with proceduralists from high-volume centres can overcome the initial lack of experience of a given group and allow for the implementation of a successful and safe programme for patients.

Late outcomes

Contemporary patients treated by TAVI represent a frail elderly patient group, often with significant comorbidities. Close follow up by different members of the heart team is often needed and dedicated cardiac rehabilitation programmes are recommended.26 In our series, 30% actively participated in rehabilitation, although it was offered to every patient before discharge.

The 8% mortality achieved by our series is markedly lower than initial experiences, such as PARTNER cohort A.27 In a contemporary experience, the US SAPIEN XT registry presented a 30-day mortality of 7.6%,28 whereas SOURCE ANZ showed a 1-year mortality of 13% for TF and 23% for TA TAVI.7 However, it is worth noting that up to half of the deaths after TAVI are noncardiac in nature, underscoring the frailty of these patients.39 Even when compared with patients from our same institution, the results are favourable. In the surgical aortic valve replacement in elderly patients experience at RPAH, the 1-year mortality was 12%, although the median EuroSCORE was much lower (10.9%).

Limitations

There are several limitations to our study. First, it represents the initial experience of a single centre, with a limited number of patients; therefore, our results are not generalisable to all TAVI procedures. Second, its observational nature does not allow making any conclusions regarding superiority over surgical valve replacement. Last, the follow up is still limited to know long-term valve outcomes and clinical results.

Conclusion

Excellent clinical results can be achieved with the introduction of a TAVI programme for high-risk patients with severe symptomatic aortic stenosis at an Australian institution. A comprehensive patient evaluation and a multidisciplinary approach based on a heart team can overcome most of the difficulties imposed by this challenging population.
The undivided patient: a retrospective cohort analysis of specialty referrals made from inpatient general medical units comparing regional to metropolitan practice

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Abstract

Background: In an era of growing subspecialisation there has been significant research into the role, determinants and outcomes of outpatient referrals but very little on inpatient specialty referrals from general medical units.

Aims: This study aims to describe and compare the rate of specialty referrals from inpatient general medical units in a regional general and a metropolitan tertiary hospital, and review associated outcomes.

Methods: Retrospective cohort analysis of general medical admissions over the 10-week period extending from 28 March to 5 June 2011. Two hospitals were included in the study; West Gippsland Hospital (WGH) and Monash Medical Centre (MMC). For all admissions, details of patient demographics, episode of care and number of inpatient referrals made per admission were extracted from the medical records. Rates and outcomes of inpatient referrals were calculated and compared.

Results: There were 116 admissions to MMC and 108 (107 available for analysis) to WGH during the study period. There were no significant differences in patient demographics between the two sites. However, there were significantly fewer active conditions (2.87 vs 4.01, \(P < 0.01\)), fewer specialty fields represented (2.50 vs 3.51, \(P < 0.01\)) and fewer specialty referrals made per admission at WGH compared with MMC (0.69 vs 1.74, \(P < 0.01\)). The referral rate per diagnosis and the rate of referrals per specialty field represented were significantly higher at MMC compared with WGH (both \(P < 0.01\)).

Conclusion: This preliminary study suggests that patients admitted to rural hospital general medical units have fewer active conditions with fewer specialty referrals made per admission, compared with a comparator metropolitan hospital general medical unit. Further research is required to investigate the reasons for such differences and implications for policy and practice.

Introduction

In the past 40 years there have been significant changes in the delivery of medicine with a move towards increasing subspecialist care.¹⁻³ The Australian Institute of Health and Welfare (AIHW) data from 2004 to 2008 reveal a 13% increase in total specialists/specialists-in-training and a concomitant 8.5% decrease in numbers specialising in general medicine.³⁻⁴ Such a change in culture means that fragmented care is an ever present threat.³⁻⁶ The role of the general physician in maintaining ‘whole person’ or undivided patient care is becoming increasingly recognised.⁵⁻⁷ Past research has shown that there are some conditions where subspecialist care is superior, these include: rheumatoid arthritis⁶⁻¹⁰; acute myocardial infarction⁶; and specific cancer diagnoses¹¹. However, as ageing patients present with increasingly complex and undifferentiated medical conditions the role of general medical units remains central.¹²

As inpatient subspecialty referrals become a routine part of patient care, issues around communication, collaboration, coordination and integration of care are under scrutiny.¹³⁻¹⁴ Both over- and under-referral present dangers; over-referral leading to fragmented care, over-investigation, repeat testing and polypharmacy; under-referral leading to inappropriate, cost-ineffective and potentially dangerous treatment or delays to definitive
Significant research to date has focused on rates of outpatient specialty referrals. Forrest et al. found that one in three patients in the United States and one in seven in the United Kingdom were referred from primary care physicians to (outpatient) specialists each year. Several factors, medical and non-medical, physician-related and patient-related contribute to variations in referrals. Franks et al. found that increasing level of specialisation is associated with increased referral rates. Iverson et al. reported that, after adjusting for confounders, physicians in larger towns and cities were more likely to have higher referrals rates. All of the current research around referral rates, outcomes and determinants relate to outpatient referrals, with no available research on inpatient referrals published to date.

This study reviews inpatient subspecialty referrals from general medicine units and compares referral rates between two major Victorian hospitals (one rural and one metropolitan tertiary teaching hospital) to gain preliminary information concerning rates of inpatient referrals and associated outcomes. This study aims to discover whether the same discrepancies in referral practices exist between metropolitan and rural centres for inpatient referrals, as has been seen in previous studies for outpatients.

**Methods**

This exploratory report analyses admissions to one of the general medical units at both West Gippsland Hospital (WGH) and at Monash Medical Centre in Clayton (MMC) for the 10-week period extending from 28 March to 5 June 2011. This convenience time frame was chosen based on a junior medical staff term rotation and because data for patients admitted to both sites were available for this period. Also, during the study period, the consultants on ward service at both sites were general internal medicine physicians, which helps reduce patient selection bias.

**The setting**

MMC is a 640-bed tertiary teaching hospital located in the South Eastern suburbs of Melbourne. WGH is an 83-bed acute hospital located 98 km south-east of Melbourne. At the time of the study, MMC had five admitting general medical units and onsite access to over 25 subspecialties. In contrast, WGH had two admitting general medical units with access to less than 10 onsite subspecialties, including visiting medical officers (VMO), only two of which had admitting rights. Data were extracted from admissions to one of the general medical units at MMC (Purple) and at WGH (Medical Unit 2) for the study period. Ethics approval was gained from the Human Research and Ethics Committee (HREC) at both hospitals to conduct this research.

**Data collection**

Unit record (UR) numbers were used to identify patients admitted during the reference period. At MMC a list of the patients by UR number was obtained from the inpatient manager (IPM) system; at WGH the list was retrieved from ward lists by one of the researchers (MB) who had worked with the team during the study period. Each admission was given a unique admission ID and data were extracted from the medical record. The data extracted can be considered in three groups: (1) demographics and outcome; (2) medical issues during the admission coded using International Classification of Disease – 10th Revision (ICD-10) coding; (3) referrals made to specialty units.

1. **Demographics and outcome**

   For each admission the following were recorded: patient UR number; age; gender; admission and discharge dates; length of stay; living situation prior to admission; and discharge destination.

2. **Medical issues identified during admission**

   Medical issues identified were extracted using the medical file and ICD-10 coding and grouped as either primary diagnosis (one per admission) or secondary diagnosis (i.e. conditions actively treated during the hospital stay but not the primary reason for admission). Chronic conditions not actively treated during the admission were not recorded. Each medical issue was then classified by subspecialty field (denoted as ‘specialties represented’), regardless of whether a referral subspecialty unit was made. This was done in order to determine the number of subspecialty fields represented per admission and thus give an indication of the breadth of care.

3. **Referrals to subspecialty units**

   Subspecialty referrals during each admission were recorded and categorised as follows: phone advice; inpatient review or procedure; transfer for review; transfer of care; joint care; outpatient review.

   The data extracted were summarised in three tables, one for each group, with the unique admission ID consistent across the tables to allow for analysis.

**Data analysis**

Characteristics of patients admitted to general medicine units at the two sites, as listed above, were compared using t-test for difference in means and Chi-squared for difference in proportions. Further analyses included
summaries of the primary admitting diagnosis for each admission and associated subspecialty fields represented. Comparative analyses of the rate of subspecialty referrals per admission were calculated, and compared between the two sites as a ratio using a two sample t-test with unequal variances. Analysis was done using Excel Analysis ToolPak (Microsoft) along with the VassarStats online computation tool. Results for Table 1 were also verified using the Stata 12 data analysis software. Note that for the purpose of this analysis, each referral to a subspecialty involved in a patient’s care during one admission is recorded as one referral even if the subspecialty represented (0.49 vs 0.27, P < 0.01) (see Table 1). Referrals at MMC resulted in significantly more active conditions treated per admission, with patients at MMC (4.01) having a greater number of active conditions treated compared with those admitted to WGH (2.87), and a greater number of subspecialty fields represented per admission at MMC (3.51 vs 2.50, P < 0.01) having more patients at MMC going directly home (72.60% vs 56.03%). There was a statistically significant difference between the two groups in terms of discharge outcomes (15.52% vs 2.80%, P < 0.01) with more patients at WGH going directly home (72.60% vs 56.03%). There was a statistically significant difference in the number of active conditions treated per admission, with patients at MMC (4.01) having a greater number of active conditions treated compared with those admitted to WGH (2.87), and a greater number of subspecialty fields represented per admission at MMC (3.51 vs 2.50, P < 0.01).

Notably the number of referrals at MMC was significantly higher with more than two and a half times as many referrals per admission (1.74 vs 0.69, P < 0.01). This rate remained significant after correcting for the number of active conditions and specialty fields represented by looking at the ratio of referrals per active condition identified (0.43 vs 0.23, P < 0.01) and referrals per subspecialty represented (0.49 vs 0.27, P < 0.01) (see Table 1). Referrals at MMC resulted in significantly more inpatient reviews (50.78% vs 25.00%), whereas patients

### Table 1: Summary of patient demographics, referrals and outcomes

<table>
<thead>
<tr>
<th>MMC</th>
<th>WGH</th>
<th>Difference and 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total admissions</td>
<td>116</td>
<td>107</td>
</tr>
<tr>
<td>Average patient age</td>
<td>71.6</td>
<td>68.1</td>
</tr>
<tr>
<td>Male : Female ratio</td>
<td>1.04:1</td>
<td>1.02:1</td>
</tr>
<tr>
<td>Average length of stay (days)</td>
<td>8.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Average number of conditions</td>
<td>4.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Average number of specialties represented per admission</td>
<td>3.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Average number of referrals</td>
<td>1.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Number of referrals per active condition</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Number of referrals per specialty represented</td>
<td>0.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Living situation pre-admission

- Home alone (%) | 28.5          | 30.8                                  | −0.02 (-0.15 to 0.10), P = 0.70 |
- Home with others (%) | 55.2         | 62.6                                 | −0.07 (-0.20 to 0.05), P = 0.26 |
- Nursing home (%) | 11.2          | 5.6                                   | 0.06 (-0.02 to 0.13), P = 0.13 |
- Other supported accommodation (%) | 4.3          | 0.9                                   | 0.03 (-0.01 to 0.07), P = 0.11 |
- Overseas (%) | 0.9          | 0.0                                   | 0.09 (-0.08 to 0.03), P = 0.34 |

Discharge destinations

- Deaths (%) | 12.1          | 6.5                                   | 0.06 (-0.02 to 0.13), P = 0.15 |
- Rehabilitation (%) | 15.5         | 2.8                                   | 0.13 (0.05 to 0.20), P < 0.01 |
- Returned home (%) | 56.0          | 72.9                                 | −0.17 (-0.29 to -0.05), P < 0.01 |
- Other supported living (%) | 1.7          | 0.0                                   | 0.02 (-0.06 to 0.04), P = 0.17 |
- Nursing home (1st time) (%) | 4.3          | 5.6                                   | −0.01 (-0.07 to 0.04), P = 0.66 |
- Transferred offsite (%) | 9.5          | 10.3                                 | 0.01 (-0.08 to 0.07), P = 0.51 |
- To other unit onsite (%) | 0.9          | 1.9                                   | 0.01 (-0.04 to 0.02), P = 0.33 |
- Returned home to other unit (%) | 5.2          | 8.4                                   | −0.03 (-0.10 to 0.03), P = 0.33 |

195% confidence intervals and P-values calculated using two-sample t-test for difference in means and Chi-squared test for difference in proportions.

MMC, Monash Medical Centre; WGH, West Gippsland Hospital.

### Results

During the period of 28 March to 5 June 2011, there were 116 admissions under the General Medicine Purple unit at MMC and 108 under the General Medicine 2 unit at WGH. All of the MMC admissions were available for data extraction and all bar 1 of the WGH unit admissions were available for extraction. This left a total of 116 admissions to MMC and 107 to WGH available for analysis.

There was a slight trend to patients being younger at WGH (average age 68.05) compared with MMC (average age 71.62) and a trend towards a shorter length of stay at WGH (7.66 vs 8.58 days); however, neither of these was statistically significant. Likewise, there was no statistically significant difference between the two groups in terms of discharge outcomes (Table 1). Discharge outcomes were fairly similar; however, a significantly higher number of patients from MMC went to rehabilitation post discharge (15.52% vs 2.80%, P < 0.01) with more patients at WGH going directly home (72.60% vs 56.03%). There was a statistically significant difference in the number of active conditions treated per admission, with patients at MMC (4.01) having a greater number of active conditions treated compared with those admitted to WGH (2.87), and a greater number of subspecialty fields represented per admission at MMC (3.51 vs 2.50, P < 0.01).
admitted to WGH were more likely to be seen as outpa-
tients (30.68% vs 11.24%) (see Fig. 1).

Discussion

This study suggests that patients who are admitted to
rural hospitals under a general medical unit have com-
parable demographic characteristics with patients admit-
ted to a metropolitan teaching hospital. Those admitted
rurally appear to have fewer active conditions per admis-
sion and generate significantly fewer inpatient
subspecialty referrals per patient, a finding that remains
consistent after taking the smaller number of active
conditions into consideration. The implications of these
findings are significant when the potential harms of over-
referral are taken into consideration. These include staffing
costs, discharge delay, polypharmacy, deskilling of the
medical workforce and fragmentation of patient care.
This study is underpowered to comment on the relation-
ship between referrals and patient outcomes. However, it
is interesting to note that despite the discrepancies in
referral rates between the two sites, the length of stay and
inpatient mortality rates were not significantly different
between the two sites (see Table 1). This observation
should be further elucidated with subsequent studies. In
considering why such differences in referral rates exist
between a metropolitan and a rural site there are a
number of factors to consider, some of which have pre-
viously been examined. Beaulieu et al. looked at collabo-
ation between generalists, specialists and family
physicians, and identified a trend towards closer interac-
tions between family physicians (general practitioners)
and specialists (physicians) in rural communities espe-
cially where some of them maintain admitting rights,13 as
is the case at WGH. This may in part explain the trend
towards outpatient reviews where the GP often remains
the coordinator of care in rural areas. Auerbach et al.
compared specialty and general medical management of
patients admitted with congestive heart failure and found
that patients admitted under cardiology were younger.10
A similar trend was noted in the medical inpatients study
where younger patients with fewer comorbidities and a
lower likelihood of social factors affecting length of stay
were more likely to be admitted to specialty units as
compared with general medical units.12 This may in part
explain the trend towards younger patients with fewer
active conditions at WGH compared with MMC, where
young, less complex patients are more likely to be admit-
ted directly to specialty units rather than under general
medicine. For example, patients with an acute coronary
syndrome as the reason for admission would not be
admitted under a general medical team at MMC as a
matter of policy and are therefore more likely to be
admitted under the cardiology unit. Such cases present-
ing to WGH are, however, admitted under general med-
cine and are then usually referred for post-discharge
specialist follow-up or transferred to an offsite cardiology
unit. Similarly, patients admitted under the general

Figure 1 Referral outcomes by percentage. Error bars indicate the 95% confidence inter-
val, calculated using Chi-squared test through VassarStats.22 ( ), MMC; ( ), WGH.
medical team at MMC are by policy those patients who are not accepted for admission under subspecialty units. This means that patients admitted under MMC are a potentially biased sample. In addition to these potential factors, there is the possibility that the increased inpatient referral rate in the metropolitan hospital setting stemmed partially from availability of subspecialists. This raises an important question ‘Do we refer because we can, even when we may not need to?’ Another possibility to explain increased referrals in metropolitan hospital settings is the fear of medicolegal ramifications if a patient is not referred. Anecdotally, patients living rurally may accept receiving more general medical care, even for their subspecialty-related issues, whereas there is a possible perception that patients living in the urban settings expect subspecialty level care for all of their medical issues, leading to a reactive increase in subspecialty referral rates. Caution should be exercised in the interpretation and generalisation of these findings as this is a preliminary study comparing only two hospitals. This initial analysis only considers the broad trends without adjusting for individual comorbidities and without matching cases. The demographic similarity of the two groups belie the potential operation of a multitude of other factors affecting the number of comorbidities and the likelihood of referral, including lifestyle, relationship to general practitioner and past medical history.

Several observations regarding limitations in data collection should be noted. First, the data in this study were extracted and categorised by a single researcher who was not blinded as to the site of the admission. This introduces a potential for bias in classification and data collection. Second, allied health consultations were not included as referrals in this analysis. This is because anecdotal evidence suggests that access to allied health is relatively consistent across both the hospitals. Third, in the allocation of active conditions to subspeciality field, delirium was characterised under neurology or psychiatry depending on the nature and progress of the presentation. However, delirium has a multifactorial pathogenesis in most cases and the attribution of causation to one organ system is not particularly useful. Fourth, WGH does not have an intensive care unit on site so referrals to intensive care would mandate a hospital transfer. Fifth, Aged Care Assessments and assessments by the Rehabilitation and Aged Liaison Services (RALS) were not included in this analysis. An equivalent multidisciplinary service is provided at both hospitals; however, at the time of data collection; at MMC this service includes an assessment by a geriatrician, whereas at WGH it did not. Last, for the purposes of analysis general and upper gastrointestinal surgery were considered together as these are only offered as separated subspecialties at MMC, whereas at WGH the general surgical team provides upper gastrointestinal surgical management also.

**Conclusion**

Despite the noted limitations, this study provides useful information to inform further research and clinical practice. Further research and analysis is required to investigate the reasons for such differences in subspecialty referral rates including an examination for potential availability bias and fear of litigation, and the implications for policy and clinical practice. Analysis on matched cases may be helpful to elucidate further this using mixed qualitative and quantitative methods.

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Effect of hospital-based telephone coaching on glycaemic control and adherence to management guidelines in type 2 diabetes, a randomised controlled trial

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Key words
diabetes mellitus, type 2, diabetes complication, guideline adherence, randomised controlled trial, patient education.

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Abstract
Background: Failure to achieve treatment targets is common among people with type 2 diabetes. Cost-effective treatments are required to delay the onset and slow the progression of diabetes-related complications.

Aims: This study aimed to measure the effect of a 6-month telephone coaching intervention on glycaemic control, risk factor status and adherence to diabetes management practices at the intervention’s conclusion (6 months) and at 12 months.

Method: This randomised controlled trial recruited 94 adults with type 2 diabetes and an HbA1C > 7% from the Diabetes Clinic of St Vincent’s Hospital Melbourne. People who were non-English speaking, cognitively impaired, severely hearing impaired or without telephone access were excluded. Participants were randomised to receive usual care plus 6 months of telephone coaching focusing on achieving treatment targets and complication screening, or usual care only. The primary outcome was HbA1C at 6 months; secondary outcomes included other physiological and monitoring measures.

Results: Significant interaction effects were observed between group and time at 6 months, demonstrating improvement in HbA1C, fasting glucose, diastolic blood pressure and physical activity. The intervention’s effect on these parameters was not sustained at 12 months. Intervention group participants also improved compliance with foot examination and pneumococcal vaccination by 6 months and retinal screening by 12 months.

Conclusions: Telephone coaching improved glycaemic control and adherence to complication screening in people with type 2 diabetes, for the duration of its delivery, but these effects were not maintained on withdrawal of the intervention. Strategies that assist patients to sustain these benefits are required.

Introduction

Australian guidelines regarding type 2 diabetes (T2DM) management emphasise risk factor modification, complication screening, early treatment and self-care activities.1 Despite this, failure to achieve treatment targets and poor adherence to diabetes management practices are widely reported.2-4 Cost-effective interventions that improve diabetes management are required to prevent or delay diabetes-related complications and reduce healthcare costs.

Communication technologies such as the internet and telephone are recognised as potentially effective, cost-effective platforms for healthcare delivery.3 The convenience afforded by the telephone, enabling frequent contact between patients and clinicians, at a place of the patient’s choosing and at potentially low cost, may improve healthcare access. While several studies have investigated the effect of telephone coaching in participants with diabetes, reporting between-group, post-intervention differences in HbA1C of −0.4 to −1.3%,6-8 few Australian studies exist.9,10 Among these, one was non-randomised;10 neither measured glycated haemoglobin (HbA1C),9 and neither recruited participants from...
public hospital clinics where a higher prevalence of complications might be expected.\textsuperscript{11}

A key question that remains unanswered is the extent to which intervention effects are maintained in the post-intervention period. Determining this is crucial, as sustained improvements in glycaemic control and cardiovascular risk factors are needed to affect clinical endpoints.\textsuperscript{12} Determining the longevity of intervention effects may also influence decisions concerning follow up and support in the post-intervention period, the provision of which might facilitate the maintenance of intervention gains.\textsuperscript{13}

This study sought to address this question, comparing with usual care, the effects of a 6-month telephone coaching intervention on glycaemic control, risk factor status and adherence to self-care and monitoring requirements, both at the intervention’s conclusion (6 months), and in the post-intervention period (12 months).

**Methods**

This randomised controlled trial was approved by the St Vincent’s Human Research Ethics Committee.

**Participants**

A convenience sample of 94 participants was recruited over 13 months, from the Diabetes Clinic of St Vincent’s Hospital Melbourne (STV), an Australian public teaching hospital. The principal researcher (JV) approached eligible patients (adults with T2DM and HbA1C >7%) in the diabetes clinic. Patients who were unable to provide informed consent, non-English speaking, cognitively impaired, receiving palliative care, severely hearing impaired or without telephone access were excluded. The mean (95% confidence interval (CI)) age (years) of patients attending the diabetes clinic in the recruitment period was 64.1 (63.2 to 65.0). Fifty-nine per cent were male and 29% required an interpreter.

**Randomisation**

A researcher, not involved in recruitment, randomised participants into intervention and control groups. Computer-generated block randomisation was undertaken to obtain a one-to-one balanced design. Allocation blinding was maintained until randomisation, after which participants and the principal researcher were informed of randomisation outcome.

**Intervention**

In addition to usual diabetes care, intervention group participants received 6 months of telephone coaching, delivered by a dietitian with experience in cardiovascular disease and T2DM (JV). Initial coaching sessions occurred within 2 weeks of randomisation and subsequent sessions occurred approximately monthly. Coach session duration was flexible, determined by time required to establish participant goals. Typically, initial and follow-up sessions took 45 and 20 min respectively. Intervention group participants received 6.0 (95% CI 5.5–6.5, range 4–9) coaching sessions. Advice given in coaching sessions was consistent with Australian guidelines. During initial coaching sessions, a diet history was taken. Participants were encouraged to follow a low saturated fat, high-fibre diet, with 50% of energy from carbohydrates,\textsuperscript{1} and were encouraged to exercise for 150 min per week.\textsuperscript{1} Risk factor status and adherence to monitoring requirements were based on information collected at baseline. For treatment goals and risk factors not at target levels, the dietary, lifestyle and medication changes required to improve these parameters were discussed. The coach delivering the intervention did not prescribe medication, therefore, participants were advised to discuss medication changes with their general practitioner (GP). Discrepancies between participants’ adherence to self-care activities (diet and physical activity) and monitoring requirements (foot checks, eye checks and vaccinations) were highlighted and the appropriate management schedule was explained. Participant goals were then agreed, be this a change in diet or a podiatry appointment for an overdue foot examination. Following each coaching session, the participant and their GP received a letter summarising the participant’s goals.

During subsequent coaching sessions, progress towards treatment goals, risk factor status, adherence to self-care and monitoring requirements were reassessed. If goals were not achieved, barriers to goal attainment were identified, an action plan addressing these barriers was agreed and new goals were established. This process was repeated throughout the intervention.

**Control group**

Controls did not receive the telephone coaching intervention, or any contact from the researchers, with the exception of telephone calls to arrange baseline, 6- and 12-month assessment appointments. Control group participants could access STV usual care services, including a diabetes clinic staffed by endocrinologists, diabetes educators and dietitians. STV patients typically attend the diabetes clinic 3–6 monthly, with GP visits occurring at the patient’s discretion.

**Outcomes**

The primary outcome was HbA1C at 6 months, adjusted for baseline value. Secondary outcomes included adjusted
mean HbA1C at 12 months, as well as 6- and 12-month-adjusted mean fasting glucose, lipids, blood pressure (BP), weight, waist circumference, body mass index, physical activity and Kessler Psychological Distress Scale score. Participants were asked researcher-generated questions to determine adherence to guidelines recommending annual foot examinations, biennial eye examinations, annual influenza vaccinations, pneumococcal vaccination every 5 or 10 years and smoking cessation. The content validity of these questions was established using Lynn’s method, prior to their inclusion in the study protocol. Self-reported data were validated with medical record data for adherence measures, except eye examinations. The New Zealand Physical Activity Questionnaire was used to measure self-reported physical activity. Participants self-reported their year of diabetes diagnosis. The name, dose and frequency of prescribed medications were recorded using the participant’s medication list.

Participants were withdrawn from the study on their request, if they were non-contactable for over 6 weeks during the intervention period or if they did not attend 6- or 12-month assessments.

Statistical methods

United Kingdom Prospective Diabetes Study (UKPDS) data informed our sample size, using a between-group difference in HbA1C of 1%. Ninety-four participants were required to detect a significant between-group difference, with alpha at 0.05 (two-tailed) and 80% power, with equal variance assumed, a standard deviation of 1.5 and a 20% attrition rate. Analyses of quantitative data were undertaken using Statistical Package for the Social Sciences (SPSS version 20.0, SPSS, Chicago, IL, USA). Primary analyses used linear mixed models (LMM) to assess the effect of group, time and the interaction of group and time on continuous variables. Unless otherwise specified, data are presented as mean (95% CI).

LMM was selected as the primary method of analysis because it deals well with missing data. LMM allow covariates to be controlled for, providing a robust estimate of treatment effects. The baseline value of each risk factor was used as a covariate. This enabled adjustment of 6 and 12 month values according to baseline values, thereby controlling for baseline imbalances that may have influenced 6 and 12 month values.

Sensitivity analyses of change scores were conducted using independent samples t-tests, to test the extent to which inferences made from the LMM output were robust to a different analysis method.

Secondary analyses involved making between-group comparisons of raw continuous data, using independent samples t-tests. Chi-squared and Fisher’s exact tests were used to make between-group comparisons of categorical variables.

Bivariate correlations were used to examine relationships between glycaemic control and physical activity, weight and waist circumference.

Results

Baseline characteristics

Figure 1 describes the number of participants screened, excluded, randomised and completing the study. Study participants differed from the population attending the diabetes clinic in the recruitment period, being younger 61.4 (59.2–63.5) versus 64.1 years (63.2–65.0, \( P = 0.02 \)), and being less likely to require an interpreter, 0% versus 29%, \( P < 0.001 \), reflecting the study’s inclusion criteria.

Seventy-six per cent of participants completed the trial (Fig. 1). Loss to follow-up rates were comparable between the groups, and completers and non-completers had similar baseline demographic characteristics and risk factor status.

Among all participants at baseline, mean diabetes duration was 12.9 years (11.1–14.5); mean HbA1C was 8.3% (8.1–8.6) and 57% were insulin treated. The groups were balanced at baseline in terms of risk factor status and adherence to guidelines recommending foot screening, eye screening, vaccinations and smoking cessation. The intervention group participants were predominantly Caucasian; the control group had a significantly different ethnic mix with more non-Caucasian participants (Table 1).

Outcomes

A significant interaction effect was observed at 6 months for HbA1C (\( P = 0.03 \)), fasting glucose (\( P = 0.02 \)), diastolic BP (\( P = 0.03 \)) and physical activity (\( P = 0.02 \)); however, these effects disappeared by 12 months. By 6 months, proportionally more intervention group participants were compliant with foot screening, 34 (90%) versus 27 (63%), \( P = 0.005 \), and pneumococcal vaccination, 26 (68%) versus 13 (30%), \( P = 0.001 \). Among participants non-compliant with eye screening requirements at baseline (\( n = 10 \)), more intervention group participants became compliant by 12 months, 5 (100%) versus 1 (20%), \( P = 0.05 \). No other between-group differences were detected (Table 2).

The sensitivity analysis confirmed findings from the primary analysis. Between baseline and 6 months, the intervention group experienced a greater mean (95% CI) change in adjusted HbA1C than the controls: \(-0.8 (-1.2 \text{ to } -0.3)\) versus \(-0.3 (-0.6 \text{ to } -0.0)\). \( P = 0.02 \).

Sensitivity analyses of change scores were conducted using independent samples t-tests, to test the extent to which inferences made from the LMM output were robust to a different analysis method.

Secondary analyses involved making between-group comparisons of raw continuous data, using independent samples t-tests. Chi-squared and Fisher’s exact tests were used to make between-group comparisons of categorical variables.

Bivariate correlations were used to examine relationships between glycaemic control and physical activity, weight and waist circumference.

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to −0.3) versus 0.2 (−0.6 to 0.3) percentage points, \( P = 0.03 \). This effect was not apparent between baseline and 12 months.

The proportion of intervention and control group participants who had new oral hypoglycaemic agents added or a dosage increase was similar, 7 (15%) versus 5 (11%, \( P = 0.54 \)) and 6 (13%) versus 5 (11%, \( P = 0.75 \)) respectively. The proportion of participants who commenced insulin and/or whose dose increased was identical between groups, 2 (4.3%) and 11 (23%), respectively. A negative correlation was observed between change in HbA1C (baseline to 6 months) and change in physical activity among all participants, \( r = -0.23, P = 0.02 \). Similarly, a negative correlation was observed between HbA1C and absolute 6-month physical activity which just failed to reach statistical significance, \( r = -0.21, P = 0.07 \). No correlation was observed between HbA1C and weight or HbA1C and waist circumference.
Discussion

Our findings support and extend those of previous telephone coaching studies conducted among people with T2DM. Consistent with existing research,6–8 the intervention contributed to improvements in glycaemic control, with HbA1C levels 0.8% lower among intervention group participants at 6 months. This was accompanied by improvements in BP, physical activity and adherence to complication screening.

The improvement in glycaemic control at 6 months was similar to that observed with many lifestyle and drug interventions.18–20 For instance, a meta-analysis of dietary interventions found that these contributed to a 0.5% between-group difference in mean, post-intervention HbA1C,18 while meta-analyses of exercise interventions have found reductions in HbA1C of up to 0.8%.20 Second- or third-line “add-on” oral hypoglycaemic agents, such as dipeptidyl peptidase 4 inhibitors, contribute to between-group differences in mean, post-intervention HbA1C of up to 0.7%.19

We identified no between-group differences in the initiation or titration of glycaemic lowering medications to account for improvements in glycaemic control. Therefore, it is likely that the intervention’s effect was attributable to lifestyle changes made by participants, both physical activity and dietary modification known to contribute to sizeable reductions in HbA1C.18,20 This is supported by our finding of a negative correlation between HbA1C and physical activity, suggesting that as some participants exercised more, they experienced a concomitant improvement in glycaemic control. Although dietary

### Table 1 Comparison of demographic characteristics, unadjusted mean risk factor levels and compliance with monitoring requirements among intervention versus control group participants at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>Intervention (n = 47)</th>
<th>Control (n = 47)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 (56–62)</td>
<td>64 (61–66)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>12.6 (10.2–15.0)</td>
<td>13.1 (10.7–15.6)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 34 (72%)</td>
<td>30 (64%)</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Female 13 (28%)</td>
<td>17 (36%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>Caucasian 46 (98%)</td>
<td>37 (79)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Asian/Indian 1 (2%)</td>
<td>8 (17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afro-Caribbean 0 (0)</td>
<td>2 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factor status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>8.2 (8.0–9.7)</td>
<td>8.5 (8.1–8.9)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>8.9 (8.0–9.7)</td>
<td>9.9 (8.8–10.9)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.1 (3.9–4.4)</td>
<td>4.5 (4.1–4.9)</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.3 (2.1–2.5)</td>
<td>2.4 (2.1–2.7)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.1 (1.0–1.2)</td>
<td>1.2 (1.1–1.2)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.9 (1.6–2.2)</td>
<td>2.0 (1.6–2.4)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>140 (134–145)</td>
<td>134 (128–140)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80 (76–84)</td>
<td>76 (72–79)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>90.9 (85.8–95.9)</td>
<td>86.5 (81–92)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.1 (30.3–33.9)</td>
<td>30.9 (29.1–32.6)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>111 (107–116)</td>
<td>107 (103–111)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Physical activity (mins per week)</td>
<td>145 (88–202)</td>
<td>116 (61–172)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Depression score (K10 score/50)</td>
<td>17 (14–19)</td>
<td>20 (18–23)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Compliance with monitoring requirements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foot examination, n (%)</td>
<td>25 (53)</td>
<td>29 (62)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Eye examination, n (%)</td>
<td>39 (83)</td>
<td>41 (87)</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Influenza vaccination, n (%)</td>
<td>24 (51)</td>
<td>31 (66)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal vaccination, n (%)</td>
<td>16 (34)</td>
<td>12 (26)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Smoking cessation, n (%)</td>
<td>42 (89)</td>
<td>39 (83)</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Glucose lowering medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin, n (%)</td>
<td>25 (53)</td>
<td>29 (62)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Sulphonylureas, n (%)</td>
<td>28 (60)</td>
<td>19 (40)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Metformin, n (%)</td>
<td>31 (81)</td>
<td>33 (70)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>10 (21)</td>
<td>9 (19)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

All results given as mean (95% CI) unless otherwise specified. Values in bold are statistically significant (P < 0.05). BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; K10, Kessler Psychological Distress Scale; LDL, low-density lipoprotein.
Variables 6 months 12 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Difference (P-value)</th>
<th>Group × time (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>7.7 (7.4 to 8.1)</td>
<td>8.5 (8.1 to 8.8)</td>
<td>-0.8 (-1.2 to -0.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>8.5 (7.7 to 9.4)</td>
<td>9.9 (9.1 to 10.7)</td>
<td>-1.4 (-2.5 to -0.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fasting cholesterol (mmol/L)</td>
<td>4.1 (3.9 to 4.4)</td>
<td>4.4 (4.1 to 4.6)</td>
<td>-0.2 (-0.6 to 0.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>Fasting LDL cholesterol (mmol/L)</td>
<td>2.2 (2.0 to 2.4)</td>
<td>2.4 (2.2 to 2.6)</td>
<td>-0.2 (-0.5 to 0.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>Fasting HDL cholesterol (mmol/L)</td>
<td>1.1 (1.1 to 1.2)</td>
<td>1.6 (1.1 to 1.22)</td>
<td>-0.1 (-1.0 to 0.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Fasting triglyceride (mmol/L)</td>
<td>2.0 (1.7 to 2.2)</td>
<td>2.0 (1.8 to 2.2)</td>
<td>0 (-0.4 to 0.3)</td>
<td>0.88</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>130 (126 to 135)</td>
<td>135 (131 to 140)</td>
<td>-5 (-11 to 1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>74 (71 to 77)</td>
<td>79 (76 to 81)</td>
<td>-5 (-9 to 1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.1 (86.8 to 89.3)</td>
<td>88.9 (87.7 to 90.1)</td>
<td>-0.8 (-2.5 to 0.9)</td>
<td>0.33</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.4 (30.9 to 31.9)</td>
<td>31.7 (31.3 to 32.2)</td>
<td>-0.4 (-1 to 0.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>108 (107 to 110)</td>
<td>110 (108 to 111)</td>
<td>-2 (-3 to 0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Physical activity (mins per week)</td>
<td>183 (143 to 223)</td>
<td>119 (81 to 156)</td>
<td>65 (10 to 120)</td>
<td>0.99</td>
</tr>
<tr>
<td>K10 depression score (score/50)</td>
<td>18 (16 to 20)</td>
<td>18 (16 to 19)</td>
<td>0 (-2 to 2)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Values in bold are statistically significant (P < 0.05). BMI, body mass index; BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2: Between-group comparison of mean (95% CI) risk factor values at 6 and 12 months using linear mixed model analysis which adjusts for baseline value

Despite an initial estimate of the intervention's benefits, further follow-up periods, enabling an assessment of the longer-term maintenance of intervention benefits, is necessary. This finding is consistent with previous telephone coaching trials.8,9,25–27 While completers and non-completers had similar baseline risk factors, participants who continued with treatment had better maintenance outcomes. Limitations include the loss to follow-up and the use of a usual care control group. Furthermore, while completers and non-completers had comparable baseline characteristics, reasons for attrition were not collected. Attrition may be related to participant motivation or desire to maintain lifestyle changes. Accordingly, evidence suggests that participant motivation is important in achieving sustained disease outcomes in T2DM.21 According to a systematic review, relatively few lifestyle intervention are transient in people with T2DM.21 While improvements were observed in HbA1C and other parameters, improving disease outcomes is continuous and requires long-term follow-up. Maintaining encouragement and support is important in achieving sustained disease outcomes. Our study extended the telephone coaching intervention to a longer-term maintenance period (35%). Such maintenance periods are critical for diabetes prevention and control. While improvements were observed in HbA1C and other parameters, improving disease outcomes is continuous and requires long-term follow-up. Maintaining encouragement and support is important in achieving sustained disease outcomes. Our study extended the telephone coaching intervention to a longer-term maintenance period (35%).
of group assignment influenced outcomes through favourable expectations associated with randomisation to the intervention group. The study did not determine physiological mechanisms that mediated the intervention’s effects, because neither dietary change nor medication adherence records were collected. However, given data suggesting that interventions which improve medication adherence contribute to only marginal improvements in clinical outcomes, it is not considered likely that this was an important factor driving the intervention’s effect. Finally, our reliance on self-reported data may have contributed to inaccuracies owing to recall bias.

The intervention was delivered by a single person, to participants recruited from one site. To ensure generalisability, a multicentre trial is needed. Having excluded non-English speaking patients, a similar trial among non-English speaking participants may be considered a future research priority, particularly given Australia’s ethnically diverse population and the increased prevalence of T2DM among non-Caucasians.

Conclusion

Telephone coaching is an effective treatment for Australians attending tertiary referral centres for management of their poorly controlled T2DM, contributing to improvements in glycaemic control and adherence to complications screening. Given that intervention effects diminished with the intervention’s withdrawal, cost-effective strategies to facilitate the maintenance of intervention gains are required if disease outcomes are to be affected.

References


22 Bandura A, Adams NE, Beyer J. Cognitive processes mediating...
Use of ‘rainy day’ autologous haemopoietic stem cells: a single-institution experience over 10 years

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Key words
stem cell transplantation, haematological malignancies, haematopoietic transplantation, autologous transplantation, rainy day.

Abstract
Background: High-dose chemotherapy and autologous haematopoietic stem cell transplantation is an important therapeutic modality in the treatment of many haematological malignancies. Generally, stem cells are collected close to the time of the transplant, but an alternative is to collect and cryopreserve cells at an early stage of the illness so they are available for later use (‘rainy day harvesting’). Although this practice has been commonplace in Australia, there is little evidence to document eventual use of cells collected in this manner.

Methods: We conducted an audit of indications for and eventual transplantation of ‘rainy day’ harvests performed at our institution over a 10-year period.

Results: Although there was some variation across different disease groups, we found that only 14% of cells were transplanted. The median delay to transplantation was 19 months.

Conclusion: Together with recent advances in stem cell mobilisation techniques, results from this audit suggest that the practice may not be an effective use of limited health resources.

Introduction
High-dose therapy and autologous haemopoietic stem cell (AHSC) transplantation is an important therapeutic modality in the treatment of many haematological malignancies. The administration of myeloablative chemotherapy is followed by the transplantation of AHSC in order to reconstitute haemopoiesis. This type of treatment affords the possibility of cure in relapsed aggressive non-Hodgkin lymphoma1 and Hodgkin lymphoma,2,3 and improved progression-free survival and overall survival in follicular lymphoma4 and multiple myeloma.5,6

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Diabetes telephone coaching study

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A ‘rainy day’ harvest refers to the collection of AHSC for long-term storage. These cells are reserved for transplantation in the event of disease relapse in the future, that is, they are put away for a ‘rainy day’. A rainy day harvest (RDH) is performed early in the disease course, usually when a patient has achieved a remission after induction therapy. There are theoretical reasons why this may be desirable. The chance of a successful harvest may be maximised if performed early in the disease course. Risk factors for mobilisation failure have been well described, and include extensive prior chemotherapy and exposure to stem cell toxic agents such as fludarabine. Cells collected at an earlier harvest when the patient is in remission after treatment may be less likely to be contaminated by disease. Reinfusion of disease-contaminated stem cells may be the cause of relapse in some patients.

There are many reasons why performing an AHSC harvest must be a carefully considered decision, and the process is not without risk. Stem cell mobilising agents such as filgrastim may cause morbidity, such as bone pain. Good vascular access is necessary, and in some patients central venous access is required. During the apheresis process, fluid shifts and electrolyte disturbance (particularly hypocalcaemia) with associated cardiovascular instability may occur. Thrombocytopenia and infection are further possible complications. Although specific Australian figures are not available, international literature confirms that AHSC harvests are costly and resource-intensive. A further consideration is the limit on storage space for stem cells in some centres as the cells must be preserved in liquid nitrogen tanks.

The collection of ‘rainy day’ AHSC has been common in Australia. In New South Wales (NSW) in 2008, the harvest to transplant ratio was estimated at 3:2, with 1700 autologous stem cell harvests reported to be in storage in eight stem cell laboratories at that time. However, there is a distinct lack of published evidence to support this practice and little evidence to document eventual use of ‘rainy day’ AHSC. Despite theoretical benefits, there is also no evidence to support the proposition that patients have improved clinical outcomes using stem cells harvested in this manner (rather than those that are collected at the time of relapse, or in second or later remission). Recognising the paucity of data in this area, in 2008, a survey of transplant physicians from the Bone Marrow Transplant Network of New South Wales was conducted. The physicians were asked whether they would perform an RDH in certain clinical scenarios. From these responses, authors developed disease-specific consensus guidelines as to when an RDH should be performed. These published guidelines are based on physician experience and a general consensus, and are not substantiated by formal analysis.

We sought to investigate the eventual use of stem cell products collected for ‘rainy day’ indications, as well as to determine the length of delay between collection and subsequent transplantation for different indications (which has implications for duration and cost of storage). We also sought to document the outcomes of autologous transplantations performed using ‘rainy day’ stem cell products.

Methods

This was a retrospective audit of RDH at the Royal Hobart Hospital (RHH) from 1 January 2001 until 31 December 2010. The Statewide Bone Marrow Transplant Service at the RHH maintains a comprehensive database with extensive details about all patients who have stem cells collected and transplanted. RDH was defined as the collection of stem cells where transplantation was not anticipated in the following 6 months.

Most patients who received a transplant more than 6 months after collection were deemed to have had rainy day transplants. A small number of patients had a transplant 6–9 months after collection. These cases were reviewed as to physician intent in regard to transplantation at the time of collection. In some patients, the intent of the collection was for immediate use and, for varying reasons, reinfusion was delayed past 6 months. These patients were not considered to have had an RDH.

Information collected included patient age at collection, disease, time until transplant, time until platelet and neutrophil recovery and survival. The disease categories considered were multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and its subtypes, Hodgkin lymphoma (HL), acute lymphoblastic leukaemia, acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), myeloproliferative disorder (MPD) and myelodysplastic syndrome. For all of these indications, with the exception of MM, the aim was to collect sufficient stem cells for a single transplant. For transplant-eligible patients with MM, it is our standard practice to collect sufficient stem cells for two transplants (four million CD34/kg). Only those MM patients whose first transplant was performed with a delay of greater than 6 months were included in the ‘rainy day’ group.

Results

During the audit period, 532 collections occurred in 474 patients for haematological malignancies. A total of 342 collections occurred for rainy day indications (Fig. 1). Overall, 72% of the patients in our database were collected with the intent of long-term storage rather than
immediate transplant. The median follow-up of patients who had a ‘rainy day’ collection was 55 months (range 0–128 months). Of the 342 patients who had an RDH, 48 had been transplanted as of 30 June 2012. This gave an overall transplantation rate of 14%.

Figure 2 shows the proportion of transplants resulting from rainy day collections for different indications. MM gave the highest overall rate of transplantation, with 12 transplants occurring in 44 patients (27%). Three patients with MM had two autologous transplants, two after relapse occurred and one to consolidate response to the initial transplant. The remaining nine patients had a single transplant. The reasons why they did not receive a second transplant included death for two patients and insufficient cells for two patients. Five patients are still alive and have not required a second transplant. We did not include in our rainy day group another 65 patients with MM who had stem cells collected and underwent high-dose therapy and autologous transplantation within 6 months. Of this group, 22 (34%) underwent a second transplant that comprised 17 tandem transplants and five delayed transplants.

HL was the indication for RDH in 41 patients, and six patients were eventually transplanted (15%). NHL had the highest number of both collections (203) and transplants (28), with an overall transplantation rate of 14%. Very few transplants resulted from patients collected for MPD (1/21, 5%) or AML (1/20, 5%). There were no transplants resulting from collections for CML.

The NHL group was further classified according to histopathological subtype. Follicular lymphoma (FL) comprised the largest group of rainy day collections (92) with a transplant rate of 8%. The second largest group was diffuse large B cell lymphoma (DLBCL) (55 collections) with a transplant rate of 20%. T-cell lymphoma represented the indication for 17 RDH, and there were four transplants in this group (24%). There were small numbers of collections and transplants for other types of lymphomas (Fig. 3).

The median time from collection to transplantation was 19 months, ranging from 7 to 113 months. Specified optimal time limits for engraftment were set as 21 days for platelets (>20/nL) and 14 days for neutrophils (>0.5/nL). A total of 77% of patients engrafted within these limits. The median time to neutrophil engraftment (>0.5/nL) was 10 days (range 9–18 days). The median time to

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Figure 1 Underlying disease of patients who underwent a rainy day collection. Total number of collections was 342. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; MM, multiple myeloma; MPD, myeloproliferative disorder; NHL, non-Hodgkin lymphoma.

Figure 2 Proportion of ‘rainy day’ high-dose therapy and autologous haematopoietic stem cell collections that have resulted in transplantation. Non-Hodgkin lymphoma (NHL) (143), multiple myeloma (MM) (27%), Hodgkin lymphoma (HL) (15%), myeloproliferative disorder (MPD) (53), acute myeloid leukaemia (AML) (51), acute lymphoblastic leukaemia (ALL) (5), chronic myeloid leukaemia (CML) (5). Not transplanted. Transplanted.
platelet engraftment (>20/nL) was 13 days (range 9–44 days). Compared with our upfront transplantation group, there was no difference in the time to neutrophil or platelet engraftment (P > 0.05, Student’s unpaired t-test).

Of the 296 patients who had RDH that have not been transplanted, 255 (86%) are still alive. The reason for the lack of use of ‘rainy day’ stem cells was death for 41 patients (14%). For the remainder, the most common reason for lack of use was disease remission/stability. Unfortunately, it was not possible to determine from our database how many were not transplanted due to change in eligibility for transplantation. Of the 48 patients who were transplanted, 26 (54%) are still alive.

Discussion

This audit of eventual transplantation of RDH at a tertiary institution provides important insights into the utility of this practice. Over a 10-year period, the overall rate of transplantation of RDH was 14%. This rate varied depending on disease indication, and not surprisingly was highest for MM (27%) where upfront high-dose therapy and autologous stem cell transplantation is typically performed in eligible younger patients, and most clinicians will store adequate cells for a second transplant if required. Thirty-four per cent of patients who received an upfront transplantation for MM during the same time frame of our audit went on to receive a second transplant.

In NHL, the overall rate of transplantation was 14%. The rate of transplantation was higher for DLBCL (20%); however, the utility of these pre-emptive collections may be questioned for two reasons: first, with improved outcomes as a result of immunochemotherapy approximately two thirds of patients will be cured with frontline therapy; second, the CORAL study demonstrated that 90% of patients with relapsed DLBCL had a successful stem cell collection after salvage chemotherapy.

The majority of RDH in NHL were for FL. There is little international literature to document the frequency of this practice. In Australia, this practice has anecdotally been widespread but varies between institutions. A survey of NSW transplant physicians in 2008 found that 68% of respondents agreed with the collection of autologous stem cells in first molecular remission of FL in transplant-eligible patients. Furthermore, they predicted that the eventual utilisation rate would be high given the relapsing nature of FL and the role of autologous transplantation in consolidation of a second remission. However, results of our audit show a transplant rate in this group of only 8%. This may increase as patients continue to relapse over time, particularly given that 86% of the patients who have not been transplanted are still alive. At the time of this audit, the median time for storage in this group is 66 months.

Our findings are in keeping with a recent audit performed by the Mayo group who found that utilisation rates of RDH in FL were similarly low at 10 years. They concluded that routine collection and storage early in the disease course is not recommended. Given that current immunochemotherapy in FL is highly effective with median remission duration of first-line therapy in excess of 5 years, it is clear that the majority of cells would need to be stored for long periods for the small number of patients who will eventually use them. Given that the median age of diagnosis of FL is in the sixth decade it is conceivable that transplant eligibility may change from collection to the time of second or subsequent relapse. In addition, with improved mobilisation techniques, such as the use of the CXCR4 antagonist plerixafor, there is a high efficacy of collection of cells at the time of relapse, reported to be as high as 97% by some groups. Thus, the utility of RDH for all patients with FL in first remission is questionable. There may be a role in a very young patient for whom no sibling donor is identified, although this would clearly come at a significant cost given the large numbers needed to treat and the long storage times involved.
In HL, approximately 15% of collections were eventually used. In advanced HL, treatment with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) results in event-free survival of approximately 71% at 7 years.17 Thus, a significant proportion of patients treated with ABVD will progress and require salvage chemotherapy, followed by high-dose chemotherapy and autologous transplantation. With intensified approaches, such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), fewer patients will progress.17 Our study showed that 85% of pre-emptive collections are not used, suggesting that the collection of cells at the time of relapse is likely to be a preferable strategy. While there may be concerns about a higher incidence of failed mobilisation after therapy such as BEACOPP, published evidence does not appear to bear this out, with the German group reporting on mobilisation experience in a cohort of 105 patients with relapsed HL of whom 33% had received BEACOPP. In this study, 97% of patients could be mobilised after salvage therapy.18

Several indications showed very low rates of eventual transplantation, including acute leukaemias, MPDs and CML. This is not surprising given the limited role of autologous transplantation in these settings. There were very few collections from patients with CML and no transplants resulting from these collections. Although a high proportion of physicians in the NSW survey reported in 2008 agreed with an RDH for a young patient with CML in major molecular response without a sibling donor,10 the rapid rate of therapeutic advance in this area over the last decade has rendered this practice obsolete.

As our database does not systematically capture adverse events, we were not able to quantify the risks of RDH. Although many patients are being mobilised from chemotherapy given for their underlying disease, in some cases additional chemotherapy was given expressly for the purpose of mobilisation. Complications can result from the effects of chemotherapy, granulocyte colony stimulating factor (G-CSF) administration, as well as those of central venous catheters and leukapheresis.

Costs to the health system of this considerable activity are clearly substantial and accrue at several levels, including nursing, medical and laboratory staff time and expertise, as well as inpatient and outpatient admissions for leukapheresis and management of complications. We estimate that an uncomplicated AHSC collection at our institution with G-CSF mobilisation costs approximately A$6500 (comprising approximately A$4000 drug costs and A$2500 apheresis costs). The cost is clearly higher if chemotherapy such as cyclophosphamide is administered for stem cell mobilisation and if inpatient admission is required for management of complications. The median delay to transplantation in our study was 19 months. Relatively prolonged storage times are significant as many institutions have limited storage space and there are ongoing costs associated with cryostorage, which range from A$150 to A$600 per patient annually depending on the number of bags stored.

The ideal study of the usefulness of RDH would be a randomised comparison of clinical outcomes of patients who had ‘rainy day’ cells collected compared with those collected at the time of relapse. Such a study is unlikely ever to be performed. Thus, in spite of these limitations, our ‘real-world’ study adds useful information to inform future guidelines for this common practice.

Conclusions

Our audit over a 10-year period showed that the majority of AHSC collected with ‘rainy day’ intent was not transplanted. These results together with recent advances in stem cell mobilisation suggest that ‘rainy day’ collection is not justified in the vast majority of cases. Collection of AHSC at the time they are required is a preferable strategy in most situations, in particular for NHL which comprised the majority of ‘rainy day’ collections at our institution.

References


Adherence to guideline-based antibiotic treatment for acute exacerbations of chronic obstructive pulmonary disease in an Australian tertiary hospital

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1School of Medicine, 2School of Pharmacy, University of Queensland and Departments of 3Clinical Pharmacology (Advanced Trainee), 4Clinical Pharmacology, 5Internal Medicine, Princess Alexandra Hospital, Brisbane, Queensland, Australia

Abstract

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are an important cause of acute hospital admissions and incur significant costs, which include antibiotic costs.

Aims: This study aimed to (i) define antibiotic prescribing practice in patients admitted to a tertiary hospital with AECOPD and compare this with current locally and nationally recognised antibiotic prescribing guidelines and (ii) correlate variations in guideline-concordant antibiotic prescribing with mean length of stay (LOS) and rates of unplanned readmission to hospital.

Methods: Retrospective case series of 84 consecutive patients with uncomplicated AECOPD who met pre-specified selection criteria.

Results: Seventy-two of 84 participants (85.7%) received guideline-discordant antibiotics, of whom the majority (76%) received intravenous antibiotics. Mean LOS was significantly lower among patients receiving guideline-concordant therapy compared with those receiving guideline-discordant therapy (mean 1.6 days vs 3.7 days; P = 0.002). There was no significant difference between groups in rates of readmission. Estimated excess costs per patient associated with guideline-discordant therapy equalled $2642 which, if eliminated, would save approximately $300 000 per annum.

Conclusion: In a tertiary hospital, Australian guidelines for treating patients with an AECOPD were rarely followed. The use of guideline-discordant therapy resulted in longer hospital stays and incurred greater costs. Studies are required to determine the reasons behind such discordant practice and to develop initiatives to improve antibiotic prescribing.

Introduction

In Australia, chronic obstructive pulmonary disease (COPD) accounts for 4% of all deaths1,2 and in the 2004–2005 financial year incurred $560 million of healthcare expenditure, mostly due to hospital admissions.1

An acute exacerbation of COPD (AECOPD) is characterised by cardinal symptoms of worsening dyspnoea, cough and sputum production.3 Frequent exacerbations of COPD are associated with an increased risk of death, deterioration of lung function and diminished quality of life.4

In treating AECOPD and improving outcomes, the Lung Foundation of Australia has formulated the COPD-X Plan3 which currently endorses Therapeutic Guidelines (TG) recommendations to prescribe bronchodilators, a short course of systemic corticosteroids and oral antibiotics.3,5 The recommended antibiotic is either amoxycillin or doxycycline.3,5

However, past studies involving Australian hospitals demonstrate use of antibiotic regimens that differ from guideline recommendations.6–10 It has been postulated that, in the case of AECOPD, initial diagnostic uncertainty or guidelines promoting early use of intravenous (IV) antibiotics in all patients with suspected pneumonia11 may partly explain inappropriate use of antibiotics. Unfortunately, overuse of antibiotics contributes to the

Key words
pulmonary disease, chronic obstructive, antibacterial agent, guideline adherence, hospital, outcomes assessment.

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Table 1: Guideline-based antibiotic regimens for acute exacerbations of chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th>PAH prescribing guidelines</th>
<th>Therapeutic guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin 500 mg PO q8h. Treat for 5 days</td>
<td>Amoxicillin 500 mg orally, 8 hourly for 5 days</td>
</tr>
<tr>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>Doxycycline 200 mg initially and then 100 mg PO daily. Treat for 5 days (recently updated to 100 mg twice daily for 5 days).</td>
<td></td>
</tr>
</tbody>
</table>

PAH, Princess Alexandra Hospital.

Table 2: Baseline characteristics

<table>
<thead>
<tr>
<th>Guideline-concordant antibiotic prescribing</th>
<th>Guideline-discordant antibiotic prescribing</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>12 (14.3)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>75</td>
</tr>
<tr>
<td>Mean (±SD) age</td>
<td>70.6 ± 12.4</td>
</tr>
<tr>
<td>% Current smokers</td>
<td>41.7 (n = 12)</td>
</tr>
<tr>
<td>Mean (±SD) pack years</td>
<td>51.1 (±28.6)</td>
</tr>
<tr>
<td>Mean (±SD) Charlson Score</td>
<td>4.75 (±1.87)</td>
</tr>
</tbody>
</table>

Admitting service, n (%) |
- General medicine: 11 (91.7) | 41 (56.9) |
- Respiratory: 1 (8.3) | 27 (37.5) |
- Other: 0 (0.0) | 4 (5.6) |

n in parentheses refers to the number of subjects for which data were available when data sets were incomplete.

Method

A retrospective case series study design was applied which ascertained all 155 consecutive patients coded as having presented to the emergency department (ED) of the Princess Alexandra Hospital (PAH) with an AECOPD between 30 July 2011 and 28 March 2012. Patients were excluded if they:
- were not admitted to hospital during the study period (n = 47)
- required non-invasive or invasive ventilation at any time during the admission (n = 14)
- had evidence of sepsis (as defined by the Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008, n = 1)
- had clinical or radiological signs of pneumonia (n = 5)
- had an altered state of consciousness on presentation (n = 1)
- were not for active treatment (i.e. palliative, n = 3).

Guideline-concordant antibiotic prescribing was defined as that which accorded with recommendations contained within the TG and the PAH Prescribing Guidelines (Table 1).

As the majority of patients (66.7%) were given a stat dose of IV antibiotics on first presentation in the ED, patient management in the ED and as an in-patient were analysed separately.

Data were collected on patient demographics, need for domiciliary oxygen, presence of cardiac disease (ischaemic heart disease or cardiac failure), previous spirometry, clinical features on presentation, presence of cardinal symptoms and what non-antibiotic treatments were given during the admission. A combined Charlson comorbidity and age-related score was calculated for each patient. All unplanned readmissions for AECOPD were recorded at 1 and 3 months following index discharge.

Statistical analysis

Normally and non-normally distributed continuous measures were compared using t-test and Mann–Whitney U-test respectively. Discrete binary measures were compared using Pearson Chi-squared test. Statistical significance was denoted by P value <0.05.

Results

Of 155 patients coded as presenting to ED with an AECOPD, 84 patients were selected for analysis after applying exclusion criteria. Only 12 (14.3%) patients were deemed to have received guideline-concordant antibiotic therapy. Baseline characteristics of patients receiving guideline-concordant versus guideline-discordant therapy are listed in Table 2, for which there were no statistically significant differences between groups. Of the 12 patients who were prescribed guideline-concordant treatment, 11 were admitted to the general medicine service and 1 to a respiratory service. Of the 72 patients receiving guideline-discordant therapy, 41 were admitted to the general medicine service and 27 to the respiratory service.
Figure 2 illustrates the antibiotic regimen prescribed as an inpatient. 84.5% of patients were prescribed an antibiotic, with a lower proportion (45%) receiving IV antibiotics. Again the most commonly prescribed regimen was a beta-lactam antibiotic and macrolide (oral or IV) which occurred on 38% of occasions. More than half of all patients (n = 44; 52.3%) received at least two antibiotic classes during their admission, with the majority (n = 56; 66.7%) receiving IV antibiotics on first presentation. In only a minority of cases (8.9%) was the antibiotic changed by the admitting team to guideline-concordant therapy.

Antibiotics were continued after discharge in 52.3% of patients. Amoxicillin/clavulanate and a beta-lactam with macrolide comprised 38.6% and 29.5% of antibiotic regimens prescribed respectively.

There was a statistically significant difference in mean LOS between patients receiving guideline-concordant versus guideline-discordant therapy (mean 1.6 (±1.3) days, median = 1 day vs mean 3.7 (±2.4) days, median = 3 days; P = 0.002).

There was one death reported among patients receiving IV antibiotics (which was guideline-discordant) and this was attributed to a pulmonary embolus. No adverse drug reactions were reported.

There was no statistically significant difference in unplanned readmission rates at 3 months between guideline-concordant and guideline-discordant groups (25% vs 18%; odds ratio: 0.66 (95% confidence interval 0.32–2.78)).

Of the n = 39 patients treated with oral antibiotics as in-patients, the lowest readmission rate (11.1%) was seen in those who received doxycycline as a single agent (Fig. 3), although this was not statistically significant.

Among all admissions, there were 50 positive sputum cultures (Fig. 4). Cultured species included Haemophilus influenzae (n = 14; 28% of positive cultures), Pseudomonas aeruginosa (n = 13; 26%), Staphylococcus aureus (n = 4; 8%), Streptococcus pneumoniae (n = 4; 8%), other Gram-negative species (n = 6; 12%) and atypical organisms (n = 9; 18%). Pathogens resistant to beta-lactamases were grown in 34 (68%) of positive cultures with the remainder all sensitive to a penicillin (Fig. 5). No patient had their antibiotic therapy changed on the basis of sputum culture result and only one patient had antibiotics prescribed which were chosen in accordance with results of culture reports.

**Costs**

In regards to cost, patients receiving guideline-concordant antibiotics incurred significantly lower mean antibiotic costs than those receiving guideline-discordant antibiotics. Total antibiotic costs incurred per patient according to
the antibiotic prescribed, including drugs prescribed at discharge and consumables, were as low as $1.30 in patients who received only doxycycline (guideline-concordant therapy) and as high as $313.30 in those who received combination IV antibiotics (guideline-discordant therapy). Total bed-day costs were, on average, $2642 higher among patients receiving guideline-discordant than among those receiving guideline-concordant therapy. While this may relate to greater disease severity and comorbidity burden in the former, the absence of any statistically significant differences between groups in baseline patient characteristics render this explanation less valid. Higher cost may also be due to guideline-discordant use of other non-antibiotic therapies (e.g. utilisation of bronchodilators, corticosteroids etc) and investigations which our study did not measure.

Nevertheless, if this excess cost which accrues, at least in part, from inappropriate antibiotic use and longer LOS could be eliminated for every patient presenting to PAH with uncomplicated AECOPD, this could amount to annual saving of approximately $300 000.

**Figure 1** Antibiotics prescribed on first presentation.

**Discussion**

**Overview of results**

The results of this study conducted in an Australian tertiary hospital suggest that at this site Australian guidelines for treating an AECOPD, which recommend oral antibiotics, are rarely followed. We found no evidence of superior clinical outcomes of guideline-discordant antibiotic prescribing in terms of reduced LOS, readmission rates or costs of antibiotics and hospitalisation. Indeed, there was evidence to the contrary. Importantly, in the absence of supporting data that patients who received guideline-discordant therapy had a more severe exacerbation than those receiving guideline-concordant therapy, the longer LOS in patients who received IV antibiotics is likely due to the frequent delay in switching to oral agents.

According to guidelines, patients with an AECOPD should only receive one antibiotic class (i.e. either a penicillin or a tetracycline). However, more than one half
of our patients received at least two antibiotic classes during their admission, with the majority receiving IV antibiotics on first presentation. Less than 10% of these patients had the antibiotic changed by the admitting team to reflect the guidelines and remain in accordance with results of sputum cultures.

**Study limitations**

Our study is limited by being a retrospective chart review of a relatively small sample of patients admitted to a single hospital. Inaccuracy of assessment and diagnosis of AECOPD in the ED may have led to patients being missed...
who were admitted and subsequently coded as having AECOPD based on discharge data. Our dataset was also incomplete and potentially inaccurate for various variables such as duration and severity of presenting symptoms or timing of spirometry. Legitimate reasons why antibiotic prescribing varied from guidelines may not have been ascertained from chart entries if they were not recorded.

**Comparisons with other studies**

Similar to other international studies of antibiotic use in AECOPD, the present study of patients admitted to an Australian tertiary hospital revealed poor concordance with guideline recommended therapy.

In one systematic review, guideline adherence was low for in-hospital management of AECOPD, but little information was provided on antibiotic use. In a clinical audit of COPD patients requiring hospital admission in 129 Spanish hospitals, wide variability was also observed in relation to hospital adherence to guidelines. In 2010–2011, a European audit of care against the 2010 Global Initiative for Chronic Obstructive Lung Disease standards was performed in patients from 384 hospitals in 13 countries. The recommendation with regard to antibiotics was that these should be given to:

- patients with the following three cardinal symptoms: increased dyspnoea, increased sputum volume and increased sputum purulence;
- patients with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms, and
- patients that require mechanical ventilation.

Antibiotic use was considered appropriately high (90.5%) in patients meeting all three criteria, but was
similarly prevalent (79.7%) in patients who did not meet these criteria. There was wide variation in management between hospitals and between countries. However, in all three studies, there were no data on antibiotic choice.

Implications for practice

Despite study limitations, the clear message is that antibiotic prescribing deviates substantially from current guidelines with overuse of IV antibiotics, no alignment of antibiotic choice with probable respiratory pathogens based on clinical presentation and sputum cultures, and prolonged LOS. In addition, inappropriate use of broad-spectrum IV antibiotics, including macrolides, predisposes to greater carriage of MDR bacteria in patients with COPD.\(^1\)\(^{,21}\) Of particular concern is the emergence of multi-resistant *Pseudomonas aeruginosa* which can increase mortality, risk of treatment complications, duration of admission and costs.\(^21\)\(^{,22}\)

There was a significant preference to using a β-lactam antibiotic together with a macrolide in patients with an AECOPD which we presume was done to cover a wide spectrum of pathogens including atypical organisms (*Mycoplasma, Chlamydia* species). However, atypical species that would be covered by this deviation in antibiotic choice were isolated in only 2% (1/50) of positive cultures in this population, and was sensitive to doxycycline.\(^2\) Moreover, studies show that single agent therapy with either azithromycin or amoxicillin in patients on amoxicillin/clavulanate in light of the prevalence of β-lactamase producing organisms. However, the superiority of amoxicillin/clavulanate over amoxicillin has not been established for patients with an AECOPD with one non-inferiority trial showing both to be equally effective.\(^2\)\(^{,24}\)

As our study found no advantages for guideline-discordant therapy, we hypothesise that such practice may be driven by initial diagnostic uncertainty, with many patients assumed to have, or be developing or at risk of developing, pneumonia and treated accordingly. Indeed, guidelines published by the Infectious Diseases Society of America in 2003 specified that patients suspected of having pneumonia should be treated with IV antibiotics within 4 h of hospital presentation.\(^2\)\(^{,25}\) However, strict adherence to this recommendation has led to increased misdiagnosis and inappropriate utilisation of antibiotics with no reductions in frequency of treatment failure or time to clinical stability.\(^2\)\(^{,26}\)\(^{,27}\) Moreover, pneumonia is easily diagnosed on clinical examination and plain chest X-ray and, in any case, choice of antibiotics in our study did not, in most cases, correspond to current Australian pneumonia guidelines.\(^2\)\(^{,27}\)

Efforts to promote guideline-concordant antibiotic therapy might include regular audits of current practice and feedback of results to all involved clinicians. Clinical pharmacists should question the indication for IV antibiotics in AECOPD in association with educational campaigns that raise guideline awareness. As a last resort, restrictions on the prescribing of IV antibiotics in patients with a provisional diagnosis of AECOPD may need to be considered as part of a broader programme of antibiotic stewardship. As suggested by infectious disease experts, rates of identified bacterial resistance and *Clostridium difficile* infections should be monitored as a guide to the success of these interventions.\(^3\)\(^{,27}\)

Conclusion

Despite the existence of Australian guidelines for treating an AECOPD, this study of patients admitted to a tertiary hospital showed that guidelines are rarely followed even though there are no evident barriers to their implementation. Guideline-concordant therapy was associated with longer hospital stays and greater overall costs. More studies are required in determining the reasons behind such guideline-discordant practice and countering them by way of awareness raising initiatives, regular audit and feedback, pharmacist intervention and, if necessary, prescribing restrictions.

References

5. Moulds R (ed.). *Acute Exacerbation of COPD. eTG Complete* [Internet].
HOW I TREAT

Thiamine in the treatment of Wernicke encephalopathy in patients with alcohol use disorders

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Key words: thiamine, Wernicke encephalopathy, alcohol use disorder.

Abstract

Wernicke encephalopathy is an acute, reversible neuropsychiatric emergency due to thiamine deficiency. Urgent and adequate thiamine replacement is necessary to avoid death or progression to Korsakoff syndrome with largely irreversible brain damage. Wernicke Korsakoff syndrome refers to a condition where features of Wernicke encephalopathy are mixed with those of Korsakoff syndrome. Although thiamine is the cornerstone of treatment of Wernicke encephalopathy, there are no universally accepted guidelines with regard to its optimal dose, mode of administration, frequency of administration or duration of treatment. Currently, different dose recommendations are being made. We present recommendations for the assessment and treatment of Wernicke encephalopathy based on literature review and our clinical experience.

Introduction

Wernicke encephalopathy is an acute neuropsychiatric emergency due to thiamine deficiency.1–4 It occurs mainly, but not exclusively, in malnourished alcohol-dependent patients, or as a consequence of malnutrition from other causes (Table 1).

Wernicke encephalopathy is readily reversible if treated with adequate doses of parenteral thiamine, preferably within the first 48–72 h of the onset of symptoms.3,4 Failure to treat Wernicke encephalopathy with adequate doses of thiamine may lead to death in up to 20% of cases,1,3 or progression to Korsakoff syndrome.6 Autopsy studies report a prevalence of Wernicke encephalopathy between 0.4% and 2.8%,5,7–10 with Australia having the highest prevalence (1.1–2.8%) in the Western world;1,2,5,11 in patients with alcohol use disorders, the prevalence increases to 12.5%.1,2,10

Korsakoff syndrome, a chronic largely irreversible sequela of untreated, or inadequately treated Wernicke encephalopathy, is characterised by dense anterograde amnesia and short-term memory loss associated with compensatory confabulation, with relative preservation of long-term memory and other cognitive skills.

Current issues regarding diagnosis and treatment of Wernicke encephalopathy/Wernicke Korsakoff syndrome

The clinical diagnosis of Wernicke encephalopathy is missed in 75–80% of cases1–3,11 as the classical triad of gait ataxia, eye signs (nystagmus, ophthalmoplegia) and global confusion, as described by Karl Wernicke in 1881, is seen in only 16–20% of patients.1,2,10 To compound the problem, Wernicke encephalopathy is not only difficult to differentiate from drunkenness and other causes of confusion, but it also often coexists with other disorders that cause confusion, such as alcohol withdrawal, benzodiazepine withdrawal, sepsis, hypoxia, hepatic encephalopathy and head injury.

We do not know how many Australians in aged care facilities and psychiatric institutions with ‘dementia’ have
Table 1: Other common causes of Wernicke encephalopathy in non-alcoholic patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>18.1%</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>16.8%</td>
</tr>
<tr>
<td>Hyperemesis gravidarum</td>
<td>12.2%</td>
</tr>
<tr>
<td>Starvation/fasting</td>
<td>10.2%</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>7.7%</td>
</tr>
<tr>
<td>AIDS</td>
<td>5.0%</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>4.2%</td>
</tr>
<tr>
<td>Dialysis and renal disease</td>
<td>3.8%</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>3.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.4%</td>
</tr>
<tr>
<td>Psychiatric disease, for example, eating disorders, schizophrenia</td>
<td>2.4%</td>
</tr>
<tr>
<td>Others, including infections, intoxication, thyroid disease, diarrhoea, unknown</td>
<td>0.3–3%</td>
</tr>
</tbody>
</table>

Adapted from Galvin et al.\(^5\). AIDS, acquired immune deficiency syndrome.

Wernicke Korsakoff syndrome/Korsakoff syndrome as a result of undiagnosed or inadequately treated Wernicke encephalopathy.

Table 2 illustrates the lack of universally accepted guidelines or consensus regarding the optimal dose regimen for thiamine. While a study found that 200 mg thiamine I/M once daily for 2 days is superior to smaller doses,\(^21\) the Cochrane review concluded that there is ‘insufficient evidence from randomised controlled trials to guide clinicians in the dose, frequency, route or duration of thiamine treatment for prophylaxis against or treatment of Wernicke Korsakoff syndrome’.\(^22\)

**Recommendations for assessment, diagnosis and treatment of Wernicke encephalopathy/Wernicke Korsakoff syndrome**

1. **Have a high index of suspicion** of Wernicke encephalopathy/Wernicke Korsakoff syndrome in confused patients with alcohol use disorders and/or dietary deficiency/malnourishment or any other deficiency states, particularly those who are living alone

2. **Good history taking.** Ask about the quantity, frequency, pattern, duration of alcohol use, and time of last use; enquire about nutrition, vomiting or diarrhoea; seek collaborative information from family/friends; also take a history of benzodiazepine and other substance misuse

3. **Clinical examination.** Excess alcohol affects almost every system of the body, so examine all body systems to look for evidence of alcohol-related harm; look for signs of poor self care and protein calorie malnutrition, for example cheilitis, glossitis, bleeding gums, etc; note that alcohol provides calories but does not contain micronutrients or vitamins, so a malnourished alcohol-dependent patient may not necessarily appear emaciated

Consider Wernicke encephalopathy/Wernicke Korsakoff syndrome in patients with two of the following:\(^5,23,24\)

- Dietary deficiency/malnourishment and a history of alcohol use disorder, or any other deficiency states (Table 1)
- Oculomotor abnormalities: nystagmus, ophthalmoplegia (gaze palsy, VI nerve palsy – diplopia)
- Cerebellar dysfunction (gait ataxia, nystagmus)
- Confusion (either an altered mental state or mild memory impairment).

Other symptoms and signs that have been described in Wernicke encephalopathy include irritability, tachycardia, hypotension, hypo or hyperthermia, hearing loss, seizures, spastic paraparesis, delirium, coma, acute psychosis, miosis, anisocoria (unequal pupil size), papilloedema and retinal haemorrhages.\(^1,18\)

Wernicke encephalopathy should be included in the differential diagnosis of all patients presenting with confusion, acute delirium, acute brain syndrome or acute ataxia.\(^8,9,18\)

**4 Investigations.** Routine investigations: electrolytes, urea and creatinine; full blood count; liver function tests; Coags; thyroid function tests; blood sugar level; serum magnesium; B12; folate; calcium; phosphate; blood alcohol concentrations (note that raised gamma glutamyltransferase and macrocytosis may sometimes be useful biological markers of excess alcohol).

Other investigations. A normal computed tomography of the brain does not rule out the diagnosis of Wernicke encephalopathy. A brain magnetic resonance imaging supports the diagnosis of Wernicke encephalopathy,\(^23,24\) but it is important not to delay treatment with thiamine while waiting for the results. For the same reason, estimation of thiamine, thiamine pyrophosphate levels and low erythrocyte transketolase activity,\(^8,9\) while helpful, is not routinely performed.

Formal neuropsychological testing determines the degree of cognitive impairment.

**Treatment of Wernicke encephalopathy/Wernicke Korsakoff syndrome with thiamine replacement therapy**

Thiamine is an essential cofactor for transketolase, alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase in the pathways of carbohydrate metabolism. Chronic alcohol consumption results in thiamine deficiency by causing inadequate nutritional intake,
Table 2: Some guidelines for thiamine replacement dosage regimen in alcohol-dependent patients with Wernicke encephalopathy/Wernicke Korsakoff syndrome (WE/WKS)

<table>
<thead>
<tr>
<th>Prophylaxis for patients with suspected WE/WKS or at high risk of WE/WKS</th>
<th>Treatment of patients with a definitive diagnosis of WE/WKS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 100 mg I/M t.d.s for 3–5 days (b) 250 mg I/M daily for 3–5 days</td>
<td>(a) At least 100 mg I/V for 5 days (b) 500 mg t.d.s for 2 days; if no response, discontinue; if there is response, continue with 250 mg I/M or I/V for 5 days</td>
<td>Royal College of Physicians (UK)(^3)</td>
</tr>
<tr>
<td>At least 100 mg I/M for 3–5 days</td>
<td>(a) At least 100 mg t.d.s I/V for 5 days (b) 500 mg I/V t.d.s. for 2 days; if no response discontinue; if there is response, continue with 250 mg I/M or I/V daily for 5 days, or longer if improvement continues (UK)</td>
<td>Oxford Specialist Handbooks: Addiction Medicine (Latt et al., 2009)(^1)</td>
</tr>
<tr>
<td>Follow with oral thiamine as an outpatient</td>
<td>200 mg I/M or I/V t.d.s (preferably I/V)</td>
<td>European Federation of Neurological Sciences (EFNS) guidelines (Galvin et al., 2010)(^5)</td>
</tr>
<tr>
<td>(a) For healthy, low-risk patients: &gt;300 mg orally daily during detoxification (b) For malnourished/unwell high-risk patients: 250 mg I/M or I/V once daily for 3–5 days, or until no further improvement is seen</td>
<td>&gt;500 mg I/M or I/V for 3–5 days, followed by 250 mg once daily for a further 3–5 days depending on response</td>
<td>British Association for Psychopharmacology (BAP) guidelines (Lingford-Hughes et al., 2012)(^10)</td>
</tr>
<tr>
<td>Low-risk patients: 100 mg orally daily (b) Patients who drink excess alcohol: 100–200 mg I/M or I/V daily for 3 days and then 100 mg orally daily</td>
<td>500 mg I/V infusion over 30 min t.d.s for 2–3 days, and then 250 mg I/M or I/V for 3–5 days, or until clinical improvement is seen</td>
<td>Etg Therapeutics Guidelines (<a href="http://etg.hcn.com.au/tgc/gig/5209.htm)%5C(%5E11%5C">http://etg.hcn.com.au/tgc/gig/5209.htm)\(^11\</a>)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Treatment of</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>250–500 mg in 100 mL saline over 30 min intravenous infusion t.d.s for 3 days (recommended) or if, less preferred 100 mg I/V once daily</td>
<td>Wernicke encephalopathy, Best Practice, BMI Evidence Centre(^\ast)</td>
<td><a href="http://bestpractice.bmj.com.acs.hnc.com.au">http://bestpractice.bmj.com.acs.hnc.com.au</a></td>
</tr>
<tr>
<td>500 mg thiamine I/V infused over 30 min t.d.s for 2 days and 500 mg I/V or I/M once daily for an additional 5 days in combination with other B vitamins</td>
<td>Charness et al.(^8) (^9)</td>
<td><a href="http://www.UpToDate.com">www.UpToDate.com</a></td>
</tr>
<tr>
<td>(a) For healthy patients with good dietary intake: 100 mg t.d.s orally (b) For chronic drinkers with poor diet: 300 mg IVM or I/V for 3–5 days, followed by 300 mg orally for several weeks 100 mg IV or I/M on Day 1, and then 100 mg orally daily</td>
<td>500 mg I/M or I/V for 3–5 days, followed by oral or parenteral thiamine 300 mg for 1–2 weeks</td>
<td>Guidelines for the treatment of alcohol problems Australian Department of Health and Ageing. Commonwealth of Australia (Haber et al., 2009)(^19)</td>
</tr>
<tr>
<td>100 mg I/V or I/M daily for 3 days and then orally</td>
<td>NSW Drug and Alcohol Withdrawal Clinical Practice Guidelines. Mental health and Drug &amp; Alcohol, NSW Department of Health 2007(^20)</td>
<td></td>
</tr>
</tbody>
</table>
decreased absorption and impaired utilisation. Thus, although the daily requirement of thiamine is only 1–2 mg, some clinicians recommend very initial high doses of parenteral thiamine (500–1500 mg daily) to enable diffusion of thiamine across the blood brain barrier to restore vitamin status, prevent irreversible brain damage, and improve clinical signs and prevent death.

Thiamine is typically administered either intramuscularly or intravenously for 5 days. The three times a day dosage regimen is based on the short half-life of thiamine (96 min or less).

Although there is currently no evidence to determine precise doses of thiamine in the prevention or treatment of Wernicke encephalopathy/Wernicke Korsakoff syndrome, until further studies are available, the following recommendations are based on available literature (Table 3).

<table>
<thead>
<tr>
<th>Treatment of patients with a definitive diagnosis of Wernicke encephalopathy/Wernicke Korsakoff syndrome</th>
<th>Depending on the state of malnutrition:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At least 200–500 mg t.d.s I/V for 5–7 days, followed by oral thiamine,</td>
</tr>
<tr>
<td></td>
<td>100 mg t.d.s. for 1–2 weeks, then 100 mg daily thereafter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prophylactic treatment of patients with suspected or at risk of Wernicke encephalopathy/Wernicke Korsakoff syndrome</th>
<th>(I/M if I/V not possible)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At least 100–200 mg t.d.s. I/M or IV for 3–5 days, followed by oral thiamine,100 mg t.d.s. for 1–2 weeks and 100 mg daily thereafter</td>
</tr>
</tbody>
</table>

Precautions to be taken when administering parenteral thiamine

1. Monitor for anaphylaxis, and have appropriate facilities for resuscitation and for treating anaphylaxis readily available, viz. adrenaline, corticosteroids.

Anaphylaxis has been reported at the rate of approximately four per one million pairs of ampoules of Pabrinex (a pair of high potency vitamins available in the UK containing 500 mg of thiamine (1.250000 I/V administrations). The incidence of penicillin induced anaphylaxis of one to four episodes per 10 000 administrations.) I/M thiamine is reported to have a lower incidence of anaphylactic reactions than I/V administration. In Australia, where thiamine is only available as 100 mg ampoules, the Australian Adverse Drug Reaction Advisory Committee (ADRAC) database reports two cases of anaphylactic shock (1991, 1997) and four anaphylactoid reactions (1993, 1993, 2001 and 2004) (ADRAC, pers. comm. 2012).

2. Administer intravenous thiamine slowly, preferably by slow infusion in 100-mL normal saline over 15–30 min.

Other measures for the management of Wernicke encephalopathy/Wernicke Korsakoff syndrome

- Nurse confused patient 1:1 in a dimly lit, quiet room, reassure, orientate
- Regular 2–4 hourly observations, blood pressure, pulse, respiration (O₂ saturation), temperature, neurological observations, Alcohol Withdrawal Score (AWS) or Clinical Institute Withdrawal Assessment for Alcohol score (CIWA-AR). If AWS ≥5, or the CIWA-AR score ≥10, sedate with diazepam (taking special precautions in patients with concurrent hypoxia, hepatic encephalopathy or head injury)
- Avoid dehydration, maintain fluid and electrolyte balance
- Exclude, and treat, any concurrent causes of acute brain syndrome/delirium
- Always administer I/V or I/M thiamine before a glucose drip or a carbohydrate load as a glucose load may precipitate acute Wernicke encephalopathy
- Ensure that serum magnesium levels are normal; magnesium is an essential cofactor in many thiamine-dependent enzymes, and low levels of magnesium have been implicated in thiamine deficiency and Wernicke encephalopathy, and failure to respond to parenteral thiamine replacement
- Add oral multivitamin supplements.

Outpatient management

Advise all patients with alcohol dependence to strive for a goal of total abstinence from alcohol, together with a healthy lifestyle, exercise, and regular nutritious meals supplemented with oral thiamine 100 mg daily and multivitamins. In addition, patients with ongoing cognitive impairment require memory training techniques, a familiar environment, and a strong supportive network of family, carers and various community services.

For the 20% of patients with Korsakoff syndrome who require long-term institutionalised care, finding appropriate supported accommodation is challenging and may require a guardianship order.
Thiamine in Wernicke’s encephalopathy

Incidence of deep venous thrombosis: a comparison of two Australian hospitals

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Key words
Australia, deep venous thrombosis, private hospital, admission, venous thromboembolism.

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Abstract
In this retrospective observational study, we observed that principal and comorbid diagnoses of deep venous thrombosis (DVT) occurred at a rate of 1.02 and 4.86 per 1000 admissions. Principal DVT diagnosis admissions were more common in the public hospital (1.29 vs 0.57 per 1000; \( P < 0.001 \)), while the private hospital had nearly three times the admissions with comorbid DVT (2.99 vs 8.23 per 1000; \( P < 0.001 \)). In-hospital mortality was uncommon (0.2% and 1.6% for principal and comorbid DVT diagnoses, respectively), and this did not differ significantly between the two hospitals.

Deep venous thrombosis (DVT) is a common condition in Australia, with an estimated incidence of 0.5 per 1000 population in the community1 and up to 257 per 1000 surgical patients.2 While comparable to Europe and the UK,3,4 the rates in Australia are almost half those reported in the US.5,6 Despite widespread awareness of these problems and the efficacy of preventative measures,7 adherence to venous thromboembolism (VTE) prophylaxis guidelines remains low in many countries, including Australia.2,4

Examination of patterns of hospital admissions can give insights into the aetiology and clinical burden of a disease, as well as insights into improvements in diagnosis and management, providing data on which further efforts aimed at reducing the incidence of DVT can be based. The aims of this study were to analyse patterns in the incidence of DVT in two Australian hospitals, and to identify predictors of differences in health outcomes between the public and private healthcare systems.

We obtained the data through the NSW Health Admitted Patients Data Collection from two co-located hospitals in Sydney, one public and one private. Using the International Classification of Diseases (10th Revision) codes I80.1 (phlebitis and thrombophlebitis of femoral vein) and I80.2 (phlebitis and thrombophlebitis of other deep vessels of lower extremities), we extracted data on all admissions for DVT between 2001/2002 and 2010/2011, including the year of admission, patient age and gender, principal diagnosis (the main reason for hospitalisation), comorbid diagnoses, and principal and secondary procedures. Due to the increase in the total number of admissions from both hospitals over the study period, we standardised them into a rate per 1000.

Mann–Whitney \( U \)-tests were used to assess the differences between the medians of groups for continuous variables with skewed distributions, while \( t \)-tests were used to compare means. Categorical variables were compared using Pearson chi-squared tests. Binomial tests were used to compare differences between genders. Linear regression was used to assess the change in rates of morbidity and mortality over time. Logistic regression analysis was used to identify predictors of dichotomous outcome variables after adjusting for other factors, including age, sex, comorbidities and surgical procedures. A \( P \) value of 0.05 was considered to be statistically significant. Ethics approval for the study was obtained from the University of Notre Dame, Australia.

Over the 10-year study period, there was a total of 3394 admissions for either a principal or comorbid DVT diagnosis from both hospitals (1797 public and 1697...
private), corresponding to a rate of 5.84 per 1000 admissions.

There were 618 admissions over the study period for a principal diagnosis of DVT, 82.4% in the public hospital. In both 2001/2002 and 2010/2011, the admission rate from the public hospital was higher than that in the private hospital (1.24 and 0.51, and 1.25 vs 0.37 per 1000 admissions respectively). Linear regression revealed a non-significant increase in admissions for principal DVT diagnosis in the public hospital ($R^2 = 0.35$, $\beta = 0.07$, $P = 0.07$) and a non-significant decrease in the private ($R^2 = 0.01$, $\beta = -0.01$, $P = 0.81$).

Demographic and disease characteristics of patients with a principal diagnosis of DVT are shown in Table 1. The median age of the study sample was 63 years (range 18–96). Females predominated in the youngest (<40) and oldest (>80) age groups, while males were more frequently represented in the 40–75 year age group (Fig. 1). The median age of males was significantly lower than that of females (66 vs 62 years, $P = 0.029$). Patients over 60 years were over-represented in the private hospital when compared with the public hospital (71.6 vs 52.4%, $P = 0.027$).

Sixty-seven admissions (10.8%) suffered a comorbid pulmonary embolism (PE), with significantly more in the private hospital (16.5 vs 9.6%, $P = 0.036$). Males were significantly more likely to suffer PE than females (13.3 vs 7.4%, $P = 0.02$). Hospital type was not associated with comorbid PE ($P > 0.05$).

The proportion of patients with underlying diseases did not differ significantly between the hospitals. Only one death (0.2%) occurred in all patients with a principal diagnosis of DVT during the study. Logistic regression demonstrated that inferior vena cava (IVC) insertion rates were not associated with hospital type, age, sex or comorbid condition ($P > 0.05$).

There were 2876 admissions with a comorbid diagnosis of DVT, of whom 51.3% were male ($P = 0.36$). There was a significant increase in admissions with a secondary diagnosis of DVT in the private hospital over the study period ($R^2 = 0.61$, $\beta = 0.88$, $P = 0.008$), but no change in

### Table 1 Principal diagnosis of deep venous thrombosis (DVT): patient characteristics by hospital type from 2001/2002 to 2010/2011

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Public</th>
<th>Private</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total DVT admissions</td>
<td>618 [1.02]</td>
<td>509 [1.29]†</td>
<td>109 [0.57]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>1 [0.2]</td>
<td>0 [0.0]</td>
<td>1 [0.9]</td>
<td>—</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>361 (58.4)</td>
<td>307 (60.3)</td>
<td>54 (49.5)</td>
<td>0.038</td>
</tr>
<tr>
<td>Female</td>
<td>257 (41.6)</td>
<td>202 (39.7)</td>
<td>55 (50.5)</td>
<td>—</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;49</td>
<td>166 (26.9)</td>
<td>147 (28.9)</td>
<td>19 (17.4)</td>
<td>—</td>
</tr>
<tr>
<td>50–59</td>
<td>107 (17.3)</td>
<td>95 (18.7)</td>
<td>12 (11.0)</td>
<td>0.027</td>
</tr>
<tr>
<td>60–69</td>
<td>104 (16.8)</td>
<td>81 (15.9)</td>
<td>23 (21.1)</td>
<td>—</td>
</tr>
<tr>
<td>70+</td>
<td>118 (19.1)</td>
<td>186 (36.5)</td>
<td>55 (50.5)</td>
<td>—</td>
</tr>
<tr>
<td>Median length of stay (days)</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopaedic disease</td>
<td>200 (32.4)</td>
<td>168 (33.0)</td>
<td>32 (29.4)</td>
<td>0.460</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>100 (16.2)</td>
<td>88 (17.3)</td>
<td>12 (11.0)</td>
<td>0.106</td>
</tr>
<tr>
<td>Malignancy</td>
<td>80 (12.9)</td>
<td>66 (13.0)</td>
<td>14 (12.8)</td>
<td>0.972</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>67 (10.8)</td>
<td>49 (9.6)</td>
<td>18 (16.5)</td>
<td>0.036</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopaedic surgery</td>
<td>2 (0.3)</td>
<td>1 (0.2)</td>
<td>1 (0.9)</td>
<td>0.229</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>15 (2.5)</td>
<td>10 (2.0)</td>
<td>5 (4.6)</td>
<td>0.053</td>
</tr>
<tr>
<td>IVC filter inserted</td>
<td>85 (13.8)</td>
<td>70 (13.8)</td>
<td>15 (13.8)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Given as total numbers, percentage of total (%), or rate [per 1000 admissions]. †417 (81.9%) were admitted through the emergency department. IVC, inferior vena cava.

Figure 1 Total admissions due to principal diagnosis of deep venous thrombosis (DVT) from 2001/2002 to 2010/2011 by 5-year age group and sex. □ Males; □, females.
admissions in the public hospital ($R^2 = 0.35, \beta = 0.10, P = 0.07$) (Fig. 2). There were two notable increases in admission rates for a comorbid DVT in the private hospital between 2002/2003 and 2004/2005, and between 2005/2006 and 2007/2008.

The median age of males with a comorbid DVT diagnosis was significantly younger than that of females (67 vs 72 years, $P < 0.001$) (Fig. 3). Patients in the public hospital were more likely to be younger (65 vs 71 years, $P < 0.001$), be male (57.6 vs 46.9%, $P < 0.001$) and have a shorter length of stay (7 vs 8 days, $P < 0.001$) than patients in the private. There were also significant differences in comorbidities and in the procedures undergone between the two hospitals (Table 2).

A total of 261 patients (9.1%) with comorbid diagnosis of DVT suffered PE, with public hospital patients twice as likely as private hospital patients (12.1 vs 6.9%, $P < 0.001$). Patients in the public hospital were three times more likely to have an IVC filter inserted (11.4 vs 3.4%, $P < 0.001$), with logistic regression finding the public hospital associated with higher rates of IVC filter insertion (OR 0.5, 95% CI 0.34–0.71).

In-hospital mortality was recorded for 47 patients with a comorbid diagnosis of DVT, with significantly more deaths occurring in the public than the private hospital (2.6 vs 0.9%, $P = 0.001$). Logistic regression found that after controlling for confounders, hospital type was not a significant predictor of in-hospital mortality ($P > 0.05$).

**Discussion**

DVT incidence among hospital inpatients in this study was 5.84 per 1000 admissions, similar to that found in the US and UK,\(^5-12\) but higher than that in France\(^{13}\) and
Table 2 Admissions with a comorbid diagnosis of deep venous thrombosis (DVT): patient characteristics by hospital type from 2000/2001 to 2010/2011

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Public</th>
<th>Private</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total DVT admissions</td>
<td>2876 [4.86]</td>
<td>1188 [2.99]</td>
<td>1688 [8.23]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>47 [1.6]</td>
<td>31 [2.6]</td>
<td>16 [0.9]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1475 [51.3]</td>
<td>684 [57.6]</td>
<td>791 [46.9]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1401 [48.7]</td>
<td>504 [42.4]</td>
<td>897 [53.1]</td>
<td></td>
</tr>
<tr>
<td>Total admissions over the</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>study period, by age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70+</td>
<td>1414 [49.2]</td>
<td>491 [41.3]</td>
<td>923 [54.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median length of stay</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[days]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Principal diagnoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopaedic disease</td>
<td>877 [30.5]</td>
<td>54 [4.5]</td>
<td>823 [48.8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>883 [30.7]</td>
<td>628 [52.9]</td>
<td>255 [15.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trauma</td>
<td>118 [4.1]</td>
<td>62 [5.2]</td>
<td>56 [3.3]</td>
<td>0.011</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopaedic disease</td>
<td>1141 [39.7]</td>
<td>556 [46.8]</td>
<td>1179 [69.8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>261 [9.1]</td>
<td>144 [12.1]</td>
<td>117 [6.9]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>1075 [37.4]</td>
<td>110 [9.3]</td>
<td>965 [57.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>General surgery</td>
<td>189 [6.6]</td>
<td>89 [7.5]</td>
<td>100 [5.9]</td>
<td>0.186</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>179 [6.2]</td>
<td>50 [4.2]</td>
<td>129 [7.6]</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Given as total numbers, percentage of total (%), or rate [per 1000 admissions]. 1912 (76.8%) were admitted through the emergency department. IVC, inferior vena cava.

Sweden. However, rate of admissions for a principal diagnosis of DVT (1.02 per 1000) was twice than previously noted in Australia. The actual DVT incidence may be substantially higher, with asymptomatic DVT occurring in up to one in four surgical patients, even with appropriate prophylaxis.

Although public hospital patients had twice the admission rate for a principal DVT diagnosis, private hospital patients had three times the rate of comorbid DVT. While differences in rates of principal DVT diagnoses likely relate to the presence of an emergency department in the public hospital only, variations between hospitals in the rates of comorbid DVT reflect other factors. Patients with a comorbid DVT in the private hospital were significantly older than public hospital patients, explained as age is an independent risk factor for DVT. However, the most likely contributor to the higher rates of comorbid DVT in the private hospital was the increased surgical activity (especially joint arthroplasty) in the private hospital.

Notably, orthopaedic surgery occurred in 70% of private hospital patients who developed a comorbid DVT, with such procedures resulting in VTE between 1% and 25% of patients.

Increased VTE awareness in the private hospital may have been a factor, given that the largest increases in the rates of comorbid DVT diagnoses coincided with observation periods of two studies performed at this institution. Interestingly, the higher rate of DVT diagnoses in the private hospital was not associated with a higher mortality rate, suggesting that either the high index of suspicion in this group did not change outcome or these were clinically unimportant DVT. Studies in the US, UK and South Africa have previously demonstrated overdiagnosis of PE and DVT, with diagnosis of clinically insignificant DVT prolonging hospital stays, and increasing healthcare costs and complications secondary to anticoagulant therapy.

In the present study, we observed a significant increase in admissions with comorbid diagnosis of DVT in the private hospital only, in contrast to the overall increase in DVT diagnoses observed in the US from 1960 to 2000. An increased focus on VTE prophylaxis among hospital inpatients may have influenced the rates observed in this study acting to prevent VTE occurrence, despite poor adherence to prophylaxis guidelines both in Australia and internationally. The increase in patients with a secondary diagnosis of DVT in the private hospital is likely due to increasing awareness and increasing utilisation of non-invasive imaging, such as Doppler ultrasound, in private hospital inpatients. The expense of VTE prophylaxis is less than 3% of total VTE costs, making financial restrictions no justification for failure to implement guidelines across all hospitals.

IVC filters were inserted in rates consistent with several US studies. Insertion of IVC filters in patients with a comorbid diagnosis of DVT was found to be more frequent in the public hospital, likely due to the higher proportion of patients with a principal diagnosis of trauma, and to private hospital patients being more likely to undergo elective procedures, thus having fewer contraindications to anticoagulation.

Government datasets (such as those used in this study) have several limitations, including the incomplete recording of comorbidities and adverse events, and the inability to identify readmissions of individual patients. In addition, these data do not allow assessment of illness severity. Further, up to 60% of VTE occur after discharge, so they would not be included in this analysis. However, the utility and accessibility of discharge coding information make it a very useful research resource.
In conclusion, this study demonstrated a marked difference in rates of DVT between public and private hospital systems. Principal diagnosis of DVT was much higher in the public hospital, likely due to the different patterns of admission between the private and public systems. The higher incidence of comorbid DVT diagnosis in the private hospital appears to be associated with a higher number of elective orthopaedic procedures. In this study, the diagnosis of DVT was associated with very low rates of in-hospital mortality.

References

Rapid rule out of myocardial infarction with the use of copeptin as a biomarker for cardiac injury

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1Cardiology Department, Gold Coast University Hospital, 2School of Medicine, Griffith University, Southport, 3School of Medicine, Bond University, Gold Coast, Queensland, 4Division of Cardiology, Manning Rural Referral Hospital, Taree, 5School of Rural Medicine, University of New England, Armidale and 6Medical Registrar, Concord Repatriation General Hospital, Sydney, New South Wales, Australia

Key words
copeptin, arginine vasopressin precursor, troponin, acute coronary syndrome, myocardial infarction, emergency department.

Abstract
Copeptin is a non-specific marker of an endogenous stress response. A dual biomarker marker approach involving the simultaneous use of troponin and copeptin assays may assist early exclusion of acute coronary syndrome in Australian emergency departments. The utility and limitations of this approach are discussed.

Chest pain is a common symptom in patients presenting to the emergency department (ED) worldwide. It is important to identify expeditiously or exclude potentially fatal conditions, such as acute coronary syndrome (ACS), pulmonary embolism, aortic dissection and spontaneous pneumothorax. ACS, encompassing unstable angina and myocardial infarction, is by far the most common to rule out. The current political climate mandates that circumscribed time pressures be applied to all Australian ED due to the National Emergency Access Target (NEAT), a hospital-wide initiative to alleviate ED overcrowding. It is thought that such a practice has enabled timely patient care without demonstrable adverse effects. Further, funding available to hospitals is anchored to their ability to align with NEAT key performance indicators, providing a clear monetary impetus to expedite admissions, discharges or inter-hospital transfer processes. It is, therefore, imperative to establish an effective and accurate approach to diagnosis of ACS to identify patients for whom medical or surgical treatment needs to be instigated promptly. At the same time, patients suffering from non-life-threatening conditions might be spared from repeated blood tests, X-rays and prolonged monitoring that contribute to ED overcrowding.

The gold standard of ‘ruling in’ a diagnosis of acute myocardial infarction (AMI), aside from clinical symptoms and electrocardiography (ECG) findings, is currently based largely on cardiac markers – elevation of cardiac troponin with a rising or falling pattern. Cardiac troponin provides excellent specificity but does not reliably rule out AMI without a repeat negative measurement within a 6–12 h period. The release of necrosis markers from the cardiomyocytes involves delay, which might explain the weakness in sensitivity of the conventional troponin assays immediately after myocardial infarction. Local ACS guidelines in Australia and New Zealand reflect the evolution of troponin assays, namely high-sensitivity troponin versus standard-sensitivity troponin assays.6

The definition of a clinically significant ‘change’ in troponin level suggestive of myocardial ischaemia in current clinical practice algorithms involves a mindfulness of the type of assay utilised (20% for standard-sensitivity assay vs 50% for high-sensitivity assays). These recommendations remain consensus opinion and await further research for validation.6 High-sensitivity
Troponin assays have an increased sensitivity for the detection of ‘myonecrosis’ at the expense of reduced specificity. This increased sensitivity places high-sensitivity troponin assays in a good position to ‘rule out’ myocardial ischaemia. However, even with these improved assays, a delayed repeat serial troponin level remains the main temporal hindrance of early exclusion of cardiac ischaemia in patients who present early (within 6 h). This is where the use of a cell marker independent of cell necrosis may play a role.7 The vast majority of patients presenting to the ED with suspected AMI are proven not to have it.8 Recent recognition of the synergistic value of adding the novel cardiac biomarker copeptin to troponin assays has shown impressive results in ruling out AMI.

Copeptin is a 39 amino acid glycoprotein of unknown function, derived from the C-terminal portion of the arginine vasopressin (AVP) precursor. AVP is a non-peptide hormone produced by the hypothalamus, subsequently released from the neurohypophysis, which promotes renal water conservation and contributes to osmoregulation and cardiovascular haemostasis.9 The regulatory role of AVP on the hypothalamic–pituitary–adrenal axis mediates an individual’s stress response.10 In vitro measurement of AVP is difficult owing to a short half-life (t1/2 < 15 min) and being platelet-bound; however, its levels can be ascertained by the more stable surrogate biomarker, copeptin.11,12

Copeptin is a non-specific marker of an endogenous stress response and is thought to have clinical implications in a variety of non-cardiovascular (pneumonia and sepsis) and cardiovascular conditions (heart failure and ACS). Can this biomarker play a diagnostic role in the detection or ruling out of AMI? Khan et al. first described the role of copeptin in AMI. They detected an increase in copeptin concentration post-AMI, with the highest values noted on day 1 with subsequent decline in the next 2–5 days. This led to further research to evaluate the role of copeptin in the diagnosis of AMI.13 A study by Reichlin et al. demonstrated the presence of elevated copeptin levels 4 h after the onset of AMI symptoms at a time where troponin T was still undetectable in many patients. This implies a rapid rise in circulating copeptin after a myocardial infarction even before cardiac troponins are detectable. This study also revealed an inverse relationship between copeptin levels and time since symptom onset in AMI patients, which is in contrast to troponin being positively co-related with time since symptom onset (Fig. 1). Furthermore, copeptin levels were significantly higher in patients with AMI as opposed to patients having other diagnoses (P < 0.001).13,14

As copeptin is a marker of stress levels, it would be expected to be elevated in many conditions besides AMI (i.e. low specificity). It is, therefore, not suitable as a standalone marker of myocardial infarction.

In the study by Reichlin et al., the combination of copeptin and troponin T at initial presentation resulted in area under the receiver-operating characteristic curve of 0.97, which was significantly higher than that obtained from troponin T alone (0.86). Interestingly, copeptin level <14 pmol/L in combination with troponin T <0.01 correctly ruled out AMI, with a sensitivity of 98.8% and a negative predictive value of 99.7% (specificity of 77.1% and positive predictive value of 46.2%). Keller et al., in a larger study, demonstrated that using both copeptin and troponin provides a remarkable negative predictive value of 99.0% (cut-off: troponin I <0.04 ng/mL and copeptin >9.8 pmol/L) for AMI at the expense of reduced specificity (63%) and positive predictive value (49%), hinting at an early and safe ‘rule-out’ of myocardial infarction.15 Important to note is that the negative predictive values are dependent on the designated cut-off for copeptin, as the 99.0% in the Keller et al. study is reduced somewhat to 98.3% for a higher copeptin cut-off of >13.0 pmol/L. Theoretically, using this dual marker approach, AMI can be excluded in around 65% of study populations.14,15

More recently, Moeckel and Lindahl presented a study to address the non-inferiority of this troponin and copeptin dual biomarker approach as compared with the conventional approach. Patients suspected of ACS with a negative initial troponin were randomised to a standard ACS arm (serial cardiac troponins, ECG and care in accordance with current guidelines) or experimental arm (copeptin levels measured from initial blood sample).
It was unclear as to whether the troponin assays utilised were standard-sensitivity or high-sensitive assays. In the experimental arm, copeptin level $\geq 10$ pmol/L was considered positive, and hence treated with standard ACS care. However, if copeptin levels were $< 10$ pmol/L, patients were discharged into ambulant care and scheduled for an outpatient visit within 72 h. This appears to be a lower copeptin cut-off than the 14.0 pmol/L and 13.0 pmol/L used in the Reichlin et al. and Moeckel and Lindahl studies respectively (which would likely yield a higher negative predictive value). At 30 days with intention to treat analysis, the rate of major adverse cardiovascular events (MACE) was noted to be 5.46% (95% confidence interval (CI), 3.52–8.14) in the experimental copeptin arm and 5.5% (95% CI, 3.49–8.08) in the standard care arm, a difference that was not statistically significant. MACE at 30 days was used as a composite end-point designed to compare the two investigative approaches. The $\sim 5.5\%$ MACE rate at 30 days from this multicentre study appears somewhat higher than that of a recent single-centre Australian study wherein low and intermediate risk patients were less than 2.4%. Whether this discrepancy is due to epidemiological differences or a function of study design is not clear. The discharge rate from the ED among patients in the experimental arm was 66% compared with 12% among patients treated with standard care. The authors concluded that the results have the potential to change clinical practice with the employment of a dual biomarker approach to rule out ACS safely and expedite patient discharge from the ED.

The need always to complement investigative tools with clinical acumen was reflected in the ‘miss-rate’ of the experimental arm (consisting of 451 patients) wherein of 14 patients with negative troponin and copeptin levels, 12 were overruled clinically, and the two

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**Figure 2** Moeckel et al. study design for BIC-8. ACS, acute coronary syndrome; CPU, Chest Pain Unit; ECG, electrocardiography; MACE, major adverse cardiovascular event.

**Figure 3** An algorithm proposed for the management of patients presenting to the emergency department with symptoms suggestive of acute myocardial ischaemia (AMI) ($\geq$ elevated troponin T $>0.01$ μg/L, elevated copeptin $>14$ pmol/L). Active monitoring in hospital would involve consideration of differential diagnoses if an AMI is thought unlikely (e.g. pulmonary embolism, aortic dissection, etc.). ECG, electrocardiography; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction.

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who were discharged later required invasive coronary intervention within 30 days. Cardiac biomarkers in isolation do not diagnose or exclude ACS in the absence of a formal clinical assessment. It is important to acknowledge that there are still insufficient clinical data to support the use of dual biomarker rule-out strategy in the current clinical practice (Fig. 2).

Copeptin, in combination with troponin, has the potential for clinical use to facilitate quicker and safe discharge of patients assessed for ACS in ED. A dual biomarker approach may obviate the need for serial blood draws and ECG monitoring, leading to resources saved for the healthcare system and positive benefits to the patient. More large clinical studies would be required to investigate further this rapid rule-out algorithm to validate the promising European results. Once supported by more data, this dual biomarker approach may indeed have the potential to change practice in the ED.

A ‘rapid rule-out’ algorithm suggesting the use of combined copeptin and troponin in clinical practice is depicted in Figure 3.

References

Recurrent life-threatening reactions to platelet transfusion in an aplastic anaemia patient with a paroxysmal nocturnal haemoglobinuria clone

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Key words
PNH, platelet transfusion, recurrent reaction, washed platelet, aplastic anaemia.

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Abstract
A 60-year-old woman was diagnosed with non-severe aplastic anaemia when she presented with anaemia and thrombocytopenia. She developed recurrent life-threatening hypotensive reactions during transfusion of leukodepleted platelet concentrates, and washed platelet concentrates prevented the development of such reactions subsequently. A paroxysmal nocturnal haemoglobinuria clone was detected on investigating for aplastic anaemia, which has been speculated to play a role in the recurrent hypotensive reactions.

The incidence of adverse reactions to blood products is higher with platelet transfusions than red cell transfusions.1 Historically, most reactions were associated with donor leukocytes in the platelet concentrates; the incidence has been dramatically reduced since the introduction of universal leukodepletion of all cellular blood products.2 Occasionally, adverse events can also occur with leukodepleted blood products, and in certain situations such reactions can be recurrent. We report a patient diagnosed with aplastic anaemia and paroxysmal nocturnal haemoglobinuria (PNH) clone who developed recurrent life-threatening reactions during transfusion of leukodepleted platelet concentrates.

A 60-year-old white woman, who was previously healthy, presented with widespread purpura and extensive ecchymosis of 1 week in duration. She was a multiparous woman, and there was no history of allergies. At presentation, her full blood counts showed bicytopenia with haemoglobin of 77 g/L, white cell count of 3.4 × 10⁹/L, neutrophil count of 2.0 × 10⁹/L and low platelet count (14 × 10⁹/L). Her biochemical tests were unremarkable, and viral serologies for HIV, hepatitis B and C were negative. Bone marrow biopsy showed a reduced marrow cellularity of 30% with an increase in fat spaces and moderate reduction of haemopoietic precursors consistent with a diagnosis of non-severe aplastic anaemia. There were no identifiable causes for the hypoplastic marrow. The patient had red cell transfusions for symptomatic anaemia. When platelet concentrates (group-specific, pooled, leukodepleted and irradiated) were transfused for the first time, she developed a feeling of doom with tachycardia (heart rate of 140 per min) and hypotension (drop in blood pressure from 130/80 mmHg to 90/70 mmHg) without rise in body temperature, drop in oxygen saturation or cardiac arrhythmias. After stopping the platelet transfusion, hydrocortisone and promethazine were administered, and blood pressure and heart rate returned to normal after 45 min. There was no evidence of bacterial contamination, transfusion-associated acute lung injury or haemolysis, and direct antiglobulin test was negative. Subsequently, group-specific, apheresis platelets (<24 h from collection) were transfused on two different days after premedication with hydrocortisone and promethazine. She still developed hypotension and tachycardia on both the occasions with less than 10 mL of transfused platelets.

Investigative tests were performed in our laboratory and Australian Red Cross Blood Service, Melbourne, and...
The incidence of adverse reactions to blood products is commonest, followed by febrile reactions and circulatory distress. Severe reactions leading to circulatory distress are commonly due to leukocytes in the platelet concentrates, and can be caused by anti-leukocyte antibodies, histamine or cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6). The breakdown of leukocytes in platelet concentrates stored at room temperature can release these substances into the plasma. The incidence of such reactions has reduced significantly since the introduction of leukocyte reduction of platelets at source. Products released from platelets, such as serotonin and platelet-activating factor, can also rarely lead to circulatory compromise. Hypotensive reactions have also been reported to occur in patients on angiotensin-converting enzyme inhibitors having platelet transfusions.

Some conditions are known to cause recurrent reactions to platelet transfusions. Transfusion of blood components to IgA-deficient patients can lead to anaphylactic transfusion reactions due to an interaction between the donor’s transfused IgA and the recipient’s anti-IgA antibodies. These can be prevented by administration of blood components from IgA-deficient donors. Chido (Ch) and Rodgers (Rg) antigens are plasma proteins that are secondarily adsorbed to cell membranes. The prevalence of Ch and Rg negativity is 1.7% and 3% in the general population respectively. Anti-Ch or anti-Rg antibody can be produced by Ch or Rg negative recipients, and these antibodies have been implicated in severe anaphylactic reaction with platelet transfusion. Anhaptoglobinaemia is an extremely rare condition characterised by an inherited deficiency of plasma haptoglobin. Antibodies to haptoglobin can develop in such patients, which can lead to allergic transfusion reactions, or in severe cases can cause anaphylaxis. For all these three conditions, transfusion of cellular products washed relatively free of plasma or stored in artificial media has been recommended to prevent transfusion reactions.

For our patient, a PNH clone was identified when investigated for aplastic anaemia. It is not clear whether there was any relationship between the recurrent platelet reactions and the presence of PNH clone. In PNH, complement activation with generation of cytokines, such as IL-6 and TNF-α, is important in the pathogenesis of thrombosis. Since these cytokines released from leukocytes are also implicated in hypotensive reactions during platelet transfusions, we postulate that the plasma component in platelet concentrates triggered activation of complement-causing cytokine release, leading to recurrent hypotensive reactions in our patient. The lack of reactions to red cell transfusions in our patient may relate to the fact that the current packed red cell units contain

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Table 1: Blood investigations done for evaluation of recurrent hypotensive reactions

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA levels</td>
<td>2.6 g/L</td>
<td>0.8–4.5 g/L</td>
</tr>
<tr>
<td>Chido (Ch) antigen</td>
<td>Positive</td>
<td>—</td>
</tr>
<tr>
<td>Rodgers (Rg) antigen</td>
<td>Positive</td>
<td>—</td>
</tr>
<tr>
<td>Haptoglobin levels</td>
<td>1.37 g/L</td>
<td>0.40–2.10 g/L</td>
</tr>
<tr>
<td>Anti-human leukocyte antigen</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>(HLA) antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-human platelet antigen</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>(HPA) antibodies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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no apparent cause for these recurrent severe reactions to platelet transfusions was evident (Table 1). Flow cytometric analysis for PNH was performed for workup of aplastic anaemia. There was a reduced expression of CD55, CD59, FLAER and CD24 in 10% of monocytes and neutrophils, confirming the presence of a PNH clone. However, other clinical manifestations of PNH, such as haemolysis and thrombotic episodes, were absent.

For management of symptomatic thrombocytopenia, washed apheresis platelet concentrates were trialled, and these were well tolerated. Platelets are washed using the protocol by the Australian Red Cross Blood Service, Melbourne Processing Centre (Appendix I). Since washed platelets should be transfused within 24 h of the production, they were prepared soon after apheresis collection and shipped by special air freights from Melbourne to Launceston.

Our patient was re-challenged with unwashed apheresis platelet concentrates, at 3 months and 12 months after the first episode, and hypotension and tachycardia recurred on both the occasions. Tryptase and IgE levels were only slightly increased after the platelet transfusions when compared with the pre-transfusion values, and these were non-diagnostic for severe allergic or anaphylactic reactions. Repeat bone marrow biopsies after 12 and 18 months demonstrated persistence of moderate marrow hypoplasia; however, the PNH clone size in peripheral blood had increased from 10% to 22%, without any further clinical deterioration. The patient opted not to have immunosuppressive therapy (antithymocyte globulin and cyclosporine) for aplastic anaemia. Prophylactic washed platelets were transfused on a regular basis, and her post-transfusion platelet count increments were consistently good. Fortunately, she never developed similar transfusion reactions with washed platelets and unwashed red cells to date.

The incidence of adverse reactions to blood products is higher with platelet transfusions than red cell transfusions. Among the non-haemolytic transfusion reactions to platelet transfusion, allergic reactions are the commonest, followed by febrile reactions and circulatory distress. Severe reactions leading to circulatory distress are commonly due to leukocytes in the platelet concentrates, and can be caused by anti-leukocyte antibodies, histamine or cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6). The breakdown of leukocytes in platelet concentrates stored at room temperature can release these substances into the plasma. The incidence of such reactions has reduced significantly since the introduction of leukocyte reduction of platelets at source. Products released from platelets, such as serotonin and platelet-activating factor, can also rarely lead to circulatory compromise. Hypotensive reactions have also been reported to occur in patients on angiotensin-converting enzyme inhibitors having platelet transfusions.
very little plasma. Washing of platelet concentrates is performed to remove plasma proteins and cytokines, and helps prevent transfusion reactions mediated by them.\textsuperscript{11} Historically, washed red cells were transfused to prevent complement-mediated haemolysis in PNH patients, and they are no longer recommended due to lack of evidence.\textsuperscript{12}

To our knowledge, this is the first reported case of recurrent hypotensive reactions to platelet transfusions in PNH. Since there was no identifiable cause after extensive investigations, we speculate that these reactions were triggered by activation of complement in the plasma component of platelet concentrates, and washing of platelet concentrates had prevented the recurrence of such reactions.

**Acknowledgements**

The authors thank Dr Ni Ni Aung, Dr Frank Hong and Dr Chris Hogan, the transfusion medicine specialists at Transfusion Medicine Service, Australian Red Cross Blood Service in Melbourne, Australia, for their assistance in the management of this patient and their expert opinions on this case report.

**References**


**Appendix I**

**Steps in the preparation of washed platelets**

1. Apheresis platelets collected from the donor.
2. Spin for 6 min at room temperature and 3750 r.p.m.
3. Supernatant removed and 300 mL SSP + (MacoPharma) added
4. Mix and spin for 6 min at 3750 r.p.m.
5. Remove the supernatant
6. Add 300 mL SSP+
7. Rest the platelets for 1 h
8. Place on shaker
Severe cardiomyopathy revealing antineutrophil cytoplasmic antibodies-negative eosinophilic granulomatosis with polyangiitis


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Key words
eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, myocarditis, hypereosinophilia.

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Abstract
Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare form of systemic vasculitis in which cardiac involvement is frequent and severe, and accounts for half of EGPA-related deaths. ANCA-positive EGPA differs from ANCA-negative EGPA in that the former is significantly associated with renal involvement, peripheral neuropathy and biopsy proven vasculitis, whereas the latter is associated with cardiac involvement. Herein, we report a case of EGPA with myocarditis in a woman, who was successfully treated with steroids and cyclophosphamide. This report highlights the importance of diagnosing cardiac involvement in EGPA early, especially in ANCA-negative patients.

A 63-year-old woman with a history of mild asthma for 20 years, diabetes and hypertension was referred for acute chest pain and dyspnoea, which required oxygen therapy at 1 L/min. Blood pressure was 120/84 mmHg, pulse rate 90 bpm and body temperature 37.3°C. Cardiovascular, pulmonary and cutaneous examinations were unremarkable. The electrocardiogram revealed left bundle branch block. Chest radiography was normal. Troponin I and NT-pro brain natriuretic peptide (NT-Pro BNP) were high at 10 ng/mL and 22 000 pg/mL (normal range <300 pg/mL) respectively. However, coronary angiography performed on the day of admission was normal (Fig. 1A,B). Echocardiography revealed severe hypokinesia and impaired ventricular function. Cardiac magnetic resonance imaging (MRI) confirmed the marked decrease in the left ventricular ejection fraction, evaluated at 17%, and showed a pericardial effusion and a late gadolinium-enhanced lesion with a patchy pattern in the midmyocardium and the subepicardium (Fig. 1C,D). A full blood count revealed leukocytosis (14 G/L) with hypereosinophilia (3.48 G/L). Serum creatinine was normal and C-reactive protein was high (45 mg/L). Serum was negative for antineutrophil cytoplasmic antibodies (ANCA) and antinuclear antibodies. There was no evidence of drug allergies or parasitic infection. The absence of clonal T lymphocytes and the absence of Fip1-like 1 (FIP1L1)-platelet-derived growth factor receptor-α (PDGFRA) gene fusion made a diagnosis of idiopathic hypereosinophilic syndrome very unlikely. The serum level of interleukin 5 level was <4 pg/mL and total IgE were high at 4015 kU/L.

Additional investigations revealed a history of nasal polyposis, allergy and recurrent sinusitis. The patient also reported fever and myalgia occurring 10 days before admission. Endomyocardial biopsy was performed and revealed inflammatory cell infiltrates with eosinophils in the myocardium and the subendocardium, subendocardial fibrosis, and parietal thrombosis. However, there were no signs of vasculitis in this biopsy (Fig. 2). Based on these findings and the history of asthma, nasal polyposis, sinusitis and hypereosinophilia, the diagnosis of eosinophilic myocarditis related to eosinophilic granulomatosis with polyangiitis (EGPA, ‘Churg-Strauss’ syndrome) was retained. As our patient presented cardiomyopathy, which is one of the poor-prognosis factors defined by the five-factor score (FFS), she was given three pulses of methylprednisolone (15 mg/kg/day), followed by oral glucocorticoids (1 mg/kg/day) and six intravenous pulses of cyclophosphamide (CYC) (0.6 g/m²/14 days for the first three pulses, then 0.7 g/m² every 3 weeks for the three others). The methylprednisolone pulses triggered atrial tachycardia, which was treated with amiodarone.

K. Bouiller and M. Samson contributed equally to the drafting of this article.
One day after the onset of the treatment, eosinophils had dropped to 0.3 G/L. One week later, NT-Pro BNP had decreased to 5000 pg/mL and C-reactive protein (CRP) was 10 mg/L. One month later, left ventricular ejection fraction had improved to 55%, and the patient was symptom-free. Six months later, under 20 mg/day of prednisolone and 2 mg/kg/day of azathioprine, the patient was considered in remission, with no dyspnoea and no asthma flares. Blood assays showed a normal eosinophil count (0.13 G/L) with no inflammatory syndrome (CRP <2.9 mg/L); ANCA were still negative and the level of NT-Pro BNP had dramatically decreased (1500 pg/mL).

EGPA is a rare systemic vasculitis involving small vessels and characterised by eosinophilia, typically late-onset severe asthma with a history of allergy, and the presence of ANCA in about 40% of cases, mainly with a perinuclear fluorescence pattern and directed against myeloperoxidase. In the present case, even though there was no evidence of vasculitis in the myocardial biopsy, the diagnosis of EGPA was confirmed by the presence of four of the six criteria of the American College of Rheumatology classification.

We also suspected idiopathic hypereosinophilia syndrome (HES). There is indeed some overlap between the symptoms of ANCA-negative EGPA and those of lymphoid HES, the former differing mainly by the presence of systemic vasculitis, whereas a T-cell clone with often a CD3+CD4−CD8− phenotype is usually detected in lymphoid HES. However, cardiac involvement is more frequent in myeloid than in lymphoid HES. The excellent response to corticosteroids and the absence of FIP1L1-PDGFRα gene fusion in our patient ruled out this diagnosis. Cardiac involvement has been reported to be one of the more severe manifestations of EGPA, and is the leading cause of death, accounting for about half of EGPA-related deaths. In a recent study reporting 383 EGPA patients, cardiac involvement was detected in 16% of cases, mainly in ANCA-negative patients and those with higher eosinophil counts, as was the case in our observation.

Recent publications have emphasised the distinction between ANCA-positive and ANCA-negative EGPA, the first being significantly associated with renal involvement, peripheral neuropathy and biopsy-proven vasculitis, whereas the latter is associated with cardiac involvement. EGPA has been associated with different cardiac manifestations, including myocarditis, coronary vasculitis, valvular heart disease, pericarditis and/or rhythm disorders. Histologically, myocardial damage is rarely caused by small-vessel vasculitis but rather by the in situ production of toxic mediators, thus supporting the phenotypic differences between ANCA-positive and ANCA-negative EGPA. The ECG usually shows non-specific conductance disturbances or patterns of acute coronary

Figure 1 (A,B) Normal coronary angiography. Cardiac magnetic resonance imaging in four-chamber (C) and short-axis views (D) (gadolinium-enhanced T1-weighted), showing delayed hyper-enhancement in the lateral wall and in the septum with a patchy pattern (full white arrows) and pericardial effusion (dotted white arrows). No evidence of endocardial fibrosis was seen.
syndromes. Transthoracic echocardiography can show impaired contractility, ventricular wall thickness and/or the presence of pericardial effusion. Cardiac MRI is the most sensitive technique to investigate cardiac involvement in EGPA. When FFS ≥1, as was the case for our patient, treatment must associate glucocorticoids and CYC. Then, remission has to be maintained by azathioprine or methotrexate with low-dose corticosteroids since relapses frequently occur during the course of EGPA. Several studies have demonstrated that ANCA-negative phenotype EGPA is associated with a lower risk of relapse but a higher mortality rate. EGPA has to be considered in cases of myocarditis associated with hypereosinophilia, especially if ANCA are negative. Corticosteroids and intravenous CYC are effective if started quickly.

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LETTERS TO THE EDITOR

Clinical-scientific notes

Association of heme oxygenase-1 gene promoter polymorphism and blood pressure in an Iranian population

Hemeoxygenase-1 (HO-1) is an isomerase of hemeoxygenase that has crucial cytoprotective functions by modifying endothelial cell integrity and oxidative stresses.1 Of note is a (GT)n repeat in the 5-flanking region of HO-1 gene promoter that is extremely polymorphic. The length of the (GT)n repeat appears responsible for the variations in the level of HO-1 expression, in particular the shorter the (GT)n repeat length the greater the expression of HO-1 protein.1,2

Our previous studies investigated the relationship between HO-1 polymorphism and metabolic syndrome, demonstrating no relationship between them.3 In a recent study, we recruited 78 metabolic syndrome patients and 74 aged-matched healthy individuals (75 males and 77 females, mean age: 57.54 ± 9.92). Arterial blood pressure (BP), waist and pelvic circumference, height, and weight were documented.

Participants’ (GT)n repeats were recorded in the range of 7–41, with a mean of 27.09 ± 5.024 (median of 27 and mode of 25). Alleles were then categorised into two groups: ‘class S (small)’ for alleles with <27 GT repeat and ‘class L (large)’ for alleles with ≥27 GT repeats. Individuals carrying at least one S allele were considered as group A (SS and SL, n = 100), and group B composed of individuals with class L alleles (n = 52).

There were no significant differences between groups A and B when comparing age, sex, weight, waist, pelvic circumference, metabolic syndrome status or smoking. However, group A had significantly lower BMI, diastolic BP and MAP (P = 0.025 and 0.046 respectively). Participants with the S allele(s) were associated with lower diastolic BP (76.48 ± 1.7 vs 81.12 ± 1.5, P = 0.011) and mean arterial pressure (MAP) (90.84 ± 1.4 vs 95.86 ± 1.8, P = 0.018). The difference in systolic BP was not statistically significant (119.58 ± 2.1 vs 125.35 ± 2.8, P = 0.053).

Groups A and B were then further divided according to metabolic syndrome status. No significant differences were found in the healthy subjects according to our variables. In metabolic syndrome patients, however, group A had significantly lower BMI, diastolic BP and MAP (P = 0.049, 0.025 and 0.037 respectively). These results support a recent Taiwanese study that demonstrated that short (GT)n repeat length is a protective factor hypertension development.4

HO-1 gene promoter polymorphism may be associated with diastolic BP, MAP, BMI and anthropometric measures.

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References


A case of iatrogenic Cushing syndrome and apparent mineralocorticoid excess presenting with accelerated hypertension and proteinuria

A 60-year-old woman was referred for the investigation of recent onset proteinuria and difficult to manage hypertension. Hypertension was diagnosed 5 years prior and inadequately controlled with lisinopril and propranolol. Six years before referral, she underwent hysterectomy and bilateral salpingo-oophorectomy with pelvic irradiation for an endometrial carcinoma. Adjunctive medroxyprogesterone acetate (MPA) 200 mg bd (4.5 mg/kg/day) was commenced based on positive peritoneal washing for adenocarcinoma cells. Examination revealed blood pressure (BP) of 180/110 mmHg with grade II hypertensive retinopathy. There was no heart murmur or renal bruits. Renal imaging was normal. Urinalysis was negative for blood, and proteinuria was quantitated at 0.6 g/day. Amlodipine was initiated to optimise BP control.

Over the next 10 months, she complained of increasing abdominal girth, progressive weight gain and hirsutism requiring frequent shaving. She had prominent cushingoid facies, a buffalo hump, marked centrifugal obesity (body mass index: 35 kg/m²), proximal myopathy and scattered bruises. Her adrenocorticotrophin (ACTH) was suppressed with low 24-h urinary cortisol excretion (<30 nmol). A short ACTH stimulation (Synacthen) test showed a subnormal response. Bone mineral density revealed evidence of osteoporosis, and she had biochemical evidence of high bone turnover (Table 1). The constellation of cushingoid phenotype, secondary hypoadrenalism and suppressed plasma renin activity (PRA) suggested exogenous glucocorticoid intake.

After thorough evaluation, the high-dose MPA was weaned over 4 months. Unfortunately, she developed symptoms of adrenal insufficiency 2 weeks after MPA withdrawal requiring cortisone replacement that was tapered and discontinued over 3 months guided by sequential Synacthen test. Her cushingoid features and proteinuria completely resolved after MPA withdrawal. BP control improved such that amlodipine was withdrawn and remained at 130/80 mmHg with lower doses of propranolol.

Sporadic reports of Cushing syndrome (CS), adrenal insufficiency and hypertension in association with MPA use support its intrinsic glucocorticoid activity.1,2 Gradual discontinuation of MPA with/without corticosteroid replacement is the mainstay of management. MPA is a potent synthetic progestin. High-dose progestin has the capacity to bind to and activate the glucocorticoid receptor (GR). This may contribute to glucocorticoid-induced selective renal vasodilatation, increasing renal blood flow and glomerular filtration leading to reversible increase in urinary protein excretion.3

Aldosterone regulates sodium and water homeostasis in the distal nephron through the epithelial sodium channel (ENaC) and the serum and glucocorticoid-regulated kinase 1 (SGK1), which redistributes ENaC from the cytosol to apical membrane. Although MPA (1 mg/kg/day) mediates an increase in ENaC and SGK1 expression through the GR, some groups suggest that it does not result in clinically significant sodium reabsorption.5 Despite this, a recent animal study demonstrated that MPA (3 mg/kg/day) could induce upregulation of the ENaC giving rise to clinical features that mimic the mineralocorticoid excess syndrome manifesting as low PRA, hypertension with/without hypokalaemia.6

The novel features of this patient were the presence of proteinuria in association with CS, which resolved after MPA withdrawal; the onset of apparent mineralocorticoid excess syndrome and proteinuria can
precede the classical features of CS and is an important consideration in the differential diagnosis of accelerated hypertension.

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Sudden cardiac death complicating acute myocardial infarction following synthetic cannabinoid use

Synthetic cannabinoids represent a large and heterogeneous group of agents, broadly producing psychotropic effects of a similar nature to tetrahydrocannabinol (THC), the active component of cannabis. In recent years, a variety of such preparations has become readily available, with a perception that these may represent a safe and legal alternative to cannabis use.

The advent of these synthetic cannabinoids exposes the user to as yet unrecognised adverse effects on the cardiovascular system, in addition to the established and anticipated psychotropic actions of these agents.

We report a case of sudden cardiac death in a known user of synthetic cannabinoids caused by multi-vessel myocardial infarction complicating acute thrombosis of all three main epicardial coronary arteries.

A 45-year-old man with a background of untreated hypertension presented with sudden cardiac death following an unwitnessed collapse while in the toilet. The patient’s past history was characterised by a background of heavy tobacco use and alcohol ingestion. There was no history of prior coronary artery disease or reproducible exertional chest typical of myocardial ischaemia. The patient had, however, commenced using a synthetic cannabinoid, colloquially known as ‘black widow’, in the weeks preceding his demise.

During the week preceding his abrupt presentation, the patient noted nonspecific chest discomfort, believed to be musculoskeletal in origin.

On post-mortem examination, the most striking finding was thrombosis of all three major coronary arteries with associated features of acute and chronic ischaemic heart disease. The myocardium confirmed a spectrum of ischaemic changes, including cardiac dilatation (648 g), evidence of previous anterior myocardial infarction with an apical aneurysm containing mural thrombus, thinning of the anterior papillary muscle of the mitral valve, patchy fibrinoid pericarditis and evidence of recent posterior septal myocardial infarct.

The left anterior descending coronary artery had severe atherosclerosis with luminal thrombosis and recanalisation (Fig. 1a). The right coronary artery and left circumflex coronary artery demonstrated moderate atherosclerosis with intraluminal thrombus (Fig. 1b,c). The lungs had smoking-related changes, including emphysematous changes. The cranial and abdominal cavities were not examined.

Post-mortem toxicology screen obtained from femoral venepuncture confirmed low levels of opiates (codeine and metabolites, morphine, and hydromorphone) and multiple analgesics (paracetamol, diclofenac and ibuprofen). There is presently no routine assay for the detection of synthetic cannabinoids.

Death was attributed to ischaemic heart disease from coronary artery atherosclerosis and acute superimposed thrombosis, on a background of recent synthetic cannabinoid use and associated cardiovascular risk factors.

Synthetic cannabinoids have been produced in various guises over the past several years. Several preparations, including Spice Gold, Kronic, K2 and black widow, are readily available inexpensive agents that exert similar psychotropic effects to THC.1,2 The cardiovascular effects of these ‘designer’ drugs are not well established despite these agents’ widespread dissemination.

In addition to the anticipated psychiatric manifestations, which appear to be more common in younger users,3,4 including paranoia, anxiety and psychosis, additional adverse effects are increasingly recognised; there is evidence that synthetic cannabinoids may be associated with increased toxicity compared with THC, including reports of fatal psychiatric complications.3,6 This toxicity may reflect the likely variability in the concentration of the active constituents in synthetic cannabinoids.

A tendency to awareness of tachycardia has been documented in up to one third of users, with concomitant

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alcohol use seen to predispose to a greater frequency of side-effects. Myocardial infarction following synthetic cannabinoid use has been reported in three young patients previously, with acute renal injury complicating acute tubular necrosis also described. The use of THC has been associated with a tendency to thrombotic vascular complications, including coronary artery thrombosis, coronary artery spasm, posterior circulation stroke and limb arteritis. Effects on the circulation include an increase in heart rate and blood pressure through changes in the autonomic nervous system, with an associated increase in cardiac output and myocardial oxygen demand. Vascular spasm is also a presumed mechanism of both stroke and myocardial infarction complicating THC use. These effects may predispose to myocardial ischaemia in susceptible individuals, as well as increase the risk of atrial and ventricular tachyarrhythmia, particularly with concomitant cocaine use. Furthermore, THC may be associated with vascular inflammation and increased platelet activation, which is a potential mechanism of plaque rupture and the association with increased risk of myocardial infarction documented after THC use.

Given the reported adverse effects of THC on cardiovascular system, in particular the possible predisposition to vessel thrombosis, it is plausible that the use of synthetic cannabinoids may similarly be contributory to myocardial infarction in our patient, in keeping with previously published reports. The cardiovascular risk of these agents is potentially more acute in those with a background of cardiovascular risk factors, as in our patient.

More broadly, synthetic cannabinoids form part of an important component of the larger issue of emerging synthetic recreational drugs. These include synthetic cathinones (the so-called bath salts), a heterogeneous group of sympathomimetic agents structurally related to amphetamine. The legality and drivers for use of these types of emerging drugs are complex and presently in a state of evolution. This, in part, reflects current attempts at legislation to restrict use, in contrast to the previous relative ease of access, either through the use of internet-based distributors or certain retail outlets. The inability of an adequate test to identify the use of these agents will also potentially influence ongoing demand, reflecting the imperative for the development of a rapidly available assay to detect these substances. Data regarding the nature of potential side-effects remain limited and may evolve with changing patterns of use. The generation of a national registry documenting adverse outcomes seen in the use of these agents may allow for the collective experience to define better the cardiovascular risk of these drugs, noting that adverse events, while recognised, are likely underreported.

With the increased availability of these new synthetic cannabinoids, physicians need to be aware of the potential cardiac sequelae in patients with established risk factors for coronary artery disease, noting that these agents may also affect young individuals not typically felt to be at risk of myocardial ischaemia. The presence of such adverse cardiovascular outcomes may have complex, important public health implications given appropriate concerns regarding the ease of access to these agents, lack of effective legislation to limit use and likely marked variations in the chemical composition of these drugs.

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The consultant physician and his role in team medicine

The recent article by Marck et al.1 published in the Journal reporting research on the neglected problem of cancer patients dying in emergency departments is a welcome breakthrough, and I rejoice in the broadened policy that is now clearly operating. The paper concludes that ‘more training is required’: one that includes the family, who are often ill-prepared and have not used the advantage of an advanced care directive to prevent ‘futile treatment’.

In my recent hospital admission at the age of 82, I gained a ‘no way’ reaction as I dutifully attempted to show my consultant physician my advanced care directive. He strongly confirmed the point that more training was needed in this troubled and controversial team field – particularly for members of the family.

Our sister college, the Royal Australian College of General Practitioners, has leapt into the fray with an excellent document on its website ‘The silver book’ that explains the legalities of advanced care directives.

My aged cohort needs to have consultant physicians on side!

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