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Join us in Melbourne in 2012!

On behalf of the ANZSNM, I would like to invite you to join us in the vibrant city of Melbourne for the 42nd Annual Scientific Meeting in 2012.

A panel of experts from all over the world will be sharing their expertise in all aspects of Nuclear Medicine and Molecular Imaging, incorporating therapy and emerging technology.

Melbourne, set around Port Philip Bay in Victoria, is a lively cosmopolitan city, boasting creative arts, fine food and wine, a love of sports, and is a city which has multiculturalism at its heart. The Melbourne Convention Centre, the venue for the Scientific Meeting, is a 6-star green rated environmentally friendly convention centre with state-of-the-art facilities, making it the perfect setting for us to meet our industry partners and hear about developing issues around Australasia.

The Pre-Conference Symposium will be focused on therapy and held on 27 April 2012. The emphasis of this year’s scientific program will be on Continuing Education and Interactive Sessions, with local and international experts providing us their pearls of wisdom, which we can incorporate into our daily practice. There will also be an innovative approach to the poster demonstration with a larger display and dedicated Poster Sessions showcasing the best of the best.

Together with our panel of experts on the Scientific Committee, I look forward to welcoming you all in Melbourne for the 42nd Annual Scientific Meeting, which will be held from 27 – 30 April 2012.

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OECD nations face a mismatch between healthcare demand, supply and affordability. The question is how to influence the behaviour of healthcare providers so as to reduce the demand for and cost of healthcare. Clearly, provider behaviour is linked to system quality, but even apparently sensible remuneration may not result in ‘good’ health worker behaviour. A holistic approach to ‘reward’ appears essential.

We will review Australasian systems, compare the UK and US experiences, discuss the psychology of paying healthcare providers to perform and then suggest four work streams.

Australia and New Zealand have mixed public and private health systems. Australia has a high level of private elective procedures and the right to private healthcare is enshrined in the constitution. The underpinning fee for service system has been vigorously protected by the Australian Medical Association. The non-procedural medical specialties are less financially rewarding in both countries; the procedural specialties inevitably attract relatively more doctors, as do urban centres. Substantive upfront payments and higher salaries are used to attract doctors and nurses to remote and rural Australia. This has had an adverse effect on the New Zealand workforce. These incentives have had mixed success and have not guaranteed retention. Four-year visas issued to migrant healthcare workers can mandate a workplace region, but many are subsequently accepted for permanent residence and relocate.

Australia’s Medicare covers 85% of scheduled general practice fees. Attempts have been made to incentivize for better outcomes and improved team work through the Medicare Benefits Schedule – for example, paying for coordinated care plans for chronic conditions and for mental health nurses to be employed through general practices. Both countries will be challenged to fund the growing demands of the aged-care sector; those working in residential settings are relatively lowly paid.

Primary care payments differ. Australia has a fee for service system, whereas New Zealand introduced a capitation in 2001. Until recently, both jurisdictions tried to control costs by limiting the number of doctors trained or the cohort able to achieve reimbursement, as there is a strong correlation between the number of doctors and services rendered. New Zealand Medical Council data show that capitation has neither increased overall general practitioner ‘productivity’ nor shifted care to areas of need.

There is considerable relevant international experience. A Cochrane review examined the impact of payment systems in primary care. Although more services are delivered in a fee for service system compared with capitations and salaries, there is no difference in patient outcomes.

The Quality and Outcomes Framework (QOF) was introduced into the UK in 2004. About 25% of general practice income is determined by performance metrics. These include clinical standards in coronary heart disease, cancer, asthma and diabetes; standardized surveys of patient experiences; organizational standards; plus, additional services, such as screening and maternity care. The most recent study of patient outcomes found that there was no change in blood pressure management attributable to the QOF, nor reduced incidence of stroke, myocardial infarction or heart failure, and concluded that financial incentives may not be enough to improve quality of care. An evaluation of chronic disease management and patient access reached similar conclusions. By contrast, attainment of desired metrics by general practitioners exceeded that expected to the extent of ‘embarrassing’ some local budgets. Overall, it would seem that general practitioners were paid to do what they were doing already and or what they should have been doing anyway; arguably, a culture arose in which practices concentrated on incentivized interventions.

The arguments for and against the QOF were addressed in the British Medical Journal last year; the conclusion was that the QOF distorts priorities and is not as effective in improving patient outcomes as enhancing team work and facilitating evidence-based practice. Not surprisingly, following an extended focus on payments, emphasis in the UK has shifted to staff satisfaction and engagement, as measured by career opportunities, workload, participation in decision-making and team work. These latter factors appear to correlate with better patient experiences.
We identify 11 key lessons from the UK experience. (1) Do not reward people for what they are doing anyway. (2) Involve clinicians in system design and extensively road test putative schemes. (3) Be clear about scheme objectives and desirable changes. (4) Create a system that can evolve. (5) Avoid creating large bureaucracies and do not over-engineer changes. (6) Publish comparative provider data as benchmarking, peer review and collective responsibility are influential, but ensure data are accurate and clinically owned. (7) Do not rely on remuneration alone to improve performance. (8) Be careful in linking quality improvement activity and rewards as this can lead to both gaming and unexpected perverse effects. (9) Invest in leadership. What are needed are middle managers and clinician leaders who can set and measure performance goals, and can use available improvement tools. (10) Employ a national reward framework, but ensure system flexibility for local applications. (11) Incentivize role and task substitution.

In their review of the US experience, Rosenthal and Frank concluded that performance payments had little impact on clinician behaviour. A RAND meta-analysis found mixed results regarding the link between paying physicians for performance and the provision of appropriate care, while a separate study found that performance payments could worsen inequalities. Although RAND also found that performance payments could be linked to positive changes in doctors’ reporting and accountability, there were no substantive improvements in quality of care. An analysis of patient experience found that communication and care coordination improved if incentives were quality- rather than productivity-focused.

These US studies demonstrate the difficulty of establishing causal links in complex systems, in part because some quality measures are questionable, data integrity is variable, and as human behaviour is variable and unpredictable.

Opinion leaders and key policy-makers in the USA, such as Don Berwick (President Obama’s appointment to head Medicare and Medicaid), Uwe Reinhardt (Princeton Professor of Economics) and Denis Cortese (Mayo Clinic President), have reservations about performance payments; variously, they believe pay is not an effective motivator for quality, the variability and complexity of healthcare makes it difficult to measure the contribution of individuals to particular outcomes, other factors, such as wider working conditions, influence behaviour, focusing on evidence-based practice risks stifling innovation, and that there will be a tendency for goals to be set too low.

Their advice is that performance-based incentives may have their place, but should preferably be at an organizational rather than individual level and appropriately targeted to motivate integrated and coordinated care rather than numbers of procedures.

Nevertheless, performance payment schemes are commonplace in US Health Maintenance Organisations. Mehrk and colleagues decided that the benefits of paying health providers for performance were marginal, but highlighted the importance of the ‘mechanism’ of payment: for example, they argue that performance payments can discourage activities for which there is intrinsic motivation.

Using behavioural economics philosophies, they suggest the following 10 steps could lead to effective performance payments. (1) Use a series of small incentives rather than one large incentive. (2) Use a series of tiered thresholds rather than one absolute threshold. (3) Minimize the time between the care episode being incentivized and receipt of the reward. (4) Use withholding measures as these are more effective than bonuses. (5) Keep incentive schemes simple. Most practitioners are risk-adverse and simplicity facilitates benefit identification. (6) Use shared-savings programmes. (7) Separate rewards for performance from usual reimbursement. (8) Use in-kind rewards rather than cash. (9) ‘Pay enough or don’t pay at all’, as small payments are much less effective than large payments and less effective than no payment at all. (10) Use a broad ‘dashboard’ of measures to prevent practitioners focusing on incentivized activities at the expense of other effective healthcare.

We would add that rewards also need to encourage and require teamwork. An example would be that interprofessional behaviour in obstetrics will likely differ between an output- (e.g. paying for a delivery) and an outcome-based scheme (e.g. rewarding for newborn and maternal well-being).

In New Zealand, we suggest four work streams. The first is to use current service reviews to identify ‘bad’ rewards elements and to fix them. This is incremental reform.

The second is more revolutionary and is to look at how the primary care capitation could be rendered productivity- and health need-responsive in accord with the lessons cited above.

Third, a rewards scheme should be introduced to enable ‘virtual’ health encounters and e-health in general. A fee for service approach will always lead to fragmentation of care as remuneration is transactional. We cite an example of a 3-month episode of poor diabetes control, which involved six provider contacts, two hospitalizations for falls and 3 days off work for another family member. Given a shared-care record and a reward system that enables ‘virtual consultations’, the same outcome could have been achieved in an hour and with
a single district health nurse contact – with neither hospitalizations nor days off work. An outcome-linked capitation (e.g., linked to hospitalization rates and the rate of progression to renal failure in diabetics in the enrolled cohort) is one possibility.

Fourth and finally, consumer-oriented incentives should be developed and tested; in addition to people ‘owning and managing’ their health records, this is a necessity if healthcare is to shift from a largely passive-consumer, provider-centred system to one in which there is real consumer engagement and accountability.

References
CLINICAL PERSPECTIVES

How we mobilize haemopoietic stem cells

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Key words
haemopoietic stem and progenitor cell, stem cell mobilization, G-CSF, stem cell factor, plerixafor.

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Received 21 March 2011; accepted 30 May 2011.

Abstract
Mobilization and collection of haemopoietic stem and progenitor cells (HSPC) is the cornerstone of autologous and allogeneic stem cell transplantation for a wide variety of haematological and some non-haematological malignancies. Centres providing this service face the challenge of optimizing the likelihood of successful collection of transplantable doses of cells, while maximizing the efficiency of the apheresis unit and minimizing the risk of toxicity as well as mobilization failure. Recent developments in the understanding of the molecular mechanisms of mobilization have led to the emergence of novel strategies for HSPC mobilization, which may assist in meeting these imperatives. The task for clinicians is how to incorporate the use of these strategies into practice, in the light of emerging evidence for efficacy and safety of these agents. Herein, the literature is reviewed, and a proposed algorithm for HSPC mobilization is presented.

Introduction
Transplantation of autologous and allogeneic haemopoietic stem and progenitor cells (HSPC) is an established therapy in haematological malignancies. In aggressive lymphoma and myeloma, autologous stem cell transplantation enables the delivery of potentially curative high-dose chemotherapy (and radiotherapy), by using HSPC infusions to reconstitute marrow function, thus improving patient survival. Allogeneic transplantation has similarly improved survival in many haematological malignancies, metabolic disorders, immunodeficiencies and marrow failure syndromes, partly by facilitating high-dose therapy and partly by the graft-versus-tumour/host effect. Mobilized peripheral blood provides greater CD34+ cell numbers than products obtained from bone marrow, resulting in more rapid haemopoietic reconstitution. This reduces hospitalization, blood product usage and infection risk. It also facilitates the treatment of older patients who may otherwise be at risk from complications.

While the minimum recommended stem cell dose for transplantation is $2 \times 10^8$ CD34+ cells/kg body weight, it is known that $\geq 5 \times 10^6$/kg provides more rapid and complete engraftment. The collection of high numbers of stem cells is also required for patients who may require repeat autografting, particularly as later attempts at collection may not succeed.

In normal volunteer donors, granulocyte colony-stimulating factor (rHuG-CSF, usually referred to as G-CSF) is the standard drug used to mobilize HSPC for collection through apheresis. In patients, mobilization regimens utilizing either G-CSF alone, or G-CSF following chemotherapy have been used. Approximately 10–20% of patients, and up to 60% of those exposed to stem cell toxic therapies, fail to collect adequate numbers of HSPC. Many strategies to improve mobilization have been attempted, but the re-mobilization success rate in prior failed mobilizers is less than 50%. Plerixafor, a CXCR4 antagonist that reduces the binding of stem cells to the marrow stroma has been available in Australia.

Funding: K. E. H. was funded by a Cancer Council of Victoria Early Career Clinician Researcher Grant. J.-P. L. was supported by a Senior Research Fellowship from the Cancer Council Queensland.

Conflict of interest: None.
since 2007. It is therefore timely to re-evaluate approaches to HSPC mobilization to maximize the efficiency of this costly procedure. Herein, a group of clinical and research haematologists recommend an optimal HSPC mobilization strategy using currently available drugs and regimens based on clinical experience and a review of the literature.

**The mechanism of HSPC mobilization: what is happening at the bone marrow level?**

Under steady state conditions, the bone marrow extravascular compartment allows a small proportion of resident HSPC to enter the circulation continuously and then return. Mobilization of HSPC is the induced amplification of HSPC microvascular re-circulation. The exact pathway(s) involved in mobilization are still not yet fully known; however, key cellular and intercellular events include HSPC proliferation, deregulation of bone marrow niches in which they reside, activation of proteases, perturbation of adhesive and chemotactic interactions between HSPC and their niche, and activation of chemotaxis.7,8

HSPC express CXCR4, the receptor for the chemokine stromal derived factor-1 (SDF-1, also known as CXCL12) in the bone marrow. The CXCR4/SDF-1 interaction promotes cellular ‘homing’ and retention in the marrow niche. One of the known mechanisms of action of G-CSF and other mobilizing cytokines is through disruption of the CXCR4/SDF-1 interaction. HSPC mobilization occurs consequent to weakening of the SDF-1 gradient that retains HSPC within the marrow, and/or by downregulation of SDF-1 expression in stromal cells in HSPC niches. Plerixafor, a novel CXCR4 antagonist, utilizes this pathway to produce its highly efficacious mobilization effect, especially in synergy with G-CSF.

G-CSF may also act by inducing the loss of a specific population of bone marrow macrophages that express the G-CSF receptor. These macrophages are necessary to maintain the function of HSPC niche cells, particularly the expression of SDF-1 and cell adhesion molecules, which retain HSPC within their niches. Three independent groups have recently shown that when these bone marrow macrophages disappear, as a result of G-CSF administration or other genetic manipulations, expression of SDF-1, Kit ligand or the cell adhesion molecule VCAM-1 by niche cells is downregulated resulting in HSPC mobilization.9–11 Myelosuppressive chemotherapy may also contribute to mobilization through similar mechanisms. Other known agents and pathways involved in mobilization are outside the scope of this article.

**Mobilization protocols**

G-CSF alone is administered at 10 μg/kg subcutaneously per day (either single dose or split over a twice-daily dose). Apheresis takes place between the fifth and seventh days following commencement of G-CSF. A dose–response relationship exists for G-CSF especially in cytokine-alone mobilization regimens, and particularly in poor mobilizers. This approach is most suited to patients with good disease response, uninvolved bone marrow, and where predictable timing of apheresis and outpatient-based mobilization is a priority. Side-effects are uncommon but include bone pain, injection-site reaction, fever and elevated alkaline phosphatase. The theoretical risk of leukaemia after exposure of healthy donors to G-CSF has been raised, but a large series using registry data of over 20 000 allogeneic donors mobilized using G-CSF found a risk of haematological malignancy similar to that in the general population.12

G-CSF with chemotherapy mobilization regimens are for patients already receiving tumour debulking chemotherapy, or if mobilization response to G-CSF alone is expected to be poor. Chemotherapy + G-CSF (5–10 μg/kg daily subcutaneously after completion of chemotherapy) mobilization may result in higher HSPC yields compared with G-CSF alone. Chemotherapy, such as CHOP, DHAP and ICE, have been used or single doses of cyclophosphamide from 1 to 5 g/m². Mobilization usually occurs when the leukocyte count is $>2 \times 10^9$/L. The disadvantages are uncertainty about timing of apheresis and the associated risk of cytopenic complications.

Stem cell factor (rhSCF) binds to c-kit on the surface of HSPC, modulating their proliferation and adhesion. As a single agent rhSCF has limited efficacy, however synergy between SCF and G-CSF has been noted in upfront-, as well as in re-mobilizations,7 and in prior fludarabine-exposed patients.6 SCF (20 μg/kg subcutaneously) is started 4 days prior to start of G-CSF and continued with the G-CSF till the end of apheresis. Because of the risk of anaphylactoid reactions, patients require histamine blockade and rhSCF is not available in many countries for this reason.

Plerixafor has proven effective and safe (usually at doses of 240 μg/m²) in mobilizing CD34+ cells either as a single agent or in combination with G-CSF in healthy volunteers and in patients with lymphoma or multiple myeloma.13,14 In prior failed mobilizers, plerixafor improves CD34+ collections by more than 50% in 84% of cases. Plerixafor plus G-CSF can achieve target CD34+ cell yields following one or two aphereses, which is more than double the yield achieved with G-CSF alone.15

Common toxicities of plerixafor include diarrhea, nausea, fatigue, injection-site erythema, headache,
arthralgia, dizziness and vomiting but in general toxicities tend to be mild.

Plerixafor has received FDA approval for mobilization in lymphoma and myeloma, and in Australia it has achieved TGA listing. A major concern with plerixafor in Australia is cost, yet re-mobilization is also costly in resource utilization and patient discomfort. Several algorithms are therefore being considered to restrict use of this drug to patients who are most likely to benefit.16,17

**How to maximize success and minimize failure**

Failure to mobilize HSPC is observed in 5% of healthy donors and up to 60% of cancer patients. The cost of failed collection is multifaceted, including the loss of transplantation as a therapeutic option, the costs of second or multiple attempts to collect cells, patient inconvenience, morbidity and occasionally mortality, plus the psychological impact that failed mobilization has on the patient or donor concerned. Strategies to minimize the risk of failure on the first attempt, as well as ways to optimize the likelihood of success on subsequent attempts for failed mobilizers, are therefore crucial (Fig. 1).

**Figure 1** Suggested algorithm for first and second mobilization attempts. G-CSF, granulocyte colony-stimulating factor.

Identifying poor mobilizers

Reliable predictors of poor mobilization have not been identified in healthy donors or pretreated autologous
patients. However, several factors are associated with poor mobilization yields.

**Patient and disease factors**

Non-modifiable factors predicting poor mobilization include advancing age, female gender and patients with bone marrow involvement at diagnosis.\(^18,19\)

**Bone marrow reserve**

The most consistent predictor for mobilization failure is pre-mobilization thrombocytopenia (either with thresholds of \(<150 \times 10^9/L\) or \(<100 \times 10^9/L\), or as a continuous variable). Other markers include steady state bone marrow CD34\(^+\) cell numbers, marrow cellularity and the requirement for G-CSF (where not given routinely) during prior chemotherapy.

**Prior therapy**

Exposure to prolonged or high-dose alkylating agents, nitrosoureas and fludarabine, as well as prior large field radiation therapy has been associated with poor mobilization. A failure rate of up to 59% for collection was described in chronic lymphocytic leukaemia patients following fludarabine use, particularly with more prior fludarabine cycles, <2 months since fludarabine exposure and prior fludarabine-cyclophosphamide combination therapy.\(^20\)

Biological agents, such as the immunomodulatory agents, may also impair stem cell mobilization although, at least with lenalidomide, this block may be overcome with the use of chemotherapy- or plerixafor-containing mobilizing regimens.\(^21,22\)

**Identifying suboptimal mobilizers during G-CSF treatment**

As CD34\(^+\) yield can be estimated based on blood levels, real-time CD34\(^+\) cell measurements on the morning of expected apheresis help to identify patients who are not mobilizing well. Thresholds for collection can then be based on individualized apheresis targets, thus facilitating the development of risk-adapted algorithms for agents, such as plerixafor.\(^23\)

**Strategies to improve mobilization yield:**

For the first mobilization, it would be preferable to perform mobilization prior to excessive exposure to stem cell toxic chemoradiotherapy. The choice between G-CSF alone or G-CSF with chemotherapy is based on institutional practice, and whether the patient is a predicted poor mobilizer or requires chemotherapy for their disease. Patients with a good risk profile are likely to succeed with either. A suggested algorithm for first and second attempts at mobilization is depicted in Figure 1.

For failed mobilizers, it is reasonable to allow at least 3 weeks for recovery prior to another mobilization attempt, particularly if chemotherapy was used initially. An alternative approach is to halt apheresis after 2–3 days, and immediately re-mobilize with an increased dose of G-CSF.\(^24\) This approach might be superseded by plerixafor.

**Options for re-mobilization include:**

1. Dose escalated G-CSF
2. Re-mobilization with chemotherapy plus cytokine may be attempted after a prior failed attempt with cytokine-alone.
3. SCF with G-CSF ± chemotherapy, probably the most widely used salvage regimen for failed mobilizers in Australia, may be superseded by the availability of plerixafor.
4. Plerixafor with G-CSF ± chemotherapy: a risk-adapted algorithm may be the most appropriate use of this regimen within Australia (see below).
5. Marrow harvest. In patients with refractory poor mobilization or contraindication to apheresis or stem cell mobilization regimens, this approach provides little benefit over repeat attempts at peripheral blood HSPC mobilization\(^23\) and haemopoietic recovery is often slower.

The addition of plerixafor to G-CSF ± chemotherapy is more likely to succeed for poor mobilizers than other salvage regimens.\(^26\) Cost considerations may limit the use of plerixafor in a pre-emptive manner as approved by the FDA. Hence a risk-adapted approach may be more suitable in Australia. Plerixafor added to G-CSF (with or without chemotherapy) could be used pre-emptively in re-mobilization attempts in prior failed mobilizer patients, and could be considered upfront for patients with prior exposure to potent stem cell toxic agents, such as fludarabine, melphalan and nitrosoureas. Alternatively, plerixafor could be added as ‘immediate salvage’ when a conventional mobilization regimen is clearly failing, as defined by (i) low blood CD34\(^+\) levels at the time of expected apheresis or (ii) low yield on the first day of apheresis, where it is unlikely that the target yield will be achieved in less than two apheresis procedures. For the former, CD34\(^+\) levels of <6/\(\mu\)L after 4 or 5 days of G-CSF or when the leucocyte count is around \(2 \times 10^9/L\) with G-CSF + chemotherapy mobilization would be considered adequate triggers. Thresholds based on PBCD34\(^+\) counts are not linear, as it has been noted that the incremental benefit in terms of improved PBCD34\(^+\) count and
yield is not linear, with the poorest mobilizers benefiting most from the addition of plerixafor.\(^27\) For yield, <50% of the target yield on the first day of apheresis could trigger the immediate salvage protocol. In this context, plerixafor is added on the evening of the trigger event, and continued until the target is reached or until the attempt is deemed a failure.

There are no Australian data on cost-effectiveness of plerixafor use. The cost of one dose of plerixafor is between that of one and two apheresis/cryopreservation so if plerixafor use leads to two fewer apheresis/cryopreservation procedures, there should be saving. Furthermore, re-mobilization would incur the cost of a second round of G-CSF/chemotherapy/neutropenia so the immediate salvage and re-mobilization use of plerixafor seems justified.

Ideally, institutions should develop site-specific algorithms for risk-adapted plerixafor-based mathematical modelling from their own historical data, thus allowing for differences in local apheresis practices and their own historical data. As an example, a suggested algorithm for risk-adapted plerixafor is depicted in Figure 2, and Table 1 proposes triggers for addition of plerixafor, aiming at successful collection within two aphereses. Institutional algorithms could have higher thresholds for addition of plerixafor if the aim to complete collection in less than two aphereses is not as strong an imperative.

**Table 1** Suggested thresholds for addition of ‘immediate rescue’ plerixafor during a conventional mobilisation regimen. (Adapted from Alexander,\(^28\) Costa et al.\(^17\) and Abhyankar et al.\(^29\))

<table>
<thead>
<tr>
<th>Target CD34(^*) + yield within two apheresis procedures</th>
<th>Add plerixafor on D4 (or expected first day of apheresis) if PBCD34(^*) count ≤</th>
<th>Or add plerixafor on the evening of day 1 apheresis if day 1 apheresis yield &lt;50% of target</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 × 10(^6)/kg</td>
<td>10(µL)</td>
<td>1 × 10(^6)/kg</td>
</tr>
<tr>
<td>3 × 10(^6)/kg</td>
<td>14(µL)</td>
<td>1.5 × 10(^6)/kg</td>
</tr>
<tr>
<td>4 × 10(^6)/kg</td>
<td>18(µL)</td>
<td>2 × 10(^6)/kg</td>
</tr>
<tr>
<td>5 × 10(^6)/kg</td>
<td>21(µL)</td>
<td>2.5 × 10(^6)/kg</td>
</tr>
<tr>
<td>6 × 10(^6)/kg</td>
<td>25(µL)</td>
<td>3 × 10(^6)/kg</td>
</tr>
</tbody>
</table>

Thresholds are based on the aim to achieve target collection within two to three apheresis procedures. PBCD34\(^*\), peripheral blood CD34\(^*\) count.
Conclusions

The imperative to achieve a successful HSPC mobilization at the first attempt in a minimum number of apheresis procedures is now more achievable with protocols based on rational patient selection, collection targets, thresholds for commencing and stopping apheresis, timing of mobilization attempts and the appropriate use of novel agents. Incorporation of these approaches will also improve the cost:benefit thereby providing for cost-effective HSPC-based therapies.

Acknowledgement

The authors thank Mrs D Landorf for administrative assistance.

References


Management of metastatic renal cell carcinoma in the era of targeted therapies

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Key words renal, carcinoma, survival, retrospective.

Background: Metastatic renal cell cancer is associated with poor prognosis and survival and is resistant to conventional chemotherapy. Therapeutic targeting of molecular pathways for tumour angiogenesis and other specific activation mechanisms offers improved tumour response and prolonged survival.

Aims: To conduct a retrospective audit of metastatic renal cell carcinoma patients treated with targeted therapies.

Methods: Data were extracted from clinical records of patients undergoing targeted treatment between 2005 and 2009 at two hospital sites. Data collected included pathology, systemic therapy class, toxicity and survival. Univariate and multivariate survival analyses were performed.

Results: Sixty-one patients were treated with 102 lines of therapy with a median overall survival (OS) of 23 months, median time to failure of first-line treatment (TTF1) of 10 months and median time to failure of second-line treatment (TTF2) of 5.2 months. Time from first diagnosis to treatment >12 months was significantly associated with improved OS, longer TTF1, TTF2 and response to first-line anti-vascular endothelial growth factor receptor tyrosine kinase inhibitors (anti-VEGF TKI) therapy. Variables associated with tumour biology, natural history and the systemic inflammatory response were associated with improved OS and TTF1. Development of hypertension was predictive of anti-VEGF TKI outcome. Toxicities were as expected for each drug class.

Conclusions: Survival and toxicity outcomes from two Australian sites are comparable to published data. The adverse event profile differs to conventional chemotherapy. Clinicians caring for patients with metastatic renal cancer will need to become familiar with these toxicities and their management as these agents enter widespread use.

REVIEW

Management of metastatic renal cell carcinoma in the era of targeted therapies
Introduction
Renal cell carcinoma accounts for 2–3% of adult malignancies.1 Surgical resection of localized renal cell carcinoma results in a 5-year survival of around 90%.2 For patients with distant metastatic disease, outcomes are significantly worse, with 5-year survival rates of 6%.1 Metastatic renal cell carcinoma is resistant to conventional chemotherapy, with objective response rates of less than 10%.3

Ninety per cent of clear cell renal carcinomas have a sporadic mutation of the Von-Hippel-Lindau (VHL) tumour suppressor gene, which is inherited in the VHL syndrome.4,5 The VHL protein downregulates hypoxia-inducible factor (HIF). VHL inactivation or hypoxia cause HIF accumulation, leading to promotion of two proteins that promote tumour angiogenesis: vascular endothelial growth factor (VEGF) and platelet-derived growth factors.4 HIF accumulation can also occur by activation of the mammalian target of rapamycin (mTOR) pathway.

Management of metastatic renal cell carcinomas has been revolutionized by therapeutic targeting of these three molecular pathways, resulting in treatments that result in tumour response and prolonged survival (Table 1).7–19 However, these targeted therapies are associated with toxicities that differ to those of conventional chemotherapy.

In this article, we share our experience of treating 61 patients with three classes of targeted therapies for metastatic renal cell carcinoma and provide an overview of the biological basis and evidence for the use of these agents, along with suggestions for toxicity management.

Methods
Clinical databases at two sites (Prince of Wales Hospital, Randwick, and Canberra Hospital) were reviewed for patients treated for metastatic renal cell carcinoma between 2005 and 2009. Some patients were treated in previously reported clinical trials.2,5,10,15,19–21 Pathology, systemic therapy, toxicity and survival data were retrieved and analysed for three classes of therapy (anti-VEGF tyrosine kinase inhibitor (TKI), mTOR, bevacizumab and interferon alpha); cross-comparisons of agents within classes were not performed. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.22

Predictors of outcome (performance status, calcium, albumin, lactate dehydrogenase (LDH), white cell count (WCC), neutrophils, platelets, haemoglobin, nephrectomy, Fuhrman nuclear grade and blood pressure) were collected at commencement of a line of targeted therapy. Patients were grouped using the Memorial Sloan-Kettering Cancer Centre (MSKCC) risk model: Karnofsky performance status < 80, haemoglobin < lower limit of normal, corrected calcium > 2.5 mmol/L, LDH > 1.5× upper limit of normal (ULN) and time from diagnosis to first-line treatment < 12 months.23 Patients were grouped as favourable (0 factors), intermediate (1, 2) and poor risk (≥3).

Univariate survival analyses were performed using the Kaplan–Meier method with log–rank (Mantel–Cox) comparisons. Overall survival (OS) was calculated from the time of commencing first-line therapy. Time to treatment failure (TTF) was calculated for first- (TTF1) and second-line (TTF2) therapy from commencement of therapy to date of progression or death. Predictors of TTF of third- and fourth-line therapy were not assessed due to small numbers. An exploratory analysis of survival and TTF was also undertaken among patients who received anti-VEGF TKIs in the first-line setting to assess prognostic or predictive factors in this subgroup. For the purposes of this analysis development of hypertension was defined as any grade of hypertension according to the CTCAE (i.e. increase by > 20 mmHg (diastolic) or to > 150/100 if previously within normal limits, or requiring intervention). Factors identified on univariate analysis as having an impact on survival or TTF with statistical significance of P = 0.1 or less were included in a multivariate analysis using the Cox proportional hazards model. The composite MSKCC risk score was not included in this model.

Analysis of response was based on clinical notes and was analysed with Chi-squared/Fisher’s exact test. Missing data (<5%) were excluded from analysis. Serum LDH was missing from 18% of patients at baseline.

This study was approved by the South East Sydney and Illawarra Area Health Service and ACT Health Human Research Ethics Committees.

Results
Patients
Between 2005 and 2009, 61 patients were treated for metastatic renal cell carcinoma at the two sites, with a total of 102 lines of therapy. One patient who received conventional chemotherapy in the first- and second-line setting prior to being referred for third-line treatment

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595
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<tr>
<th>Agent</th>
<th>Key study(s)</th>
<th>Patient group</th>
<th>Arms</th>
<th>n</th>
<th>OS (months)</th>
<th>PFS (months)</th>
<th>RR (%)</th>
<th>Grade 3/4 toxicity</th>
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<td>Anti-angiogenic monoclonal antibody therapy</td>
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<td>Bevacizumab</td>
<td>Rini et al. 2008, Rini et al. 2010</td>
<td>First-line metastatic clear cell renal carcinoma</td>
<td>Bevacizumab 10 mg/kg q 2/52 + interferon-α2b 9 × 10⁶ IU 3×/week</td>
<td>369</td>
<td>18.3</td>
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<td>25.5</td>
<td>Hypertension 9%, anorexia 17%, fatigue 35%, proteinuria 13%</td>
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<td>Placebo + interferon-α2b 9 × 10⁶ IU 3×/week</td>
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<td>17.4</td>
<td>5.2</td>
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<td>Bevacizumab 10 mg/kg q 2/52 + interferon-α2a 9 × 10⁶ IU 3×/week</td>
<td>327</td>
<td>23.3</td>
<td>10.2</td>
<td>31</td>
<td>Hypertension 3%, proteinuria 7%, fatigue 12%</td>
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<td></td>
<td></td>
<td>Placebo + interferon-α2a 9 × 10⁶ IU 3×/week</td>
<td>322</td>
<td>21.3</td>
<td>5.4</td>
<td>13</td>
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<td>Anti-angiogenic tyrosine kinase inhibitors</td>
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<td>Sunitinib</td>
<td>Motzer et al. 2007, Motzer et al. 2009</td>
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<td>Sunitinib 50 mg daily 4 weeks on,</td>
<td>375</td>
<td>26.4</td>
<td>11</td>
<td>ORR 47</td>
<td>Diarrhoea 9%, nausea 5%, HFS 9%, hypertension 12%, neutropenia 18%, fatigue 1%</td>
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<td>2 weeks off, interferon-α2a 9 × 10⁶ IU 3×/week</td>
<td>375</td>
<td>21.8</td>
<td>5</td>
<td>ORR 12</td>
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<td>Sorafenib</td>
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<td>Second-line metastatic</td>
<td>Sorafenib 400 mg bd continuously</td>
<td>451</td>
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<td>5.9</td>
<td>10</td>
<td>Hypertension 4%, HFS 6%, fatigue 5%, diarrhoea 2%</td>
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<td></td>
<td>Placebo</td>
<td>452</td>
<td>15.2</td>
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<td>Pazopanib</td>
<td>Stemberg et al. 2010</td>
<td>Treatment naive or 1 prior cytokine therapy for metastatic disease</td>
<td>Pazopanib 800 mg</td>
<td>290</td>
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<td>9.2</td>
<td>30</td>
<td>Diarrhoea 4%, hypertension 4%, LFT abnormalities 12%</td>
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<td></td>
<td></td>
<td>Placebo</td>
<td>145</td>
<td>—</td>
<td>4.2</td>
<td>3</td>
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<tr>
<td>Axitinib</td>
<td>Rixe et al. 2007†</td>
<td>Failed prior cytokines for metastatic disease</td>
<td>Axitinib 5 mg bd</td>
<td>52</td>
<td>29.9</td>
<td>15.7</td>
<td>44.2</td>
<td>Fatigue 4%, hypertension 8%, diarrhoea 5%</td>
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<td>Rini et al. 2009†</td>
<td>1 or more prior lines of therapy including sorafenib</td>
<td>Axitinib 5 mg bd</td>
<td>62</td>
<td>13.6</td>
<td>7.4</td>
<td>22.6</td>
<td>HFS 16%, fatigue 16%, hypertension 16%, dyspnoea 14%, diarrhoea 15%, dehydration 8%, hypotension 7%</td>
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<tr>
<td>mTOR inhibitors</td>
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<td>Temsirolimus</td>
<td>Hudes et al. 2007</td>
<td>First-line metastatic with poor prognostic features</td>
<td>Temsirolimus 25 mg weekly</td>
<td>207</td>
<td>10.9</td>
<td>5.5</td>
<td>8.6</td>
<td>Fatigue 11%, dyspnoea 9%, hyperglycaemia 11%, hypercholesterolaemia 3%, anaemia 20%</td>
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<td>interferon-α2a 18 × 10⁶ IU 3×/week</td>
<td>209</td>
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<td>3.1</td>
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<td>Temsirolimus 15 mg weekly + interferon-α2a 6 × 10⁶ IU 3×/week</td>
<td>210</td>
<td>8.4</td>
<td>4.7</td>
<td>8.1</td>
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<td>Everolimus</td>
<td>Motzer et al. 2008†</td>
<td>Metastatic disease after 1–2 lines prior anti-VEGF TKI</td>
<td>Everolimus 10 mg daily</td>
<td>272</td>
<td>Not reached</td>
<td>4.0</td>
<td>1</td>
<td>Stomatitis 3%, infection 3%, pneumonia 3%, anaemia 10%, lymphopenia 15%, hyperglycaemia 12%, hypercholesterolaemia 3%</td>
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<td></td>
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<td>Placebo</td>
<td>138</td>
<td>8.8</td>
<td>1.9</td>
<td>0</td>
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</table>

†Phase II data only. HFS, hand–foot syndrome; IU, international units; LFT, liver function test; mTOR, mammalian target of rapamycin; n, number; ORR, overall response rate; OS, overall survival; PFS, progression free survival; RR, response rate; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
was excluded from analysis. Table 2 shows patient demographic and tumour characteristics. Table 3 details agents and lines of therapy.

Table 2 Patient demographics and tumour characteristics at baseline (n = 60)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>41 (68.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (31.7%)</td>
</tr>
<tr>
<td>Age at diagnosis (mean, range)</td>
<td>59.2 years (36.5–82.9)</td>
</tr>
<tr>
<td>Age at starting first-line therapy (mean, range)</td>
<td>61.8 years (38.3–84.3)</td>
</tr>
<tr>
<td>Time from diagnosis to starting first-line therapy (mean, range)</td>
<td>31.5 months (0.2–227.2)</td>
</tr>
<tr>
<td>ECOG performance status at baseline (n, %)</td>
<td>0 (51.6%), 1 (38.3%), 2 (8.3%), 3 (1.7%)</td>
</tr>
<tr>
<td>MSKCC risk grouping at baseline (n, %)</td>
<td>Favourable (23.3%), Intermediate (61.7%), Poor (15.0%)</td>
</tr>
<tr>
<td>Prior nephrectomy (n, %)</td>
<td>49 (81.7%)</td>
</tr>
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<td>Histology (n, %)</td>
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<tr>
<td>Clear cell</td>
<td>47 (78.3%)</td>
</tr>
<tr>
<td>Papillary</td>
<td>4 (6.7%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>28 (46.7%)</td>
</tr>
<tr>
<td>Biochemical variables (mean, range)</td>
<td></td>
</tr>
<tr>
<td>Corrected calcium (mmol/L)</td>
<td>2.44 (2.14–3.27)</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>246 (121–768)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>37.5 (22–49)</td>
</tr>
<tr>
<td>Haematological variables (mean, range)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>126 (64–165)</td>
</tr>
<tr>
<td>WCC (x10^9/L)</td>
<td>7.50 (2.9–12.8)</td>
</tr>
<tr>
<td>Neutrophil count (x10^9/L)</td>
<td>4.93 (1.4–10.6)</td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>304 (134–872)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MSKCC, Memorial Sloan-Kettering Cancer Centre; WCC, white cell count.

Survival

Median OS was 23 months from commencing first-line therapy. At the time of analysis, there were 39 deaths: 37 from progressive metastatic disease and two from other causes. No deaths were related to treatment toxicity.

Median TTF1 was 10.0 months and TTF2 was 5.2 months. Table 4 shows a univariate analysis of factors associated with OS, TTF1 and TTF2.

Overall survival and types of therapy received

The longest OS (47.5 months) was experienced by patients exposed to all three classes of therapy. Median survival was 37.7 months with anti-angiogenic (bevacizumab and/or anti-VEGF TKI) + cytokine therapy, 17.5 months with anti-VEGF TKI + mTOR therapy, 14.7 months with anti-VEGF TKI-only therapy and 0.5 months with mTOR inhibitor-only therapy. Note that these results contain inherent selection bias associated with choice of therapy (e.g. mTOR inhibitors were largely prescribed to poor prognosis patients).

Predictors of overall survival

Univariate analysis revealed an association between significantly longer OS from the time of starting first-line targeted therapy and the following factors: superior Eastern Cooperative Oncology Group (ECOG) status (P < 0.001), clear cell histology (P = 0.006), favourable MSKCC risk group (P < 0.001), time from diagnosis to first-line therapy ≥12 months (P < 0.001), normal serum albumin (P = 0.009), no anaemia (P = 0.001) and no bone metastases (P = 0.012). There was a trend toward normal platelet count at baseline (P = 0.051) and having received a nephrectomy (P = 0.064) as being prognostic factors.

Multivariate analysis revealed an independent association between improved OS and the following factors: clear cell histology (P = 0.005), time from diagnosis to treatment >12 months (P < 0.001), neutrophils < ULN (P = 0.022) and favourable ECOG score (P = 0.032).

Predictors of time to failure of first-line treatment

Statistically significant predictors of longer TTF1 were: favourable MSKCC risk group (P = 0.035), superior from progressive metastatic disease and two from other causes. No deaths were related to treatment toxicity.

Median TTF1 was 10.0 months and TTF2 was 5.2 months. Table 4 shows a univariate analysis of factors associated with OS, TTF1 and TTF2.
### Table 4  Baseline variables associated with OS, TTF1 and TTF2 on univariate survival analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>OS (months)</th>
<th>TTF1 (months)</th>
<th>TTF2 (months)</th>
<th>P</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 60)</td>
<td>(n = 60)</td>
<td>(n = 27)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21.9</td>
<td>8.0</td>
<td>5.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35.8</td>
<td>10.2</td>
<td>6.2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ECOG performance status</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.344</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>35.8</td>
<td>12.3</td>
<td>6.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14.7</td>
<td>8.7</td>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5.9</td>
<td>3.6</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
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<tr>
<td>MSKCC risk grouping</td>
<td>&lt;0.001*</td>
<td>0.035*</td>
<td>0.445</td>
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<tr>
<td>Favourable</td>
<td>47.5</td>
<td>18.2</td>
<td>7.4</td>
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<tr>
<td>Intermediate</td>
<td>16.7</td>
<td>9.1</td>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>9.4</td>
<td>3.6</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior nephrectomy</td>
<td>0.064</td>
<td>0.193</td>
<td>0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26.5</td>
<td>10.2</td>
<td>6.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14.7</td>
<td>8.0</td>
<td>1.6</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Histology</td>
<td>0.006*</td>
<td>0.026*</td>
<td>0.593</td>
<td></td>
<td></td>
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<tr>
<td>Clear cell</td>
<td>30.4</td>
<td>11.5</td>
<td>5.2</td>
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<tr>
<td>Papillary</td>
<td>23.9</td>
<td>10.2</td>
<td>6.2</td>
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<tr>
<td>Mixed</td>
<td>14.8</td>
<td>5.4</td>
<td>7.4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sarcomatoid</td>
<td>9.4</td>
<td>5.0</td>
<td>2.1</td>
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<td></td>
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</tr>
<tr>
<td>Fuhrman nuclear grade</td>
<td>0.109</td>
<td>0.103</td>
<td>0.335</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30.4</td>
<td>17.8</td>
<td>4.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16.7</td>
<td>8.0</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>14.2</td>
<td>7.4</td>
<td>5.2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Presence of bony metastases</td>
<td>0.012*</td>
<td>0.030*</td>
<td>0.865</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Present</td>
<td>14.7</td>
<td>8.0</td>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>38.5</td>
<td>11.5</td>
<td>7.4</td>
<td></td>
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</tr>
<tr>
<td>Time from diagnosis to treatment</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.004*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>11.4</td>
<td>7.4</td>
<td>2.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>44.2</td>
<td>18.7</td>
<td>10.6</td>
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<tr>
<td>Corrected calcium</td>
<td>0.077</td>
<td>0.516</td>
<td>0.045*</td>
<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>26.5</td>
<td>10.4</td>
<td>6.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated (&gt;2.5 nmol/L)</td>
<td>14.7</td>
<td>8.7</td>
<td>1.6</td>
<td></td>
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<tr>
<td>LDH</td>
<td>0.441</td>
<td>0.518</td>
<td>0.037*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5x ULN</td>
<td>18.3</td>
<td>10.0</td>
<td>5.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.5xULN</td>
<td>39.7</td>
<td>6.1</td>
<td>28.2</td>
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<td></td>
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<tr>
<td>Haemoglobin</td>
<td>0.001*</td>
<td>0.003*</td>
<td>0.908</td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
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<td>12.3</td>
<td>6.2</td>
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</tr>
<tr>
<td>Anaemic range (&lt;115 for women, &lt;130 for men)</td>
<td>10.5</td>
<td>6.1</td>
<td>4.6</td>
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<tr>
<td>Albumin</td>
<td>0.009*</td>
<td>0.004*</td>
<td>0.695</td>
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<tr>
<td>&lt;LLN</td>
<td>10.8</td>
<td>5.0</td>
<td>4.6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>23.9</td>
<td>10.8</td>
<td>5.2</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>WCC</td>
<td>0.196</td>
<td>0.105</td>
<td>0.376</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Normal</td>
<td>23.0</td>
<td>10.4</td>
<td>5.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>10.8</td>
<td>3.7</td>
<td>4.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>0.086</td>
<td>0.048*</td>
<td>0.046*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>26.5</td>
<td>10.8</td>
<td>6.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>10.8</td>
<td>4.1</td>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>0.051</td>
<td>0.233</td>
<td>0.321</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>23.9</td>
<td>10.2</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>10.8</td>
<td>3.7</td>
<td>4.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; LLN, lower limit normal; MSKCC, Memorial Sloan-Kettering Cancer Centre; OS, overall survival; TTF1, time to first treatment failure; TTF2, time to second treatment failure; ULN, upper limit normal; WCC, white cell count.
ECOG score ($P < 0.001$), time from diagnosis to treatment > 12 months ($P < 0.001$), clear cell histology ($P = 0.026$), normal serum albumin ($P = 0.004$), no anaemia ($P = 0.003$), neutrophils < ULN ($P = 0.048$) and no bony metastases ($P = 0.030$; univariate analysis).

Predictors of superior TTF1 were: time from diagnosis to treatment > 12 months ($P < 0.001$), no bone metastases ($P = 0.042$) and neutrophils < ULN ($P = 0.020$; multivariate analysis).

### Predictors of time to failure of second-line treatment

Predictors of longer TTF2 were: prior nephrectomy ($P = 0.001$), normal serum calcium ($P = 0.045$), LDH < 1.5× ULN ($P = 0.037$), neutrophils < ULN ($P = 0.046$) and time from diagnosis to treatment > 12 months ($P = 0.004$; univariate analysis). Multivariate analysis was unfeasible given small numbers.

### Exploratory analysis among patients who received anti-VEGF TKIs in the first-line setting

Among patients who received anti-VEGF TKIs in the first-line setting, median OS was 18.3 months. Factors predictive of OS after first-line anti-VEGF TKI were: ECOG score, Fuhrman nuclear grade, MSKCC risk grouping, no anaemia, normal serum albumin, clear cell histology, no bone metastases and time from diagnosis to treatment > 12 months (univariate analysis). Multivariate analysis was limited by sample size.

Median TTF was 9.1 months. Improved TTF was associated with: no anaemia, normal serum albumin, normal WCC, neutrophils < ULN and time from diagnosis to treatment > 12 months. The only factors associated with response on univariate analysis were ECOG performance status, serum albumin and time from diagnosis to treatment > 12 months.

Development of any grade of hypertension on treatment was predictive of both TTF (16.5 vs 5.7 months, $P = 0.032$) and OS (not reached vs 11.7 months, $P = 0.003$). However, development of hypertension was not associated with treatment response.

### Toxicity

Table 5 summarizes toxicity by class of targeted therapy. Most toxicities were class-related; however, comparisons between agents were not performed because of small sample sizes. Some practice pointers based on our experience are also shown in Table 5.

Ten patients ceased treatment due to toxicity. Six cessations (9.5%) were with anti-VEGF TKIs and were due to asymptomatic decline in left ventricular ejection fraction (LVEF 1), diarrhoea (1), erythema multiforme (1), fatigue (1), asymptomatic nephrotic range proteinuria (1) and liver function test abnormalities (1). One patient ceased mTOR inhibitor therapy for toxicity (fatigue, weight loss and diarrhoea), while two patients ceased interferon ± bevacizumab because of gum hypertrophy and gingivitis (1) and interferon-related side-effects (fatigue, headaches, fever and depression, 1). Dose reductions for toxicity were required for anti-VEGF TKIs (27 patients; 43%), interferon ± bevacizumab (six patients; 50%). There were no dose reductions in patients receiving mTOR inhibitors.

As a whole treatment was well tolerated with a spectrum of toxicity comparable to previous reports with these agents. The high incidence of low grade diarrhoea, fatigue, anorexia and nausea is noteworthy, as these problems seldom necessitate treatment interruption, but can have a large effect on patient quality of life.

Two cases warrant particular mention.

A 62-year-old man receiving an anti-VEGF TKI in the first-line setting developed acute pulmonary oedema requiring hospitalization. Electrocardiography showed non-specific ST-T segment changes, troponin I was 0.19 ng/mL and coronary angiography was normal. Echocardiography revealed global left ventricular dysfunction with LVEF 25% and treatment was ceased. Carvedilol and perindopril were commenced, and serial echocardiography revealed improvement in LVEF to 55% over 4 months. Due to evidence of disease progression and a previous good response, the anti-VEGF TKI was reintroduced at a low dose with close cardiac monitoring with repeated response and no further cardiac toxicity.

A 54-year-old man receiving mTOR inhibitor therapy in the third-line setting developed progressive dyspnoea and cough after 8 weeks’ therapy, with computed tomography evidence of pneumonitis. The mTOR inhibitor was ceased and prednisolone 50 mg daily commenced with symptomatic and radiological improvement. Three weeks prior to commencing the mTOR inhibitor, the patient had completed hilar and mediastinal irradiation. It was therefore unclear if the pneumonitis was due to mTOR inhibitor or radiation toxicity. On this basis, the mTOR inhibitor was reintroduced at a reduced dose after a successful wean of steroids, with no adverse effects.

These cases are notable in that there is little literature regarding rechallenge with these agents after cardiac failure or pneumonitis. Our experience supports that cautious rechallenge is feasible with appropriate monitoring.
### Table 5  Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Class of therapy</th>
<th>Notes/practice points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-VEGF TKIs</td>
<td>mTOR inhibitors</td>
</tr>
<tr>
<td></td>
<td>n = 63</td>
<td>n = 18</td>
</tr>
<tr>
<td>All grades (%)</td>
<td>Grade 3–4 (%)</td>
<td>Grade 3–4 (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All grades (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 3–4 (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>44 (70)</td>
<td>8 (44) 0</td>
</tr>
<tr>
<td></td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>42 (67)</td>
<td>8 (44) 1 (6)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>10 (83) 0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>24 (38)</td>
<td>5 (28) 1 (6)</td>
</tr>
<tr>
<td></td>
<td>3 (5)</td>
<td>3 (17) 1 (6)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>33 (52)</td>
<td>3 (17) 0</td>
</tr>
<tr>
<td></td>
<td>2 (3)</td>
<td>0</td>
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<tr>
<td>Mucositis</td>
<td>17 (27)</td>
<td>4 (22) 0</td>
</tr>
<tr>
<td></td>
<td>1 (2)</td>
<td>0</td>
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<tr>
<td>Cutaneous toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>13 (21)</td>
<td>2 (11) 0</td>
</tr>
<tr>
<td></td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>17 (27)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Hair colour change</td>
<td>9 (14)</td>
<td>1 (6) 0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>3 (25) 0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (35)</td>
<td>3 (17) 1 (6)</td>
</tr>
<tr>
<td></td>
<td>4 (6)</td>
<td>2 (17) 0</td>
</tr>
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<td>Proteinuria</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>3 (25) 0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12 (19)</td>
<td>0</td>
</tr>
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</table>

Although the majority of fatigue, nausea, anorexia and diarrhoea were low grade (1 or 2) and seldom necessitated treatment interruption, it is likely that high rates of chronic low grade toxicity have a significant impact on the quality of life of patients treated with these agents.
Haematological toxicity

Neutropenia 7 (11) 0 1 (8) 1 (8)

Thrombocytopenia 11 (17) 4 (6) 2 (11) 0

The majority of haematological toxicity with these agents is low grade. There was no febrile neutropenia or clinically significant bleeding. As a whole haematological toxicity was managed with careful monitoring and dose adjustment without clinical consequence.

Biochemical abnormalities

Liver function test abnormalities 3 (5)

Renal impairment 1 (2) 2 (11)

Thee patients ceased therapy due to LFT abnormalities on anti-VEGF TKIs, all of whom were asymptomatic.

Given the nature of renal carcinoma it is difficult to determine if renal impairment in these cases represents toxicity of treatment or disease.

Dyslipidaemia and hyperglycaemia are class effects of mTOR inhibitors. One patient was treated with pravastatin, although the benefits of lipid-lowering agents in patients with advanced cancer are unclear. All patients with hyperglycaemia were asymptomatic and none required intervention.

Renal impairment 1 (2) 2 (11)

Patients did not routinely undergo cardiac assessment, so the incidence of subclinical declines in LVEF in our series is not known. Two patients ceased treatment due to cardiac dysfunction on anti-VEGF TKIs (symptomatic heart failure with a LVEF of 26% and asymptomatic fall in LVEF to 30%). In both cases, LVEF improved with cessation of the agent and commencement of anti-failure medication. One patient was successfully rechallenged after a 4 month break without further fall in LVEF.

Bowel perforation 1 (2) 1 (2)

Bowel perforation is a rare, but recognized, complication of anti-angiogenic therapy and was seen in one patient after 5 days of an anti-VEGF TKI. Given the short interval between treatment initiation and presentation, it is likely that this was due to the disease rather than toxicity-related.

Pneumonitis 1 (6) 1 (6)

One patient receiving mTOR inhibitor treatment required interruption due to the development of pneumonitis requiring steroids. This patient had received thoracic radiation shortly before symptom onset so it was not initially clear whether the drug was implicated. Symptoms improved with steroids and the mTOR inhibitor was reintroduced after a 2 month break without further respiratory compromise.

Thrombosis 1 (2) 1 (2) 1 (6) 1 (6)

Anti-angiogenic therapy has been associated with both arterial and venous thromboses, and patients with metastatic malignancy are inherently predisposed to thromboembolic disease. It is impossible to establish the role of treatment versus the prothrombotic state of advanced malignancy.

Bleeding 12 (19) 1 (2) 1 (6) 5 (42) 0

Some patients developed low-grade bleeding. Although there is an association between angiogenesis inhibition and increased bleeding risk, the majority of the bleeding was haematuria – which is also a symptom of metastatic renal carcinoma.

LFT, liver function test; LVEF, left ventricular ejection fraction; mTOR, mammalian target of rapamycin; VEGF TKIs, anti-vascular endothelial growth factor receptor tyrosine kinase inhibitors.
Discussion

These findings of a median OS of 23 months, median TTF1 of 10 months and TTF2 of 5.2 months for anti-angiogenic treatment in metastatic renal cancer are comparable to results of published clinical trials (Table 1). The OS finding is also in keeping with the 22 months reported by Heng in a recent retrospective review of over 600 North American patients treated with VEGF-targeted agents.24

Predictors of overall survival

The only baseline variable consistently related to OS, TTF1, TTF2 and response to first-line anti-VEGF TKI therapy was time from diagnosis to treatment > 12 months. This is a crude measure of the natural history of disease, and is an independent predictor of survival among patients treated with anti-VEGF TKIs.24

A nomogram for estimating prognosis in metastatic renal cell carcinoma identified three groups with differences in median survival of 6 months or more (MSKCC risk grouping, poor, intermediate and favourable).21 The MSKCC prognostic model was devised prior to the advent of targeted therapies, but its continuing relevance has been validated by its ability to also stratify patients receiving sunitinib by outcome. In the current study, MSKCC risk groupings were associated with OS and TTF1 (univariate analysis); however, this association did not relate to all components of the score.

In Heng’s retrospective review, components of the MSKCC risk grouping were validated and two new prognostic factors identified, neutrophilia and thrombocytosis.24 In our cohort, platelet count was not predictive of outcomes, but neutrophilia was independently associated with both poorer OS and TTF1. The systemic inflammatory response is associated with inferior outcomes in colorectal and lung cancer.28 Our findings and Heng’s support a similar adverse prognostic relationship in renal carcinoma.

The University of California-Los Angeles Integrated Staging System UISS also stratifies patients as low, intermediate or high risk and incorporates Fuhrman nuclear grade in addition to some features of the MSKCC system. In our cohort, Fuhrman nuclear grade was not independently associated with outcomes. Clear cell histology was associated with better survival than mixed or sarcomatoid tumours, a finding replicated elsewhere.30 Bone metastases are associated with poorer survival among patients with metastatic renal cell carcinoma treated with sunitinib; this was replicated here with univariate but not multivariate analysis.

The majority of variables associated with superior survival in our cohort are markers of the biological aggressiveness of the tumour or the host response. In the absence of an untreated control group, we cannot identify whether these markers are prognostic or predictive of treatment response. Similarly, our finding that patients who were exposed to all three therapy classes lived a median of 10 months longer than patients who received only two classes, should be interpreted with caution, as this may reflect the natural history of the disease.

Development of hypertension on anti-angiogenic therapy may be associated with outcome and may be predictive of treatment efficacy.32–35 Analysis of patients treated with anti-angiogenic therapy in the first-line setting supports this hypothesis, with substantial improvements in both TTF and OS among hypertensive patients. Whether this has the potential to be a predictive biomarker and influence choice and dose of therapy remains speculative, but recent information on a potential mechanism and specific biochemical markers that may precede the measurement of an elevation does heighten the interest in defining this better.

Side-effect profile

Overall, our patients experienced the expected class-related toxicities. Agents were well tolerated with low rates of grade 3 and 4 toxicity and no treatment-related deaths. However, the range of toxicity is different to that experienced with conventional chemotherapy and a few points should be highlighted.

Low-grade nausea, fatigue, anorexia and diarrhoea were common. Although such low grade toxicity generally does not require treatment interruption or dose modification, they nonetheless have the potential to impact on quality of life and given the palliative intent of treatment should be monitored closely. Class-related toxicities of the angiogenesis inhibitors were also common. Hypertension on treatment developed in over one-third of patients on anti-VEGF TKIs. This response may be predictive of outcome, and must therefore be managed so therapy can continue. Guidelines for the management of hypertension associated with these agents recommend cardiovascular risk assessment prior to commencement of treatment and management of pre-existing hypertension, particularly during the first cycle. The guidelines also offer guidance regarding cancer-related complications and comorbidities that may lead a clinician to favour one class of antihypertensive over another. For example, in patients treated with sunitinib or sorafenib, diltiazem and verapamil are not recommended as they are potent inhibitors of the enzyme responsible for TKI metabolism,
urea creams. Three per cent of patients treated with anti-VEGF TKIs developed cardiac toxicity, although our results likely underestimate the true incidence of asymptomatic cardiac dysfunction. Elsewhere, asymptomatic cardiac abnormalities have been reported in up to one-third of patients treated with sunitinib or sorafenib. There are no clear guidelines for management, and current practice includes immediate cessation, short-term treatment interruptions and use of beta-blockers and angiotensin-converting enzyme inhibitors. In the current study, cardiac dysfunction led to treatment interruptions in two patients, one of whom was safely rechallenged with the agent after institution of cardiac medication and recovery of LVEF. Although there are no clear guidelines to support such an approach, we are reassured by the findings of others that cardiac toxicity has been largely found to be a reversible phenomenon which is not associated with increased morbidity or mortality after rechallenge with institution of appropriate cardiac medication.

Angiogenesis and endothelial dysfunction in the renal vasculature cause proteinuria. Our finding of asymptomatic proteinuria in six patients differs from previous reports of 21–63%, although we did not routinely test all patients for this toxicity. In the absence of guidelines, we advocate continuing therapy for asymptomatic responding patients.

Cutaneous toxicity in the form of hand–foot syndrome was seen in almost one-third of all patients treated with anti-VEGF TKIs. This common complaint was generally manageable, although troublesome. No prospective randomized trials have evaluated the management of this problem. Practical measures include skin care, moisturizing agents, use of cotton gloves and socks and 20–40% urea creams.

Our study shows that mTOR inhibitors were well tolerated in a largely pretreated and poor prognosis population. The spectrum of toxicity was similar to that reported previously and included dyslipidaemia and hyperglycaemia. Patients receiving mTOR inhibitors for metastatic renal cell carcinoma generally have a poor prognosis and short life expectancy, so the utility of routine treatment for dyslipidaemia and hyperglycaemia is not well established. One case of pneumonitis may have been related to radiation rather than mTOR inhibitor therapy, and the patient was successfully rechallenged with the agent.

This paper presents an Australian experience with targeted therapies for renal cell carcinoma in a real world setting. Its limitations include the retrospective nature of the study and the number of analyses performed, for which statistical correction has not been applied. It is therefore possible that some of our findings may be the result of chance (e.g. it is difficult to explain why prior nephrectomy would be predictive of TTF2 but not OS or TTF1); however, we are confident that our results are generally in keeping with those published elsewhere.

Conclusions

Overall, our findings with regard to both survival and toxicity support the results of randomized clinical trials. Baseline variables of tumour biology, natural history and systemic inflammatory response were associated with OS and TTF1. In the absence of an untreated control group, we are unable to conclude whether these variables are prognostic or predictive factors. However, we have verified the experience of others that the development of hypertension on treatment is predictive of outcome with anti-VEGF TKIs.

Our study demonstrates the spectrum of class-related toxicities seen with targeted therapies for metastatic renal cell carcinoma. The adverse event profile of these agents is different to that of conventional chemotherapy. Both oncologists and other clinicians involved in the care of these patients will need to become increasingly familiar as these agents enter widespread use.

Acknowledgements

The authors thank the patients and their families who so willingly participated, and the clinical research staff who so ably managed the trials.

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**ORIGINAL ARTICLES**

**Bleeding peptic ulcer: characteristics and outcomes in Newcastle, NSW**

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**Key words**
clinical audit, peptic ulcer disease, epidemiology, upper gastrointestinal haemorrhage.

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Received 11 April 2010; accepted 5 July 2010.
doi:10.1111/j.1445-5994.2010.02357.x

**Abstract**

**Background:** Peptic ulcer disease risk factors have changed, as has the impact of treatment on morbidity and mortality. Recent data on clinical presentation and outcome are sparse in Australia.

**Aim:** To determine the characteristics and outcome of patients presenting with a bleeding peptic ulcer to a tertiary referral centre.

**Methods:** We evaluated patients diagnosed with peptic ulcer bleeding between 2004 and 2008 at a tertiary referral hospital. Variables assessed included demographic data, comorbidities, medication use and Rockall score. Outcomes of interest were the time to endoscopy, peptic ulcer treatment, transfusion requirements, urgent surgery and survival.

**Results:** Peptic ulcers were confirmed in 265 patients (55% male), of which 145 were gastric and 119 duodenal. The mean age was 71 years. On admission 38% of patients had haemodynamic instability and 92% had one or more comorbidity. Consumption of ulcerogenic medications at the time of admission was frequent (non-steroidal anti-inflammatory drugs (NSAIDs) 22%, aspirin 41%, clopidogrel or warfarin 10%) and proton pump inhibitors infrequent (15%). A gastroenterologist managed all patients according to their usual practice. Only a minority of patients received over three units of packed red cells. Few patients were referred for surgery (3%) or died (3%), but both events were significantly higher for the duodenal ulcer group.

**Conclusion:** The characteristics and outcomes in patients with peptic ulcer bleeding have changed. Peptic ulcer disease remains a public health problem with modifiable risk factors, such as *Helicobacter pylori* infection and NSAIDs, which should be targeted to reduce the burden of illness.
Introduction

In spite of improved knowledge, diagnostics and treatment options, bleeding peptic ulcers are still a significant clinical problem.1-3 The mortality from bleeding peptic ulcers has been reported at 4–14% although recent Australian data are virtually non-existent.1,2,4 Non-steroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori account for the majority of peptic ulcer bleeds. Both risk factors are more prevalent in the elderly population who are also the age group least able to tolerate ulcer complications.5 Poor compliance with NSAID and H. pylori guidelines has recently been demonstrated locally6 and overseas,7 potentially contributing to mortality and morbidity. We were interested in the morbidity associated with peptic ulcer bleeding in our referral population and its preventability. Between August 2004 and December 2008 we studied the characteristics and outcome of patients with peptic ulcer disease (PUD) haemorrhage in Newcastle, NSW.

Materials and methods

John Hunter Hospital (JHH) in Newcastle, NSW, is the major referral hospital for Hunter New England Area Health with over 550 beds. It serves an area equal to England; 130,000 square kilometres, and a population close to 1 million. We prospectively collected data from August 2004 to December 2008. Patients who either presented to JHH or were transferred there with peptic ulcer bleeding were included. Current inpatients at JHH or the referring facilities were excluded deliberately as outcomes of bleeding in established inpatients are different and outside the scope of this study.

Patients with peptic ulcer bleeding were routinely referred to one of seven gastroenterologists and managed on a dedicated gastroenterology unit. There was a focus on prompt endoscopy and cautious use of blood transfusions. Endoscopies were performed in a dedicated endoscopy suite by a gastroenterologist or gastroenterology advanced trainee under direct supervision. For intubated patients or those for whom surgery was considered, gastroscopy was performed in the operating theatre. A gastroenterologist was on-call for upper gastrointestinal haemorrhage and surgical backup was available at all times. Proton pump inhibitor (PPI) infusions were given with dosages and duration in line with current best practice.8 After 72 h this was followed by intravenous or oral PPI according to the treating gastroenterologist.

A research nurse identified patients by daily review of gastroenterological admissions and review of endoscopic findings. A search of the electronic patient management system was also performed each day to identify any additional cases. The research nurse reviewed the medical records of each patient to collect all required data. All deaths within 30 days were included. Readmissions with bleeding peptic ulcer within 30 days were included in mortality data, but not otherwise reanalysed.

SAS/STAT Software Version 9.1 was used.9 Chi-squared tests were used to identify differences in pairs of categorical variables. T-tests and analysis of variance (ANOVA) were used to analyse continuous variables across a categorical variable.

Results

We analysed data from a total of 265 bleeding episodes in 261 unique patients of which 104 were transferred from other facilities in Hunter New England Area Health (Table 1). Gastric ulcer (GU) (n = 146) outnumbered duodenal ulcer (DU) (n = 119). Patients presenting with bleeding due to PUD are likely to be male and elderly with nearly 80% aged 60 and above. While there was only one patient aged less than 30, there were 14 aged 90 and above. The mean age of patients was 71 years (SD 15). On admission 38% of patients had haemodynamic instability and 92% had one or more comorbidity. Melaena was the most common presenting complaint.

Table 2 highlights the exposure of patients to ulcerogenic medications. Nearly half of all patients took aspirin, and one in five was taking a NSAID at the time of bleeding. While some patients were taking aspirin and an NSAID, about half of all patients were taking medications with the potential to cause bleeding. Clopidogrel, heparin or warfarin were taken by nearly 10% of patients. In spite of the high frequency of risk factors, such as ulcerogenic drug use, there were only 40 patients taking a PPI. One in eight patients were reported as current smokers.

Endoscopy was performed in 44% of patients within 12 h, and 79% within 24 h (Table 3). Local treatment, such as adrenaline injection or gold probe was undertaken in 35% of endoscopies (Table 3). Fewer than 50% of patients had H. pylori testing and the majority of these were Campylobacter-like organism (CLO) tests which were either not recorded or negative. The Rockall score after endoscopy, a predictor of outcome, showed that only one in five had a score of 0–3 indicating a benign outlook.10 A score of 6 or more, indicating high risk for death was recorded in 43%.

One in three patients was not transfused and a further one in three only received one or two units. Large transfusions, six or more units, was only used in 11%. Surgery...
was undertaken in only nine patients (3.4%) of whom seven survived. The overall mortality was 3.4% with four deaths in the GU group \((n=145)\) and five deaths in the DU group \((n=119)\).

**Discussion**

This study of 265 episodes of peptic ulcer bleeding in a large tertiary hospital illustrates some of the major changes taking place in the nature of peptic ulcer bleeding. Our study shows a remarkable increase in the age of patients with bleeding peptic ulcers. A 1949–1954 audit of ulcer bleeding in this region found a modal age of 60–69 years for GU and 50–59 years for DU. The current study found patients with peptic ulcer bleeding are now substantially older with a mean age of 72 years for GU and 69 years for DU.11

Modifiable risk factors for ulcer complications are a substantial component of risk. The high incidence of NSAID use draws attention to their potential for adverse effects, particularly in the elderly. The risk for NSAID complications increases with advanced age, \(H. pylori\) infection, smoking, previous ulcer history, concurrent anticoagulant and prednisone use. Although NSAIDS and \(H. pylori\) are thought to induce ulcer disease by different mechanisms, there is a synergism between the two risk factors. \(H. pylori\) increases the risk of bleeding from peptic ulceration twofold, NSAIDS fivefold and together there is a sixfold increase. There is now strong evidence that \(H. pylori\) eradication prior to the introduction of NSAIDs will reduce ulcer complications while the data on eradication after an NSAID ulcer complication has occurred are less clear.12 A previous survey at this hospital found that 85% of patients admitted with a past history of PUD denied

### Table 1 Demographic characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gastric ulcer ((n=146))</th>
<th>Duodenal ulcer ((n=119))</th>
<th>(P)-value (univariate)</th>
<th>Total ((n=265))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>72 (14)</td>
<td>69 (16)</td>
<td>0.1025</td>
<td>71 (15)</td>
</tr>
<tr>
<td>Men</td>
<td>78 (53%)</td>
<td>69 (58%)</td>
<td>&lt;0.001</td>
<td>147 (55%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>1 (0.7%)</td>
<td>0 (0%)</td>
<td>&lt;0.0007</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>30–44</td>
<td>8 (5.5%)</td>
<td>8 (6.7%)</td>
<td>16 (6.0%)</td>
<td></td>
</tr>
<tr>
<td>45–59</td>
<td>19 (13%)</td>
<td>25 (21%)</td>
<td>44 (17%)</td>
<td></td>
</tr>
<tr>
<td>60–74</td>
<td>44 (30%)</td>
<td>33 (28%)</td>
<td>77 (29%)</td>
<td></td>
</tr>
<tr>
<td>75–89</td>
<td>68 (47%)</td>
<td>45 (38%)</td>
<td>113 (43%)</td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>6 (4.1%)</td>
<td>8 (6.7%)</td>
<td>14 (5.3%)</td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melaena only</td>
<td>79 (54%)</td>
<td>69 (58%)</td>
<td>&lt;0.001</td>
<td>148 (56%)</td>
</tr>
<tr>
<td>Haematemesis with or without melaena</td>
<td>63 (43%)</td>
<td>47 (39%)</td>
<td>110 (42%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (2.7%)</td>
<td>3 (2.5%)</td>
<td>7 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>46 (32%)</td>
<td>38 (32%)</td>
<td>&lt;0.001</td>
<td>84 (32%)</td>
</tr>
<tr>
<td>1</td>
<td>94 (64%)</td>
<td>74 (62%)</td>
<td>168 (63%)</td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>6 (4.1%)</td>
<td>7 (5.9%)</td>
<td>13 (15%)</td>
<td></td>
</tr>
<tr>
<td>Signs of HDI‡</td>
<td>53 (36%)</td>
<td>47 (39%)</td>
<td>0.2471</td>
<td>100 (38%)</td>
</tr>
<tr>
<td>Initial haemoglobin (g/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>12 (8.2%)</td>
<td>14 (12%)</td>
<td>&lt;0.001</td>
<td>26 (10%)</td>
</tr>
<tr>
<td>60–80</td>
<td>30 (21%)</td>
<td>38 (32%)</td>
<td>68 (26%)</td>
<td></td>
</tr>
<tr>
<td>81–100</td>
<td>38 (26%)</td>
<td>30 (26%)</td>
<td>68 (26%)</td>
<td></td>
</tr>
<tr>
<td>&gt;100</td>
<td>66 (45%)</td>
<td>35 (30%)</td>
<td>101 (38%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are given as number (percentage) of subjects. Information was missing for some variables. Percentages may not add to 100% due to rounding.

†Comorbidity was defined as a significant cardiovascular, respiratory, hepatic or renal disorder. ‡HDI, haemodynamic instability. This was defined as either heart rate greater than 100 or systolic blood pressure under 100 mmHg on presentation.

### Table 2 Medication use and risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gastric ulcer ((n=145))</th>
<th>Duodenal ulcer ((n=119))</th>
<th>Total ((n=265))</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID use</td>
<td>33 (23%)</td>
<td>24 (20%)</td>
<td>57 (22%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>61 (42%)</td>
<td>47 (39%)</td>
<td>108 (41%)</td>
</tr>
<tr>
<td>Anticoagulation†</td>
<td>14 (10%)</td>
<td>11 (9%)</td>
<td>25 (10%)</td>
</tr>
<tr>
<td>Past PUD</td>
<td>16 (11%)</td>
<td>18 (15%)</td>
<td>34 (13%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (12%)</td>
<td>15 (13%)</td>
<td>32 (12%)</td>
</tr>
<tr>
<td>PPI</td>
<td>18 (12%)</td>
<td>22 (18%)</td>
<td>40 (15%)</td>
</tr>
<tr>
<td>PPI + Risk factor</td>
<td>16 (11%)</td>
<td>21 (18%)</td>
<td>37 (14%)</td>
</tr>
</tbody>
</table>

†Anticoagulation defined as clopidogrel and/or warfarin and/or heparin. NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; PUD, peptic ulcer disease.
previous treatment with *H. pylori* eradication therapy and were still *H. pylori* positive. It is noteworthy that usage of NSAIDs and low dose aspirin is virtually identical in GU and DU bleeding although the association between NSAID and GU is much stronger than with DU. Another modifiable risk factor for peptic ulcer complications is smoking which one in eight patients reported.

*H. pylori* testing was done in approximately half of our patients, but there were significant problems with obtaining results, an experience that was also reflected in a recent Swedish study. This was mainly due to a failure to routinely integrate *H. pylori* test results done at endoscopy into the patient’s clinical notes available for data collection, an issue we are currently attempting to address. The validity of the CLO test (Ballard Medical Products, Draper, UT, USA) in patients with active PUD bleeding has also been questioned. The importance of *H. pylori* testing and eradication for patients with peptic ulcer bleeding in the absence of NSAIDs remains an opportunity for clinical practice improvement.

Surgical intervention rates were low despite the increasing age of the PUD population and the surgical mortality was lower than reported in a recent nationwide UK audit of 6750 patients from 250 hospitals.

The possible role of cautious transfusion in achieving improved outcomes deserves consideration. There is growing evidence that transfusion in the acute phase potentiates bleeding. The data from a recent UK audit suggested that transfusion, independent of the patient’s risk of re-bleeding as stratified by the Rockall score, is associated with an increased incidence of re-bleeding. In the only randomized controlled trial of early versus late transfusion, a significantly higher incidence of bleeding was observed in those having early transfusion. Management in a dedicated gastrointestinal unit rather than a general ward may also have been an important determinant of patient outcome.

**Conclusion**

The strengths of this study are the large size and the comprehensive and prospective database. Our outcome

### Table 3 Endoscopic intervention, transfusion and patient outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gastric ulcer</th>
<th>Duodenal ulcer</th>
<th>P-value (univariate)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to endoscopy (hours)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>1 (0.7%)</td>
<td>2 (1.7%)</td>
<td>&lt;0.0001</td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td>Within 12</td>
<td>57 (39%)</td>
<td>59 (50%)</td>
<td></td>
<td>116 (44%)</td>
</tr>
<tr>
<td>12–24</td>
<td>58 (40%)</td>
<td>35 (29%)</td>
<td></td>
<td>93 (35%)</td>
</tr>
<tr>
<td>&gt;24</td>
<td>30 (21%)</td>
<td>23 (19%)</td>
<td></td>
<td>53 (20%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.7%)</td>
<td>2 (1.7%)</td>
<td></td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td><strong>Local treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenaline</td>
<td>47 (32%)</td>
<td>42 (35%)</td>
<td>&lt;0.001</td>
<td>89 (34%)</td>
</tr>
<tr>
<td>Gold probe</td>
<td>42 (29%)</td>
<td>39 (33%)</td>
<td>&lt;0.001</td>
<td>81 (31%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>2 (1.7%)</td>
<td>0.006</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td><strong>PPI infusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial Rockall score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>79 (54%)</td>
<td>61 (51%)</td>
<td>0.1396</td>
<td>140 (53%)</td>
</tr>
<tr>
<td>4–5</td>
<td>55 (38%)</td>
<td>47 (39%)</td>
<td></td>
<td>102 (38%)</td>
</tr>
<tr>
<td>≥6</td>
<td>12 (8.2%)</td>
<td>11 (9.2%)</td>
<td></td>
<td>23 (8.7%)</td>
</tr>
<tr>
<td>Second Rockall score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>27 (18%)</td>
<td>29 (24%)</td>
<td>&lt;0.001</td>
<td>56 (21%)</td>
</tr>
<tr>
<td>4–5</td>
<td>61 (42%)</td>
<td>33 (28%)</td>
<td></td>
<td>94 (35%)</td>
</tr>
<tr>
<td>≥6</td>
<td>58 (40%)</td>
<td>57 (48%)</td>
<td></td>
<td>115 (43%)</td>
</tr>
<tr>
<td><strong>Blood transfusions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>49 (34%)</td>
<td>26 (22%)</td>
<td>&lt;0.001</td>
<td>75 (28%)</td>
</tr>
<tr>
<td>1–2</td>
<td>51 (35%)</td>
<td>38 (32%)</td>
<td></td>
<td>89 (34%)</td>
</tr>
<tr>
<td>3–5</td>
<td>33 (23%)</td>
<td>37 (31%)</td>
<td></td>
<td>70 (26%)</td>
</tr>
<tr>
<td>≥6</td>
<td>13 (9.9%)</td>
<td>16 (14%)</td>
<td></td>
<td>29 (11%)</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>4 (2.7%)</td>
<td>5 (4.2%)</td>
<td>&lt;0.001</td>
<td>9 (3.4%)</td>
</tr>
<tr>
<td>Died</td>
<td>4 (2.7%)</td>
<td>5 (4.2%)</td>
<td>0.005</td>
<td>9 (3.4%)</td>
</tr>
</tbody>
</table>

Data are given as number (percentage) of subjects. Information was missing for some variables. Percentages may not add up to 100% due to rounding. PPI, proton pump inhibitor.
data are superior to a number of other groups previously published and similar to that of a large recent Swedish review. Of note, our rate of transfusion was lower than previously recommended and consistent with more recent data. Bleeding peptic ulcers remain a significant cause of morbidity and to a lesser extent mortality. Whether outcomes can be further improved by conservative transfusion and addressing modifiable risk factors remains to be determined.

Acknowledgements

The authors would like to thank the medical, nursing and allied health staff whose skills made this possible.

References

Acute gout management during hospitalization: a need for a protocol

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Key words
gout, management, quality of healthcare, clinical guideline.

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Received 2 September 2009; accepted 14 September 2009.
doi:10.1111/j.1445-5994.2010.02165.x

Abstract

Aim: To review systematically the management of acute gout during hospitalization.

Methods: Case-file review of all episodes of acute gout occurring in a large tertiary hospital over a 20-month period.

Results: Of 134 acute gout episodes identified, the large majority (118) occurred in patients not admitted under the rheumatology unit. Baseline anti-gout medications were frequently ceased on admission and in 9% of episodes, no pharmacotherapy was prescribed. Delays in initiation of treatment occurred in up to 29% of patients. Acute management included anti-inflammatory monotherapy, or combinations of colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Of patients prescribed colchicine, 26% received >1.5 mg/day and a strong correlation was found between colchicine dose and the occurrence of diarrhoea. NSAIDs were prescribed in 29% of patients with pre-existing renal impairment. Overall, 25% of patients received inappropriate pharmacological management. In patients not under the direct care of the rheumatology unit, in-hospital rheumatology consultation was sought by the treating unit in 34% of episodes. Consultation was sought more frequently in patients with multiple joint involvement, but there were no other obvious differences in baseline clinical characteristics between cases with or without rheumatology involvement. In cases with rheumatology involvement, patients were investigated more frequently, they received more pharmacotherapeutic intervention, in particular combination anti-inflammatory therapy, and they achieved better symptomatic relief and long-term follow up.

Conclusion: Acute gout episodes in hospital are variably investigated and treated with frequent suboptimal management. We recommend establishment of a hospital-wide protocol to support decision-making regarding investigations, treatment and follow up.

Introduction

Acute gout is a common inflammatory arthritis, affecting 7% of men over the age of 65 years.1 Episodes are frequently precipitated by acute illnesses, trauma, surgery, heavy intake of alcohol, purine-rich foods and drugs that alter the serum uric acid (SUA) concentration.1-4 Acute gout occurring during hospitalization contributes to the morbidity of already sick patients, and anecdotal evidence suggests that in-hospital diagnosis and treatment of gout are often suboptimal before rheumatology involvement in management. Pharmacological treatment options for acute gout include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids. There is a general paucity of research evaluating the efficacy of these therapies for gout, with few comparative studies and limited clinical guidelines.5,6 Suboptimal prescribing practices may also impact on the effectiveness of gout management,7-9 and overall there is currently insufficient evidence to clearly inform hospital decision-making regarding whether one therapeutic alternative is superior to another.

Chronic gout is also suboptimally managed in the community,1,7,10 which may contribute to the frequency of acute gout during hospital admission. Management of recurrent gout is lifelong hypouricaemic therapy, almost invariably using allopurinol. However, suboptimal patient compliance and dosing of allopurinol are

Funding: None.
Conflict of interest: None.
frequent,\(^7\,^10\) resulting in poor SUA control.\(^8\) This study systematically reviewed acute gout management over a 20-month period in a large tertiary hospital. Specifically, we examined five key domains: (i) the continuation of baseline anti-gout medications during admission; (ii) modalities used in hospital acute gout management and the appropriateness of these therapies; (iii) allopurinol use in a hospital context; (iv) the existence of delays between symptom recognition and commencement of treatment and (v) whether rheumatology involvement improved the quality of investigations, management and follow up provided in patients experiencing acute gout in hospital.

**Patients and methods**

**Case-file review**

The study was conducted at Liverpool Hospital, Sydney, Australia, involving a systematic case-file review of all in-hospital acute gout episodes occurring between April 2005 and December 2006 inclusive. Inclusion criteria consisted of all patients experiencing acute gout during hospitalization, with symptoms starting either before or during admission, and being either a primary or secondary diagnosis. Subjects were identified by an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification* (ICD-10) search of all hospital admissions, using gout-specific codes: M10.0–10.4 and M10.9.\(^7\) To maximize inclusion of all relevant cases, records of synovial fluid sent for pathological examination were also reviewed. Of 251 potential episodes, 249 were identified by ICD-10 search criteria and an additional two were identified from synovial fluid results showing positive monosodium urate crystals. Of the files reviewed, 105 admissions were excluded as the record coding reflected chronic gout rather than acute gout episodes in hospital. Some episodes represented multiple episodes of gout in the same patient. In these cases, only the first episode occurring during the study period was included for analysis; 134 episodes were thus identified that satisfied the study criteria. All subjects had a physician diagnosis of gout, as determined by review of clinical records.

Data regarding past medical history, nature of gout attack and management were retrieved from the medical files and pathology databases. Serum creatinine level was recorded at symptom onset or at admission if symptom onset occurred before hospitalization. It was assumed that not recorded was equivalent to absent regarding past diagnoses of diabetes mellitus, coronary heart disease, chronic renal failure, hypertension, hypercholesterolaemia and medication history on admission. All other variables that were not recorded values are specified. A previous history of gout was defined by a past diagnosis recorded in the notes, allopurinol use in the absence of current chemotherapy, or presence of tophi. Alcohol consumption was categorized into low risk, risky and high risk for long-term harm based on sex, with a standard drink defined as 10 g of alcohol using Australian alcohol consumption guidelines.\(^11\) Pharmacotherapy for acute gout was defined as commencement of colchicine, NSAID and/or corticosteroid if the patient was taking no prior acute gout medications or additional therapy in those on baseline acute gout medications. Use of no pharmacotherapy was defined as the absence of the aforementioned therapies. Anti-gout treatment was classified into monotherapy or combination therapy. Renal impairment was defined as serum creatinine >90 μmol/L and high-dose colchicine as >1.5 mg/day. Rheumatology involvement was defined when a formal request for assistance on management occurred and written advice from the rheumatology unit was documented in the case record, or the patient was under the primary care of the rheumatology unit. This study was approved by an institutional ethics committee before its commencement.

**Statistical analysis**

The STATA statistical package (StataCorp.2003.Stata Statistical software: Release 8.0. College Station, TX, USA: Stata Corporation) was used for all analyses. Characteristics in recorded collected data of Group A and Group B were compared using the Chi-squared (χ\(^2\)) test for categorical variables, Student’s \(t\)-test for continuous (normally distributed) data and Mann–Whitney \(U\)-test for non-normally distributed data. A \(P\)-value of <0.05 was considered to be significant.

**Results**

**Baseline patient characteristics**

The mean age (±SD) of the study group was 67.7 ± 15.8 years (range 16–93 years), with 80% males, and mean age of males was younger (66.3 ± 14.8 years) than females (73.2 ± 18.5 years) \((P=0.04)\). The group showed a high prevalence of factors associated with increased risk of hyperuricaemia, and 71% had evidence of chronic renal impairment (Table 1). On admission, 27% of patients were taking allopurinol, with varying rates of use of colchicine, NSAID and prednisone (Table 1). The majority (72%) had a past history of gout, 9% denied a history of gout, and in 19% these data were not recorded.
Thus, of the 108 cases where gout history was recorded, 89% had previous gout. The mean (±SD) gout duration was 9.9 ± 11.0 years (recorded in only 34% of those with past gout history). Alcohol consumption was recorded in 100/134 (75%), and of these, 36% were non-drinkers, and 27%, 10% and 19% were classified as being at low risk, risky and high risk of long-term harm respectively. The remaining 8% comprised alcohol drinkers in which the level of consumption was not recorded.

### Changes to anti-gout medications on admission

The median dose of allopurinol in the 36 patients taking allopurinol on admission was 150 mg (range 50–300 mg), and the majority of these (56%) had allopurinol discontinued during the admission. In the remaining patients, 17% had allopurinol continued at the same dose, 19% had a dosage increase and 8% had a dosage decrease. Discontinuation rates for colchicine, NSAIDs and prednisone were 37%, 46% and 21%, respectively, during the admission.

### Acute gout episodes – pattern and investigations

Acute gout manifested as a monoarthritis in 57.5%, an oligoarthritis in 24.6% and a polyarthritis in 17.9% of patients (Table 2). Gout was the primary diagnosis coded in 35.8% of episodes, most of which were emergency admissions, indicating that acute gout causing immobility sufficient to justify urgent hospitalization remains a significant health issue in Australia. SUA measurement was carried out in 99 of 134 episodes (74%). In these patients, urate levels were >0.36 mmol/L in 80%. The mean (±SD) SUA level was 0.48 ± 0.16 mmol/L (range 0.12–1.04 mmol/L), with no difference between males and females. Serum creatinine was measured in all patients with a median creatinine level of 158 μmol/L (range 49–939 μmol/L). Imaging (plain radiograph) of the affected joint was carried out in 46%.

### Treatment modalities for acute gout

Anti-gout pharmacotherapy was used in 91% of patients, but 9% received analgesia alone. Where anti-gout pharmacotherapy was used, management was highly variable, and included colchicine (75%), oral NSAIDs (32%), prednisone (28%), intra-articular steroids (7%) and adrenocorticotropic hormone (ACTH) (1%). Paracetamol or other analgesics were used in 55% and 35% of cases respectively. Therapy with one of anti-gout medication (monotherapy) was used in 57.5% of cases, and therapy with a combination of two or more anti-gout medications was used in 42.5% of episodes. In those patients prescribed monotherapy, colchicine use (76%) exceeded NSAIDs (14%) and corticosteroids (10%). Where

---

**Table 1** Selected diagnoses and baseline medications in the population (n = 134)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>94 (70.1)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>69 (51.5)</td>
</tr>
<tr>
<td>Concurrent or preceding infection (e.g. urinary tract infection, pneumonia, cellulitis)</td>
<td>74 (55.2)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>95 (70.9)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>50 (37.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37 (27.6)</td>
</tr>
<tr>
<td>Concurrent or preceding dehydration</td>
<td>23 (17.2)</td>
</tr>
<tr>
<td>On chemotherapy</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Medications on admission</td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>36 (26.9)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>21 (15.7)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>21 (15.7)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>9 (6.7)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>48 (35.8)</td>
</tr>
<tr>
<td>Aspirin (150 mg or less)</td>
<td>42 (31.3)</td>
</tr>
</tbody>
</table>

NSAID, non-steroidal anti-inflammatory drug.

---

**Table 2** Arthritis presentation

<table>
<thead>
<tr>
<th>Arthritis presentation (%)</th>
<th>Total group† (n = 134)</th>
<th>Group A  (n = 78)</th>
<th>Group B  (n = 40)</th>
<th>P-value  (A vs B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoarthritis</td>
<td>57.5</td>
<td>69.2</td>
<td>40.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>24.6</td>
<td>23.1</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>17.9</td>
<td>7.7</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis (%)</td>
<td>35.8</td>
<td>21.8</td>
<td>37.5</td>
<td>0.07</td>
</tr>
</tbody>
</table>

†Includes 16 patients admitted directly under the rheumatology unit.
combination therapy was used, 35% received colchicine plus corticosteroids, 39% received colchicine plus a NSAID, 10% received a NSAID plus corticosteroid, and 16% were prescribed the triple combination of colchicine, NSAID and corticosteroids.

**Potentially inappropriate acute gout medication use**

In the 100 patients prescribed colchicine, 26% had an initial daily dose of >1.5 mg. Diarrhoea was recorded as a side-effect of therapy in 24 patients. Patients on colchicine experiencing diarrhoea had significantly higher mean initial daily colchicine dosage (1.9 vs 1.4 mg; P = 0.02), higher mean total colchicine doses (13.4 vs 8.0 mg; P < 0.005) and longer mean total days of colchicine use (10 vs 6.5 days; P = 0.05) than patients who did not experience diarrhoea. Of the 95 patients with a serum creatinine >90 μmol/L, 27 (28.4%) were administered NSAIDs. Moreover, these 27 represented 62.8% of the 43 patients in the group-prescribed NSAIDs. No clear association was observed between the number of days of NSAID use and worsening renal dysfunction, but four patients had a ≥50% increase in serum creatinine while taking NSAIDs. In 5.2% of all episodes, allopurinol was commenced during the acute presentation. In four of these seven patients, allopurinol had been earlier discontinued on admission. In total, 33/134 (24.6%) of patients received inappropriate pharmacological care (defined as one or more of colchicine daily dose of >1.5 mg, use of NSAIDs when creatinine is >90 μmol/L, or commencement of allopurinol during an acute attack).

**Rheumatology involvement in patient care**

Of the 134 episodes, 118 occurred in patients admitted under medical (81 cases) and surgical (37 cases) teams, while 16 cases occurred in patients admitted by the rheumatology unit. This latter small group of rheumatology inpatients where gout was the primary reason for admission were significantly younger (mean age 57.1 ± 17.6 years), had lower frequencies of recognized gout risk factors, and had more polyarticular involvement than cases admitted under other teams (data not shown). Excluding these rheumatology inpatients, 78 of the remaining 118 episodes of acute gout were managed by the primary admitting teams without involvement of the rheumatology unit (Group A), whereas in 40 cases, the rheumatology unit was consulted for advice (Group B). There were no major differences in baseline characteristics between these two groups apart from a lower prescription of low-dose aspirin in Group B (Table 3).

With respect to presentation, patients in Group B had significantly more joint involvement compared with those in Group A (P = 0.004) (Table 2). In terms of investigations, Group A was statistically less likely to have had a SUA level, a synovial aspirate or imaging of the affected joints carried out compared with Group B. There was no statistically significant difference in SUA levels or median creatinine at symptom onset/admission between subgroups (Table 4). Regarding pharmacotherapy, patients with rheumatology involvement had significantly more frequent administration of colchicine, prednisone, analgesia other than paracetamol, and arthroscopic joint washout compared with Group A. Additionally, combination therapy was more likely to be used in Group B compared with Group A. Although not statistically different, patients without rheumatology involvement were more likely to receive inappropriate pharmacological treatment than those in Group B (Table 5). There was no significant difference in delay between symptom recognition and pharmacotherapy commencement between patients in groups A and B (Table 4). Treatment-emergent adverse effects were more frequent in Group B compared with Group A (Table 5).

**Delays, time frames, outcomes and follow up**

The median hospital stay for the patients of this study was 11 days (range 2–117 days). Although this study was not designed with the intention of showing associations between gout and increased hospital stays, this is substantially prolonged compared with the median length of stay for the comparable general hospital population (which excludes admissions less than 2 days, day procedures/surgeries, maternity, neonatology and pediatrics) of 5 days during the same study period. In the 122 patients that received pharmacotherapy, the median delay between symptom recognition to treatment was 1 day (range 0–14). However, 29% of patients administered pharmacotherapy experienced a delay of ≥2 days and 14% experienced delays of ≥3 days. Excluding 31 cases that had no outcome recorded, 89% had documented improvement in symptoms, range of movement and/or weight bearing, 6% were discharged with ongoing symptoms, and 5% died during the admission. There was no significant difference in time to resolution of the gout attack between Group A and Group B cases. Excluding four cases where a discharge summary was absent and the five deaths, only 33 of 125 (26%) had rheumatology follow up arranged; all of these cases were from the 16 inpatients under the direct care of rheumatologists, or from Group B where rheumatology involvement had occurred (Table 5). Anti-gout drugs were prescribed on discharge in 67% of cases.
Discussion

The recognized poor management of gout within the community is evident in this study with only 27% of patients taking allopurinol on admission, despite a majority having a documented gout history. Furthermore, the mean SUA of those continued on allopurinol during admission was 0.45 ± 0.18 mmol/L, consistent with studies showing that the target SUA of <0.36 mmol is not achieved in many allopurinol-treated patients, which was further illustrated by the inadequate median allopurinol dose of 150 mg. Of concern, allopurinol continuation was low following admission; of the 36 cases taking allopurinol on admission, only 17% had allopurinol continued, with the majority (56%) discontinued upon admission or subject to dose changes (27%). There were also high discontinuation rates on admission of baseline colchicine, NSAIDs and prednisone. Although we were unable to explore the reasons for such practices, such anti-gout medication discontinuation may trigger attacks in a hospital context where there is often an aggregation of gout risk factors.

Review of treatments used in hospital revealed highly variable clinical practice. The lack of any acute gout pharmacotherapy in 9% of patients is of concern, considering that gout is a manageable condition for which treatment modalities are readily available. Of acute anti-inflammatory therapies prescribed, colchicine was the most common pharmacotherapy (75%), followed by NSAIDs (32%) and prednisone (28%). A minority received intra-articular corticosteroid injections (7%) and ACTH (1%). Studies of community prescribing practices generally show preferences for NSAID use, although Rozenberg et al. found that colchicine was the commonest pharmacotherapy in 63% of cases. The frequent use of colchicine in this study probably reflects reluctance to use NSAIDs or corticosteroids in an elderly population with comorbidities, including renal impairment and diabetes mellitus (Table 1).

Many patients received potentially inappropriate therapy. First, of those prescribed colchicine, 26% had initial daily dosages of >1.5 mg/day. Because colchicine is largely cleared by the kidney and 71% of patients had impaired renal function (Table 1), caution in using high-dose colchicine should be advised. In addition, restricting daily dosages to 1.5 mg/day or less is recommended, considering the strong association we found between high initial and total colchicine doses with diarrhoea. Second,
of patients with a serum creatinine of >90 µmol/L, 29% were administered NSAIDs. Our results support the findings of prior studies that patients with contraindications to NSAIDs or colchicine may be inappropriately administered these medications or be administered inappropriate dosages.\(^{10}\) Third, 5% of patients were commenced on allopurinol during acute attacks, a generally contraindicated practice thought to exacerbate attacks.\(^{19}\) Overall, 25% of patients received at least one of these three inappropriate managements.

There were clinically significant delays between symptom recognition and treatment commencement in a substantial proportion of patients. A delay of \(\geq 2\) days occurred in 29% of patients administered pharmacotherapy, with 14% experiencing delays of 3 days or more. This raises questions about the prioritization of gout in the context of other conditions, which may be perceived to be more urgent. Clinical experience suggests that immediate commencement of treatment upon symptom onset reduces duration and/or severity of attacks.\(^{20}\) Additionally, as symptoms tend to peak within the first day,\(^{21}\) delayed commencement of pharmacotherapy may exacerbate patient distress and potentially prolong hospitalization. In support of this, we found that patients experiencing acute gout had a prolonged median stay compared with a comparable general hospital population (11 vs 5 days respectively), consistent with recent data that show that patients with gout have increased healthcare utilization and costs.\(^{22}\)

Comparison of cases where the rheumatology unit was involved to those with no rheumatology involvement (Tables 2–5) revealed a number of instructive lessons. Rheumatology involvement, either as the primary admitting team (16 cases) or in consultation (40 cases), occurred in 42% of the overall 134 cases, and 65% of the 48 cases where gout was listed as the primary reason for admission. When the 16 cases under the direct care of rheumatology were excluded, other teams consulted the rheumatology unit for assistance in only 34% of cases. For these 118 cases of acute gout, comparisons...
those receiving rheumatology involvement received significantly higher rates of investigation (SUA measurement, synovial aspirate and imaging), and more common use of colchicine, prednisone, analgesia and combination anti-inflammatories (Table 4). Patients with rheumatology involvement were also more likely to experience resolution of gout, although this was not statistically significant (Table 5). While 53% of patients receiving rheumatology involvement received a rheumatology outpatient clinic follow-up appointment, no patients without involvement received such follow up (Table 5). Although the published guidelines for acute gout management do not advocate the use of combination anti-inflammatory therapy, this approach was used in 88% of the 16 cases under the direct care of rheumatologists in this study (data not previously shown). This finding, combined with the statistically significant trend towards combination anti-inflammatory therapy in cases with rheumatology involvement (Table 4), agrees with another report that showed a majority of rheumatologists used combination therapy to treat acute gout in the community.15

Table 5 Recorded adverse reactions, outcomes and discharge

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P-value (A vs B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reactions (%)</td>
<td>20.5</td>
<td>40.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3.9</td>
<td>7.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12.8</td>
<td>27.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Increased blood sugar level</td>
<td>2.6</td>
<td>2.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Inappropriate treatment outcome (%)†</td>
<td>26.9</td>
<td>15.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Improvement</td>
<td>85.7</td>
<td>92.3</td>
<td></td>
</tr>
<tr>
<td>Ongoing</td>
<td>8.2</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Deceased</td>
<td>6.1</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Discharge medication (%)‡</td>
<td>64.3</td>
<td>71.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Rheumatology follow up arranged at discharge (%)‡</td>
<td>0.0</td>
<td>52.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median number of days in hospital</td>
<td>17.1</td>
<td>19.0</td>
<td>0.6</td>
</tr>
</tbody>
</table>

†n = 49 in Group A, n = 39 in Group B (excluding cases where outcome was not recorded). ‡n = 70 in Group A, n = 39 in Group B (excluding five deceased patients and four cases where discharge summaries were absent from files).

A retrospective study of this type presents several limitations. Important data that may be absent in clinical records cannot be ascertained and the quality of results is dependent on the recording by medical professionals. Ideally, a prospective survey would have been most suited to achieve the study objectives. Although only 34% of cases had crystal-proven gout diagnoses, the study population appears to be representative of the general population of gout patients in terms of sex distribution, with a 4:1 male-to-female ratio, although mean age and comorbidity rate are higher than a community gout population. Despite these reservations, this study is only the second systematic review of current hospital practice regarding acute gout management and is unique in reviewing the contribution of rheumatologists to patient care.

Conclusion

This study shows significant variability in acute gout management in a tertiary hospital context, with disparities between patients receiving rheumatology unit involvement in their care and those that did not. Suboptimal management occurs relatively commonly, including significant delays to treatment commencement, potentially inappropriate use of colchicine, NSAIDs and allopurinol, and high discontinuation rates of baseline gout medications. The establishment of a hospital-wide protocol, developed by rheumatologists, to assist decision-making regarding investigations, management and follow up of acute gout, would promote standardized comprehensive patient care, particularly given that acute gout during hospitalization is primarily managed by non-rheumatologists.
Acute gout management during hospitalization

13 Dalbeth N, Kumar S, Stamp L, Gow P. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol* 2006; 33: 1646–50.
Pre-hospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease

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Key words
chronic obstructive pulmonary disease, exacerbation, ambulance, oxygen therapy, respiratory failure.

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Received 11 November 2009; accepted 23 December 2009.
doi:10.1111/j.1445-5994.2010.02207.x

Abstract

Background: High concentration oxygen is commonly administered during acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The aim of this study was to determine the association between oxygen, severity markers and poor outcomes in AECOPD.

Methods: In an audit of patients with AECOPD arriving by ambulance to the Emergency Department of Wellington Hospital, details of oxygen administration, clinical outcomes and severity markers were documented. The main outcome measure was a composite of death, assisted ventilation, or respiratory failure. Associations between oxygen therapy, severity markers and poor clinical outcomes were assessed by logistic regression.

Results: Of 250 patients 77 (31%) died, required assisted ventilation or were in respiratory failure. Increased oxygen flow was associated with increasing risk of death, assisted ventilation or respiratory failure with an odds ratio (OR) of 1.2 (95% CI 1.0–1.4) per 1 L/min oxygen flow. Increasing PaO2 was associated with a greater risk of a poor outcome with an OR of 1.1 (95% CI 1.0–1.3) per 10 mmHg higher PaO2. Home oxygen (OR 2.8, 95% CI 1.5–5.1), previous respiratory failure (OR 2.6, 95% CI 1.5–4.6), previous ventilation (OR 3.2, 95% CI 1.7–5.9) and home nebulizer use (OR 2.4, 95% CI 1.4–4.3) were associated with an increased risk of a poor outcome.

Conclusion: In AECOPD high flow oxygen in the ambulance is associated with poor clinical outcomes. A number of easily identified markers of chronic disease severity indicate an increased risk of a poor clinical outcome.

Introduction

The recently published British Thoracic Society (BTS) Guidelines ‘Emergency oxygen use in adult patients’ recommend that oxygen should only be administered to patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) if oxygen saturations are <88% and that oxygen therapy should be adjusted to maintain saturations between 88% and 92%.1 This recommendation is based on the well-established risk of hypercapnia and respiratory failure in patients with AECOPD when high concentration oxygen is administered.2–12 Similar recommendations are made by the Australasian COPD guidelines,13,14 and the New Zealand St John’s Ambulance Service.15 The clinical practice guidelines of the Wellington Free Ambulance Service state that patients with COPD should have their oxygen delivery adjusted to maintain saturations of 88–92%.16 These recommendations are important as the ambulance service is often the first medical contact for patients with AECOPD and is responsible for their management during transfer to hospital. Such transfers may take considerable time, particularly in rural areas, and the administration of inappropriately high concentrations of oxygen have the potential to lead to hypercapnia and worse clinical outcomes.

The aims of this study were to determine whether the use of oxygen in AECOPD by the Ambulance Service is consistent with local and international guidelines, whether high flow oxygen administered in the ambulance was associated with poor outcomes, and whether it is possible to identify high-risk patients based on the severity of their underlying disease or their clinical status at presentation.
Methods

We undertook a retrospective audit of 250 presentations of AECOPD admitted to Wellington Hospital (Capital & Coast District Health Board) between June 2006 and June 2007. Only patients who were brought by ambulance to the Emergency Department were included. Patients were identified by the medical records department and a list of all discharges with a primary diagnosis of COPD (ICD Code J440 or J441) was provided. This included readmissions, patients who were dead on arrival and those who died in hospital following presentation. Markers of the chronic background severity of COPD, severity markers of the acute exacerbation and clinical outcomes following presentation to the Emergency Department were reviewed. Sources of information included the ambulance case records for details of pre-hospital oxygen administration, and the hospital case records for documentation of management in the Emergency Department and subsequent medical admission.

Particular attention was paid to identifying and documenting the oxygen therapy administered by the ambulance service. Difficulties in identifying oxygen use from some of the ambulance records led us to categorize oxygen administration in two ways. First, where the exact flow rate was clearly documented, oxygen therapy was treated as a continuous variable based on the flow rate in L/min. Second, we categorized oxygen therapy as a dichotomous variable, either ‘high flow’ or ‘low flow’. Patients were categorized as ‘high flow’ if they had a documented flow rate of ≥3 L/min, or received oxygen through a medium concentration mask or a non-re-breather mask. Patients were categorized as ‘low flow’ if either ‘room air’ or a flow rate <3 L/min was documented, or if there was no mention of oxygen therapy. This categorization was based on data which indicate that 2–3 L/min of oxygen through nasal prongs delivers a FiO2 of approximately 26–30%.17 If oxygen was noted as given but no flow rate or device was recorded, the patient was excluded. All vehicles in the Wellington Free Ambulance fleet carry pulse oximeters, but not transcutaneous or end tidal CO₂ monitors. Venturi masks are not used, low flow oxygen is delivered with nasal prongs, moderate flows with a medium concentration mask, and non-re-breather masks are used with a flow rate of 15 L/min.

Logistic regression was used to describe associations between oxygen use, the main outcome measure, and the chronic and acute severity markers. For multivariate logistic regression a backwards selection process was used with a P-value for retaining a variable of 0.1. Oxygen delivery was kept in logistic regression models regardless of the variable retention criterion to adjust for the independent predictors of poor outcome. For univariate odds ratios where there were zero cell counts, Fisher’s exact test was used to generate a P-value and Peto’s method used to calculate a univariate odds ratio.

The main clinical outcome was a composite of death, requirement for invasive or non-invasive positive pressure ventilation, or respiratory failure (defined as a PaCO₂ ≥ 45 mmHg (6.0 kPa) and a pH < 7.35 documented on an arterial blood gas within 4 h of presentation). It was not possible to use death alone in multivariate models because no deaths occurred in subjects receiving low flow oxygen.

Results

There were 406 admissions with AECOPD identified from the Wellington Hospital database. Of these, 113 were not brought in by ambulance, 16 were inpatient hospital transfers and in 27 the medical records were missing, resulting in 250 cases being included in the audit. The characteristics of the patients, including chronic and acute severity markers and clinical outcomes, are shown in Table 1. The patients had severe chronic disease with...
The association between oxygen administration and clinical outcome: composite of death, positive pressure ventilation or respiratory failure

<table>
<thead>
<tr>
<th>Oxygen flow rate with poor outcome</th>
<th>Multivariate association with poor outcome†</th>
</tr>
</thead>
<tbody>
<tr>
<td>(continuous)†</td>
<td></td>
</tr>
<tr>
<td>Low flow vs high flow</td>
<td></td>
</tr>
<tr>
<td>High flow</td>
<td>1.0 (0.5–1.9)</td>
</tr>
<tr>
<td>Low flow</td>
<td>1.4 (0.6–2.9)</td>
</tr>
</tbody>
</table>

†Odds ratio for association per l/min oxygen flow. ‡Multivariate analyses adjusted for all chronic severity markers, Glasgow Coma Scale and heart rate.

Table 3 The association between adverse clinical outcome (death, positive pressure ventilation or respiratory failure) and markers of chronic and acute severity

<table>
<thead>
<tr>
<th>Chronic severity markers</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term oral steroids</td>
<td>1.1 (0.5–2.3)</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>1.4 (0.8–2.5)</td>
</tr>
<tr>
<td>Home nebulizer</td>
<td>2.4 (1.4–4.3)</td>
</tr>
<tr>
<td>Long-term oxygen therapy</td>
<td>2.8 (1.5–5.1)</td>
</tr>
<tr>
<td>Previous respiratory failure†</td>
<td>2.6 (1.5–4.6)</td>
</tr>
<tr>
<td>Previous assisted ventilation‡</td>
<td>3.3 (1.7–5.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute severity markers</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (per 10 breaths/min higher)</td>
<td>0.7 (0.5–0.9)</td>
</tr>
<tr>
<td>Heart rate (per 10 beats/min higher)</td>
<td>1.3 (0.9–1.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mmHg higher)</td>
<td>1.1 (1.0–1.3)</td>
</tr>
<tr>
<td>Oxygen saturations on air (per percentage point higher)</td>
<td>1.1 (0.9–1.0)</td>
</tr>
</tbody>
</table>

†Previous respiratory failure: PaCO2 ≥ 45 mmHg or pH < 7.35. ‡NIPPV (non-invasive positive pressure ventilation) or IPPV (invasive positive pressure ventilation).
international guidelines. Furthermore, of the patients in whom there was definite documentation of oxygen flow rates, about half received ≥8 L/min. This occurred despite most patients being at risk of serious adverse outcomes, with 53% having previous respiratory failure documented, 24% having previous invasive or non-invasive ventilation, and 25% receiving long-term oxygen therapy. This approach to oxygen delivery resulted in 75% of patients having oxygen saturations in excess of the target range of 88–92% at presentation to the Emergency Department, and nearly a third having oxygen saturations ≥98%. Although pulse oximetry is a critical part of the initial patient assessment, oxygen therapy in this study was not based on the routine assessment of oxygen saturations, with only 37% of patients having saturations documented on room air at baseline.

When oxygen was analysed as a continuous variable according to flow rate, there was a statistically significant association between increased flow rates and poor clinical outcomes, consistent with previous studies. Importantly, the strength of this association increased in the multivariate analysis, which adjusted for independent predictors of poor outcome. This indicates that there was no major confounding by severity, and that the association was not due to more unwell patients receiving higher concentrations of oxygen therapy. In addition, the observation that the risk of death, assisted ventilation or respiratory failure progressively increased with higher PaO2 levels suggests that inappropriate high flow oxygen therapy was an important contributor to poor clinical outcomes. The statistical power to detect an association between high flow oxygen therapy, when treated as a dichotomous variable, and poor clinical outcomes, was limited because of the small number of patients in the 'low flow' group. However, in multivariate analysis adjusted for acute and chronic severity markers, the point estimates were consistent with an association between high flow oxygen therapy and poor outcomes.

Our findings complement other studies investigating the relationship between high flow oxygen therapy and poor outcomes in AECOPD. In a study from the UK, there was an inverse correlation between pH and PaO2 and more than 50% of patients with a PaO2 of >10 kPa were acidotic. Their data suggested that a significant number of patients had been made acidotic by injudicious oxygen therapy and that it may be possible to correct rapidly the pH once the inspired oxygen concentration was reduced. An Australian study reported that the use of high flow oxygen therapy in patients with high PaCO2 levels contributed to an increased length of stay, more frequent admission to a high dependency unit and greater use of NIPPV. Inappropriate oxygen therapy was often initiated at the time of ambulance transfer, as 92% of patients admitted through ambulance received oxygen at a flow rate of >2 L/min despite one-third having previously documented hypercapnia. Similar findings were reported in the study by Durrington et al. in which initial high concentration oxygen therapy caused significant acidosis and hypercapnia compared with low concentration oxygen. There was a significantly increased complication rate during admission in those COPD patients receiving high concentration oxygen, particularly when ambulance journeys exceeded 30 min. This latter finding is relevant to our study in which the average ambulance transit time was 49 min. A prospective audit by Denniston et al. showed that oxygen therapy >28% was associated with acute hypercapnic respiratory failure and a higher mortality.

In our study, there were strong associations between indicators of severe chronic COPD and poor outcomes during an acute exacerbation. For example, a previous episode of respiratory failure or assisted ventilation was associated with a two- to threefold risk of death, assisted ventilation or respiratory failure in a subsequent exacerbation, albeit in the setting of initial high flow oxygen therapy by the ambulance service. In contrast to the chronic severity markers there were only weak associations with some of the acute severity markers. The increased risk associated with Glasgow Coma Score underlies its use as a severity marker in the CURB-65 score, which has recently been shown to predict risk of inpatient mortality in AECOPD, similar to its use in community-acquired pneumonia.

One potential limitation when interpreting the results of our study is that less than half the patients (108/250) received arterial blood gas sampling within 1 h of arrival to the emergency department. There are several potential reasons for this, including patient refusal, reluctance of the doctor to perform the test, a perception by the doctor that the test is not indicated, or limited time and staff resources. The current BTS Guidelines on the management of AECOPD recommend all patients have arterial blood gas sampling. Our observation that about one-third of patients who had a blood gas measurement had respiratory failure, defined as a PaCO2 ≥ 45 mmHg and a pH < 7.35 illustrates the importance of this recommendation. Similarly, Plant et al. reported that of nearly 1000 patients admitted with AECOPD, almost half were hypercapnic and 20% had a respiratory acidosis on admission.

Conclusion

This study has confirmed that the ambulance administration of high flow oxygen to patients with AECOPD is associated with poor clinical outcomes. This practice of
ambulance staff administering oxygen at high flow rates to patients with AECOPD seems entrenched despite the demonstration over 50 years of the risks.23 Our study emphasizes the importance in pre-hospital care of measuring arterial oxygen saturation before starting oxygen therapy and identifying patients with severe chronic COPD who are at higher risk of respiratory failure, assisted ventilation and death. Another strategy that has been recommended is to issue all patients with a previous episode of hypercapnic respiratory failure a 24% or 28% venturi mask and an oxygen alert card, an approach that has been shown to improve outcomes and reduce the risk of respiratory failure.23 However, the institution of an alert card system must be supported by a robust oxygen delivery policy. Large randomized controlled trials of titrated oxygen therapy are urgently required to investigate the optimal use of oxygen by ambulance staff in patients presenting acutely with AECOPD. Until then liaison with ambulance paramedics to ensure that treatment is based on current evidence-based guidelines is important if improved clinical outcomes in this vulnerable patient group are to be achieved.26

References

Prevalence and predictors of premature discontinuation of dual antiplatelet therapy after drug-eluting stent implantation: importance of social factors in Asian patients
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Key words
antiplatelet therapy, drug eluting stents, stent thrombosis and compliance.

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Received 8 May 2009; accepted 29 July 2009.
doi:10.111/j.1445-5994.2009.02104.x

Abstract
Aim: Premature discontinuation of antiplatelet therapy is an independent predictor of late stent thrombosis. We sought to determine the prevalence and predictors of premature discontinuation of antiplatelet therapy after drug-eluting stent implantation among patients in Asia.

Methods: A total of 207 consecutive patients who underwent drug-eluting stent implantation at our institution was followed up after 1 year. Premature discontinuation of antiplatelet therapy was defined as omission of aspirin and/or clopidogrel for 1 week or more.

Results: Four (1.9%) patients died and the remaining 203 patients formed the study population. Prevalence of premature discontinuation of antiplatelet therapy was 12.8% (n = 26, aspirin, n = 12; clopidogrel, n = 9; both, n = 5). The median duration between stent implantation and discontinuation of antiplatelet therapy was 2.8 months. Reasons for discontinuation included cost (n = 1), gastric discomfort (n = 1), allergy (n = 3), bleeding (n = 3), advice from doctors (n = 7) and no reason (n = 11). Logistic regression showed that living alone was the only independent predictor of premature discontinuation of dual antiplatelet therapy (50.0% vs 11.3%, P = 0.001).

Conclusion: Among Asian patients who have undergone drug-eluting stent implantation, 12.8% discontinued dual antiplatelet therapy within 12 months. Living alone is associated with a fivefold increase in risk of premature drug discontinuation.

Introduction
Drug-eluting stents (DES) have gained increasing importance in the treatment of coronary artery disease because of its significant reduction in risk of restenosis compared with bare metal stents. Each year, over one million DES are implanted throughout the world. Penetration of DES can be as high as over 80% in some centres. However, occurrence of late stent thrombosis, associated with a high incidence of fatal and non-fatal myocardial infarction, remains a major limitation of DES. Large-scale registry studies and meta-analysis have found that, among other factors, premature discontinuation of antiplatelet therapy is the single most important predictor for late stent thrombosis. In early 2007, a joint advisory body in the USA issued guidelines recommending uninterrupted dual antiplatelet therapy with aspirin and thienopyridine for 12 months after DES implantation.

Despite efforts to ensure prolonged dual antiplatelet therapy after DES implantation, premature drug discontinuation nonetheless continues to occur. Previous studies conducted in western countries found that between 6.7% and 13.6% of the patients discontinued their antiplatelet therapy after DES implantation. In the PREMIER registry, patients who stopped antiplatelet therapy within 30 days after DES implantation for acute myocardial infarction had a higher mortality over the subsequent 11 months. Although over 300 000 cases of stent implantation are performed annually in Asia, few comparable data exist for Asian patients. A recent study conducted in Japan found that 18.1% of the Japanese patients discontinued antiplatelet therapy within 12 months after sirolimus-eluting stent implantation. Although bleeding and surgical procedures were found to be the main reasons for stopping antiplatelet therapy,
there was no mention of baseline factors that predicted drug discontinuation. In this study, we sought to investigate the prevalence of premature discontinuation of antiplatelet therapy within 12 months after DES implantation among patients in Singapore. We also aimed to determine the role of baseline clinical and socioeconomic factors in predicting the compliance of patients to prolonged dual antiplatelet therapy after DES implantation.

Methods

Study design

This was a prospective registry study conducted at a University hospital in Singapore. Singapore is an Asian-populated country located at the southern tip of the Malay Peninsula. A total of 207 consecutive patients who underwent DES implantation between 30 January 2007 and 31 December 2007 was included into this study. All had successfully undergone implantation of at least one DES during the index procedure. The DES used included Cypher (Cordis Corporation, Miami Lake, FL, USA), Taxus (Boston Scientific, Natick, MA, USA), Endeavor (Medtronic Vascular, Santa Rosa, CA, USA) and Axxion (Biosensors Interventional Technologies Pte Ltd, Singapore). There were no strict indications in the use of DES at our institution, but operators were advised against using DES in patients who presented with ST-segment elevation myocardial infarction, could not take dual antiplatelet therapy for 12 months and have surgical operation scheduled over the next 12 months. All patients received loading doses of aspirin (100–300 mg) and clopidogrel (300–600 mg) prior to the procedure. They were admitted for at least 1 day after stent implantation and received counselling as a part of the cardiac rehabilitation programme regarding prolonged dual antiplatelet therapy before hospital discharge. As an in-house strategy to improve compliance, a complete 12-month course of clopidogrel was prescribed upon hospital discharge. This study complies with the Declaration of Helsinki, that the local ethics committee has approved the study. Informed consent has been obtained from the patients.

Data collection

Compliance with prolonged dual antiplatelet therapy was assessed at 1 year after stent implantation through a structured telephone interview with the patients. Apart from routine clinic visits, patients were not contacted to investigate compliance before the 1-year follow up, so as to avoid influence on actual compliance. For the purpose of this study, premature discontinuation was defined as omission of aspirin and/or clopidogrel for 1 week or more. Compliance information provided by patients was tallied with prescribed durations of antiplatelet medication whenever possible. When patients mentioned discontinuing medication, the exact duration and reason for discontinuation were pursued.

During the interview, detailed questions were asked regarding hospital admissions after stent implantation to determine incidence of cardiac adverse events, which in specific included myocardial infarction, target lesion revascularization and stroke. Patients who had passed away before the 1-year follow up were excluded from the study as compliance for dual antiplatelet therapy would be difficult to determine accurately. Causes of death were determined and categorized into cardiac and non-cardiac causes.

Baseline demographic, clinical and procedural data were entered prospectively into a dedicated web-based database for national audit purposes. Socioeconomic information, such as marital status, religion, education level and income, was collected retrospectively during the interview.

Statistical analysis

The distributions of continuous variables were described using means with 1 standard deviation, and discrete variables were presented as frequencies. We analysed and compared the baseline demographic, socioeconomic and existing medical backgrounds between patients who did and did not prematurely discontinue dual antiplatelet therapy. The statistical significance of comparisons between continuous and categorical variables was assessed using the Student’s t-test and the chi-squared test respectively. A forward stepwise conditional logistic regression model with non-compliance as the outcome variable was used to identify independent predictors of premature discontinuation of dual antiplatelet therapy. Based on pre-existing data and clinical intuition, we prespecified six predictors for inclusion in the logistic regression model: age, sex, household income, education status, occurrence of bleeding (during implantation) and whether the patient was living with a caregiver. We prespecified a parsimonious set of predictor variables and a forward stepwise method because of the limited number of expected events based on pre-existing data.9–11 Odds ratios and 95% confidence intervals were used to illustrate the association between model covariates and the outcome of premature discontinuation. For each predictor variable, we specified an α of <0.05 for entry into the model and an α of >0.20 for removal from the model. A classification cut-point of 0.5 was used and the
maximum number of iterations was set at 20. The goodness of fit of the final regression model was evaluated using the Hosmer–Lemeshow goodness-of-fit test. No imputation was performed on the final model. For all variables, less than 5% of the data were missing. The association between premature discontinuation and cardiac adverse event occurrence was further examined with the chi-squared test. No adjustments were made for multiple comparisons. A difference was regarded as statistically significant at $P < 0.05$. All data analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient profiles

Of the 207 patients who underwent successful DES implantation, four had passed away by 1 year after implantation. Of the four patients, only one died of cardiac cause (massive pulmonary embolism). The remaining 203 patients (mean age, 58 ± 10 years; male, 79.2%) formed the study cohort for analysis. The ethnic composition of these patients (Chinese, $n = 155$; Malay, $n = 19$, Indian, $n = 25$, Others, $n = 4$) was in accordance with the ethnic composition of Singapore. Of the 203 patients, 123 were Buddhists, 17 were Christians, 17 were Islams, 16 were Hindus, 8 were Catholics, 1 was Sikh and the remaining had no religion. The baseline socioeconomic and clinical characteristics of the patients are shown in Tables 1 and 2 respectively. In the majority of patients, the stented vessel was a native coronary artery ($n = 234$, 97.1%). The median stent diameter and stent length were 3.0 and 33 mm respectively. Although our institution encourages filling the entire 12-month prescription of clopidogrel upon discharge, 64 (31.5%) patients declined because of the cost involved, and elected instead to have their prescriptions filled at 3–4 month intervals.

Prevalence of premature discontinuation of antiplatelet therapy

At 12-month follow up, 177 patients (87.2%) had completed an uninterrupted course of dual-antiplatelet therapy whereas 26 patients (12.8%) had prematurely discontinued one or both of their antiplatelet medication for 1 week or more. Of those who had prematurely discontinued antiplatelet therapy, 12 (46.2%) had discontinued aspirin, 9 (34.6%) discontinued clopidogrel while 5 (19.2%) discontinued both. The median

Table 1 Socioeconomic characteristics of the 203 Asian patients who have undergone drug-eluting stent implantation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Prematurely discontinued antiplatelet therapy</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes ($n = 26$), $n$ (%)</td>
<td>No ($n = 177$), $n$ (%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>5 (19.2)</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>Married</td>
<td>17 (65.4)</td>
<td>165 (93.2)</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>2 (7.7)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Widowed</td>
<td>2 (7.7)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Living with caregiver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with caregiver</td>
<td>22 (84.6)</td>
<td>173 (97.7)</td>
</tr>
<tr>
<td>Living alone</td>
<td>4 (15.4)</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>2 (8.0)</td>
<td>19 (10.8)</td>
</tr>
<tr>
<td>Primary</td>
<td>1 (44.0)</td>
<td>44 (25.0)</td>
</tr>
<tr>
<td>Secondary</td>
<td>9 (36)</td>
<td>74 (42.0)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>3 (12.0)</td>
<td>39 (22.2)</td>
</tr>
<tr>
<td>Combined household income (monthly)$\dagger$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$51000</td>
<td>14 (52.2)</td>
<td>57 (32.3)</td>
</tr>
<tr>
<td>$51000–3999$</td>
<td>9 (34.8)</td>
<td>83 (46.8)</td>
</tr>
<tr>
<td>$40000–7999$</td>
<td>2 (8.7)</td>
<td>21 (12.0)</td>
</tr>
<tr>
<td>$80000–9999$</td>
<td>1 (4.3)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>$100000</td>
<td>0 (0.0)</td>
<td>10 (5.7)</td>
</tr>
<tr>
<td>Type of housing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Government</td>
<td>24 (92.3)</td>
<td>158 (89.2)</td>
</tr>
<tr>
<td>Private</td>
<td>2 (7.7)</td>
<td>18 (10.2)</td>
</tr>
<tr>
<td>Institutionalized</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

$\dagger$S$1 = €0.51 or US dollars $0.66.$
duration between stent implantation and discontinuation was 2.8 months. The number of patients who discontinued antiplatelet therapy within 6 months following DES implantation was 17 (65.4%), whereas the remaining 9 (34.6%) discontinued after 6 months. The Kaplan–Meier curve for drug discontinuation is shown in Figure 1.

Reasons for prematurely discontinuing antiplatelet therapy are shown in Figure 2. Among the three patients who had stopped antiplatelet therapy because of drug allergy, the allergy was only detected after DES implantation in two patients. The last patient’s allergy was known prior to DES implantation, but the patient insisted on proceeding despite being informed about potential risks. Among the seven patients who adhered to advice given by other doctors (all general practitioner) and prematurely discontinued antiplatelet therapy, the exact reasons behind the advice were unknown. None of these

Table 2. Clinical characteristics of the 203 Asian patients who have undergone drug-eluting stent implantation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Prematurely discontinued antiplatelet therapy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 26), n (%)</td>
<td>No (n = 177), n (%)</td>
</tr>
<tr>
<td>Indications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>16 (60.0)</td>
<td>118 (66.5)</td>
</tr>
<tr>
<td>Non ST-segment elevation acute coronary syndrome</td>
<td>10 (40.0)</td>
<td>56 (31.8)</td>
</tr>
<tr>
<td>ST-segment elevation myocardial infarction</td>
<td>0 (0.0)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Existing cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/ex-smoker</td>
<td>14 (53.8)</td>
<td>81 (45.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (69.2)</td>
<td>40 (22.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (38.5)</td>
<td>85 (48.3)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>22 (84.6)</td>
<td>155 (87.5)</td>
</tr>
<tr>
<td>Premature coronary artery disease</td>
<td>2 (7.7)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>5 (19.2)</td>
<td>30 (17)</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention</td>
<td>6 (23.1)</td>
<td>56 (31.8)</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft surgery</td>
<td>2 (7.7)</td>
<td>14 (8.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0.0)</td>
<td>10 (5.7)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1 (3.8)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Renal dialysis</td>
<td>1 (3.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>2 (7.7)</td>
<td>13 (7.4)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>On antiplatelet therapy for 1 month prior to PCI</td>
<td>7 (26.9)</td>
<td>55 (31.8)</td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention.

Figure 1 Kaplan–Meier curve of premature discontinuation of dual antiplatelet therapy after drug-eluting stent implantation.
patients stopped antiplatelet therapy for the purpose of preparation for surgical procedures. Only one patient prematurely discontinued dual antiplatelet therapy as a result of cost.

**Predictors of premature discontinuation of antiplatelet therapy**

Of all patient variables examined, body mass index, marital status and whether the patient was living with a caregiver showed significance as predictors for premature discontinuation of dual antiplatelet therapy. Patients who had a lower body mass index (24.3 vs 26.0, \( P = 0.04 \)), were single (19.2% vs 4.0%, \( P < 0.001 \)) and living alone (15.4% vs 2.3%, \( P = 0.001 \)) were more likely to discontinue prematurely antiplatelet therapy. A lower combined household monthly income also suggested a higher possibility of premature discontinuation of antiplatelet therapy (\( P = 0.06 \)), but was not proven statistically significant. Logistic regression analysis showed that living alone was independently associated with premature discontinuation of dual antiplatelet therapy (OR = 5.85, 95% CI = 1.23–27.8, \( P = 0.006 \)).

**One-year clinical outcomes**

For the 26 patients who prematurely discontinued dual antiplatelet therapy, none of them had myocardial infarction or stroke, but two underwent target lesion revascularization within 12 months after DES implantation. For the 177 patients who had not discontinued antiplatelet therapy, there was a total of 7 adverse events, including 5 target vessel revascularizations, 1 myocardial infarction (stent implantation related myocardial injury) and 1 stroke. There were no incidences of stent thrombosis by either conventional definition or Academic Research Consortium definition.\(^{13}\)

**Discussion**

This study aimed to investigate the prevalence and predictors of premature discontinuation of dual antiplatelet therapy after DES implantation among patients in Singapore. We found that approximately one in eight patients discontinued either aspirin and/or clopidogrel within 12 months after DES implantation. This is despite ensuring all patients received adequate counselling on the importance of prolonged dual antiplatelet therapy before hospital discharge. Most of the patients stopped antiplatelet therapy because of advice from other doctors or purely because of non-compliance. Living alone was found to be the only significant independent predictor for drug discontinuation.

DES have emerged as a state-of-the-art treatment for coronary artery disease. DES effectively suppresses neointimal proliferation, which translates into reduction in rates of restenosis and repeat revascularization, resulting in rapid and widespread adoption of this new technology. Yet, one important caveat of DES implantation is an increased risk of late stent thrombosis,\(^{14}\) which presumably is related to delayed endothelialization of stent struts. Although the absolute event rate is low in most series, stent thrombosis often presents in a catastrophic manner with high incidence of myocardial infarction and/or death.\(^{3,13}\)

Several clinical, angiographic, intravascular ultrasound parameters have been found to be associated with late stent thrombosis after DES implantation. Among these, premature discontinuation of antiplatelet therapy has been consistently found to be the most important predictor.\(^{4-7}\) In a large cohort of nearly 3000 patients, prevalence of premature discontinuation of clopidogrel was 36.8% among patients who developed stent thrombosis, in contrast to 10.7% among those who did not.\(^{6}\) Using data from 2487 patients in ARRIVE I registry,
stopping clopidogrel within 6 months after Taxus stent implantation was found to be the most important predictor (hazard ratio 5.28) for stent thrombosis. Although robust scientific evidence on the optimal duration of antiplatelet therapy after DES implantation is still lacking, registry data have suggested that extending dual antiplatelet therapy till 1 year could attenuate the associated risks of stent thrombosis.

It is encouraging that with increasing recognition of the importance of adequate antiplatelet therapy after DES implantation, efforts are being made to reinforce patient medical compliance as well as identify candidates who were more suited to receive bare metal stent implantation or coronary artery bypass grafting. However, despite the implementation of these proactive measures, the problem of non-compliance to prolonged dual antiplatelet therapy remains unresolved.

The PREMIER registry was the first multicentre registry in the USA studying compliance of dual antiplatelet therapy after DES implantation. Among the 500 patients who had undergone DES implantation for myocardial infarction, 13.8% discontinued antiplatelet therapy within 30 days. It is conceivable that this incidence would be higher if the patients were followed up at 1 year. In a similar study based in Italy, Latib et al. reported that 6.7% of the patients in the study prematurely discontinued antiplatelet therapy within 12 months after DES implantation, mostly because of bleeding and need for surgery. Another study from Japan reported findings of 18.1% incidence of premature discontinuation of antiplatelet therapy. The incidence reported in the present study was comparatively lower (12.8%). This could be attributed to the prudence of our institution in screening who might not be suitable to take a prolonged course of dual antiplatelet therapy, as reflected by the relatively low penetration (48.4%) of DES during the study period. Our existing practice of prescribing a complete 12-month course of clopidogrel upon hospital discharge if affordable for patients could have also contributed to this lower discontinuation rate. Finally, there were differences in defining premature discontinuation in the various studies.

The most common reasons for premature discontinuation of the antiplatelet therapy in our study were advice from other doctors \((n = 7)\) and patient non-compliance \((n = 11)\). This study had commenced immediately after the guidelines recommending 12-month dual antiplatelet therapy following DES implantation were published. We speculate that the dissemination of this information among non-cardiologists may have been less rapid, resulting in slower adoption of extended dual antiplatelet therapy.

The remaining patients who had prematurely discontinued antiplatelet therapy did so out of non-compliance to medical treatment. Many patients responded that they decided to discontinue medication because they felt that they were well and had ‘completely recovered’. This highlights potential inadequacies in patient education regarding the importance of prolonged dual antiplatelet therapy in reducing adverse events after DES implantation. The solution may be a coordinated effort between cardiologist, primary care physicians and nurse practitioners advocating a consistent and constantly updated message of adherence to extended dual antiplatelet therapy.

In the present study, we found that living alone was the only independent predictor for premature discontinuation of antiplatelet therapy. This finding was paralleled by a higher prevalence of premature antiplatelet discontinuation amongst single patients. Patients living alone were five times more likely to discontinue antiplatelet therapy. Apart from this factor, no other demographic, clinical or angiographic parameters in our multivariable model predicted dual antiplatelet therapy discontinuation. This finding differs from that of the PREMIER registry, which found that lower education level of the patients (not completing high school) was the only independent predictor for premature drug discontinuation. This may reflect the influence of different cultures on Asian and North American patients. Asian patients are perceived to be more family-oriented with a tendency to seek immense comfort from family support, especially during arduous times, such as being diagnosed with coronary artery disease and undergoing stent implantation. Hence, it is conceivable that the availability of family members as caregivers has an undeniably important influence on medical compliance of these patients. Asian patients also place great importance in providing and supporting their children and family. Hence, a family presence could serve as a positive reinforcement for patients to remain compliant to therapy so as to stay well and bear this responsibility.

There were several limitations in this study. This was a single-centre study involving a relatively small number of patients. The information about continuation or discontinuation of prolonged dual antiplatelet therapy was based entirely on patients’ replies and the accuracy of this information could not be completely verified. Information on drug compliance of the patients who died before 12-month follow up was also not available. However, the four patients made up a small minority of the cohort and it was hence unlikely for this information to have influenced findings of the study. Although our institution has a policy of prescribing the whole course of 12-month clopidogrel upon hospital discharge after DES implantation, it is possible that some patients might have...
denied this because of the high cost involved. This study was also underpowered to detect differences in clinical outcomes between patients who had completed and prematurely discontinued antiplatelet therapy. Finally, Singapore is a relatively well-developed country in Asia, and the results in this study may not be applicable to other Asian countries.

**Conclusion**

Among patients receiving DES in our study, 12.8% prematurely discontinued dual antiplatelet therapy within 12 months. Living alone is associated with a fivefold increase in the risk of premature drug discontinuation. Our results suggest that social factors are critical determinants of patient compliance to dual antiplatelet therapy, and highlight the need for increased vigilance of socioeconomic risk markers of premature discontinuation of dual antiplatelet therapy after DES implantation. Larger studies and studies among different patient populations are needed to validate and replicate these findings, in order to determine the true impact of socioeconomic factors on post-percutaneous coronary intervention outcomes and healthcare policy.

**References**


Assessing PaCO₂ in acute respiratory disease: accuracy of a transcutaneous carbon dioxide device

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Key words
blood gas monitoring, transcutaneous, asthma, pneumonia, hypercapnia, pulmonary gas exchange.

Abstract
Background: Pulse oximetry non-invasively assesses the arterial oxygen saturation of patients with acute respiratory disease; however, measurement of the arterial partial pressure of carbon dioxide (PaCO₂) requires an arterial blood gas. The transcutaneous partial pressure of carbon dioxide (PtCO₂) has been used in other settings with variable accuracy. We investigated the accuracy of a PtCO₂ device in the assessment of PaCO₂ in patients with asthma and suspected pneumonia attending the emergency department.

Methods: Patients with severe asthma (FEV₁ < 50% predicted) or suspected pneumonia (fever, cough and respiratory rate >18/min) were enrolled. Subjects were excluded if they had a history of chronic obstructive pulmonary disease or other conditions associated with respiratory failure. Arterial blood gases were taken at the discretion of the investigator according to clinical need, and paired with a simultaneous reading from the PtCO₂ probe.

Results: Twenty-five patients were studied with one set of data excluded because of poor PtCO₂ signal quality. The remaining 24 paired samples comprised 12 asthma and 12 pneumonia patients. The range of PaCO₂ was 19–64 mmHg with a median of 36.5 mmHg. Bland–Altman analysis showed a mean (SD) PaCO₂ – PtCO₂ difference of -0.13 (1.9) mmHg with limits of agreement of plus or minus 3.8 mmHg (-3.9 to +3.7).

Conclusion: A PtCO₂ device was accurate in the assessment of PaCO₂ in patients with acute severe asthma and suspected pneumonia when compared with an arterial blood gas. These bedside monitors have the potential to improve patient care by non-invasively monitoring patients with acute respiratory disease at risk of hypercapnia.

Introduction
The widespread use of pulse oximeters has simplified the assessment of arterial oxygenation in patients with acute respiratory disease. However, although convenient, the pulse oximeter gives no information about the arterial partial pressure of carbon dioxide (PaCO₂), a direct measure of alveolar ventilation. In a wide range of respiratory disorders, such as acute exacerbations of chronic obstructive pulmonary disease (COPD), severe asthma and pneumonia, the PaCO₂ is highly predictive of the need for assisted ventilation, intensive care unit admission and mortality. However, to measure the PaCO₂, an arterial blood gas (ABG) is required. This is an invasive procedure which can be painful and is occasionally associated with complications. Furthermore, if ongoing PaCO₂ measurements are required then multiple punctures or an arterial line may be necessary. Venous blood gases are performed as an alternative to ABG in some emergency departments (EDs), and although they are generally easier to obtain, ongoing monitoring of PaCO₂ still requires multiple venepunctures. Although end-tidal carbon dioxide monitors are available in many emergency departments, their major limitation is that they become more inaccurate in the setting of changing alveolar dead space.

Portable devices to measure transcutaneous partial pressure of carbon dioxide (PtCO₂) at the bedside provide a promising alternative to an ABG in the assessment and monitoring of patients with acute respiratory disease.
They function on the principle that CO₂ diffuses extremely well through tissues. A probe is attached to an area of skin (usually the earlobe) and warms to 42°C which ‘arterializes’ the underlying capillaries. The CO₂ diffusing through the skin changes the pH of an electrolyte membrane in the probe and the resulting signal is converted to an estimate of the PaCO₂.

Transcutaneous CO₂ devices have been studied in a variety of clinical settings, including invasive and non-invasive ventilation in intensive care units and overnight studies of sleep disordered breathing. Limits of agreement and bias have been reported in most studies, with a variety of results depending on the device used and the clinical setting. However, to our knowledge there are no studies of PtCO₂ monitors in the ED assessment of adult patients with asthma and pneumonia. If the measurement of PtCO₂ accurately estimates PaCO₂ in patients presenting to the ED with those respiratory disorders, it could make a significant contribution to the assessment and monitoring of alveolar ventilation in the same way that pulse oximetry is used to assess arterial oxygenation.

Our aim was to assess the accuracy of a bedside PtCO₂ device in the routine ED assessment of patients with severe asthma and suspected pneumonia by comparing it with the gold standard of ABG analysis.

Methods

This study was part of two randomized controlled trials of high concentration versus titrated oxygen therapy in patients with severe asthma and suspected community-acquired pneumonia attending the ED of three public metropolitan teaching hospitals. Both studies were approved by the Central Regional Ethics Committee. Patients were considered for inclusion in the studies if they presented with either severe asthma (FEV₁ < 50% predicted) or suspected community-acquired pneumonia (fever, cough, and respiratory rate >18/min). We excluded those with COPD and other risk factors for hypercapnic respiratory failure, such as obesity hypoventilation syndrome, neuromuscular disease or chest wall disease, because half the patients in each study were assigned to receive high-concentration oxygen for 60 min. We also excluded asthmatic patients unable to carry out spirometry on arrival or who required mechanical ventilation. Patients were assessed by one of the study investigators on arrival in the ED and if the enrolment criteria were met, written informed consent was obtained.

All patients in both studies had continuous monitoring of transcutaneous oxygen. The earlobe was first cleaned with an alcohol swab and the PtCO₂ probe was attached using the provided attachment clips and contact gel. A minimum of 10 min was allowed for arterialization to occur and PtCO₂ readings to stabilize, at which point the oxygen treatment regimen was started. Subjects in both studies had an ABG taken during the course of their routine assessment if the investigator felt it was clinically indicated, hence our data represent a convenience sample. The ABG samples were obtained by radial artery puncture with a 22-gauge needle into a heparinized syringe. Samples were analysed immediately with an ABG analyser (Radiometer ABL800 FLEX, Copenhagen, Denmark) and a simultaneous PtCO₂ reading was recorded using a transcutaneous CO₂ monitor (TOSCA 500; Radiometer Basel AG; Switzerland). This device has a Stow-Severinghaus electrode and a probe membrane which is replaced every 14 days as per manufacturer guidelines. It automatically calibrates every 4 h using an internal carbon dioxide canister. In vitro response times for this device are typically less than 50 s and in vitro drift is less than 0.5% per hour.

We considered limits of agreement that were less than ±4 mmHg to be clinically significant. Data are presented as a Bland–Altman plot of PaCO₂ – PtCO₂ versus the mean of PaCO₂ and PtCO₂ together with limits of agreement.

Results

Subjects were recruited between June 2007 and December 2008. There were 25 pairs of data in total but one patient was excluded because of difficulty attaching the probe to the earlobe. This resulted in a lack of signal from the ear probe and therefore unstable PtCO₂ readings. This left 24 paired samples for analysis. No patients were in shock or hypothermic and none required vasopressor or inotropic support. The 24 patients (10 men and 14 women) had a mean age of 44 years and included 12 with asthma and 12 with pneumonia. The mean FEV₁ % predicted in the asthma patients was 25.5%. The mean respiratory rate for the whole group was 27 breaths per minute. The median PaCO₂ was 36.5 mmHg with a range of 19–64 mmHg and an inter-quartile range of 32–41.5 mmHg. The ABG samples were taken at a mean time of 49.5 min after attaching the probe with a range of 15–120 min. No complications were observed from either the ABG or transcutaneous sampling.

The Bland–Altman plot is shown in Figure 1. The mean (SD) PaCO₂ – PtCO₂ difference was –0.13 (1.9) mmHg with limits of agreement of plus or minus 3.8 mmHg (–3.9 to +3.7).

Discussion

These findings show that in ED patients with severe asthma or suspected community-acquired pneumonia, a
portable PtCO₂ device accurately assesses PaCO₂ without significant bias and with clinically acceptable limits of agreement when compared with the gold standard measurement of an ABG. This approach may have an important role in the assessment of patients with acute respiratory disease, particularly where an ABG is difficult, the patient refuses or multiple assessments of PaCO₂ are required.

There are some methodological issues which need to be considered in the interpretation of our findings. We used broad inclusion criteria, meaning the results can be generalized to most patients presenting with asthma or suspected community-acquired pneumonia to the ED. However, the generalizability to standard clinical practice was limited by the research setting, in which the PtCO₂ recordings were all made by fully trained research staff familiar with the equipment. The accuracy of a PtCO₂ device is dependent on correct application of the probe with contact gel, as well as cleaning, general maintenance and regular replacement of the probe membrane. In routine clinical practice if nursing and medical staff are inadequately trained or unfamiliar with the equipment, the accuracy demonstrated in our study may not be replicated. In addition, although the range of PaCO₂ levels in our study population is broad, there were relatively few with severe hypercapnia. It should also be noted that all patients in this study were relatively stable; caution would be needed in patients with a rapidly changing clinical state; however, the device does have a short in vitro response time. However, there is no evidence from other studies to suggest that PtCO₂ devices are less accurate in assessing patients with higher PaCO₂. Another limitation was that we only assessed a single ABG/PtCO₂ pair for each patient. This meant we were unable to analyse other aspects of device performance such as signal lag and drift; however, these have been well studied by other researchers and do not appear to be clinically important. A potential source of error is taking ABG samples before the PtCO₂ probe had arterialized. This was avoided in our study as the earliest sample was taken 20 min after application of the probe. Although the sample size was only 25, when carrying out a Bland–Altman analysis the precision of the confidence interval of the mean bias increases very little with numbers higher than this. Finally, the fact that this was a convenience sample introduces the possibility of selection bias.

Our findings complement those from previous studies which have used PtCO₂ devices in a number of clinical settings. One of the earliest reports of PtCO₂ accuracy in an intensive care population analysed 26 paired samples and found a mean PtCO₂ – PaCO₂ difference of 0.75 mmHg and limits of agreement of +6 to –4.5 mmHg. More recent data from Cox et al. used a similar device to that used in our study in the setting of an acute respiratory unit delivering non-invasive ventilation for acute exacerbations of COPD. They found a small bias (a mean PtCO₂ – PaCO₂ difference of 1.1 mmHg) but had slightly wider limits of agreement (+4.5 to –6.8 mmHg) than our study. Maniscalco et al. studied 35 obese inpatients with a mixture of respiratory conditions and reported a mean PaCO₂ – PtCO₂ difference of 1.4 mmHg and similar limits of agreement to our study (+1.1 to –4.0 mmHg). A recent study of patients undergoing general anaesthesia analysed 112 data pairs and found a mean PaCO₂ – PtCO₂ difference of 2.2 mmHg and wide limits of agreement (+8.6 to –12.9 mmHg). One participant in our study with a large PtCO₂ – PaCO₂ difference of 28 mmHg was excluded from the analysis. This was an order of magnitude greater than the other participants and was due to problems with fixation of the probe. However, this experience highlights the technical difficulties that may occur, and that despite overall good agreement between the two measurements, clinical judgement and experience with this method are necessary for its use.

Conclusion

At present the use of transcutaneous CO₂ monitors is largely limited to intensive care units and sleep medicine laboratories. The data from this study show that they are an accurate and convenient non-invasive measure of

\[ \text{Difference (PaCO₂ - PtCO₂)} \]

\[ \text{Mean PaCO₂ and PtCO₂ (mmHg)} \]

Figure 1 Bland–Altman plot of the difference between PaCO₂ and PtCO₂, against the mean PaCO₂ and PtCO₂. The horizontal lines represent ±two standard deviations of the differences.
alveolar ventilation and could be recommended for more widespread use in routine clinical practice, particularly in the assessment of patients with asthma and pneumonia in the ED. This recommendation is balanced by recognition that ABG measurements remain the ‘gold standard’, and have advantages in certain clinical situations such as when pH and bicarbonate measures are also required.

References

Use and disclosure of genetic information without consent: a decision-making tool for health practitioners – who, when, why and how?

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Abstract

Background: As a result of legislative changes to the Privacy Act 1988 (Cth), Australian health practitioners in the private sector are now permitted to use or disclose patients’ genetic information, without their consent, in circumstances where the health practitioner reasonably believes that doing so is necessary to lessen or prevent a serious threat to the life, health or safety of a genetic relative.

Aim: This article aims to increase the reader’s awareness of Guidelines developed by the National Health and Medical Research Council which are intended to assist health practitioners in making decisions about the use or disclosure of genetic information in certain circumstances.

Discussion: The Guidelines establish when, by whom and in what manner, use or disclosure of genetic information may take place. The Guidelines outline the factors that health practitioners should consider when determining whether use or disclosure is necessary to lessen or prevent a serious threat to an individual’s life, health or safety.

DNA genetic testing can reveal information about an individual’s current health status or make predictions about future health. As genes and genetic mutations are shared within families this means that DNA genetic testing can also reveal health information about other family members.

In situations where a patient is shown to have a genetic disorder or is at risk of one, it is recommended that the relevance of genetic information to other members is explained. At this point patients generally decide to inform family members themselves, or give consent for health practitioners to communicate the relevant information on their behalf.

However, on rare occasions, the patient may not want the information to be used or disclosed to family members even though the information could provide genetic relatives with an opportunity to take action to reduce the risk, severity or impact of the disease to themselves (Box 1). What happens then?

Legislative changes

The Privacy Act 1988 (Cth) was amended in September 2006 to improve the protection of genetic information and regulation of the disclosure of such information. One of the amendments (Section 95AA) permits doctors and other health professionals to use or disclose genetic information about a patient without the patient’s permission.

Disclosure in these circumstances is only permitted when the health professional reasonably believes that the use or disclosure is necessary to lessen or prevent a serious threat to an individual’s life, health or safety. The threat does not need to be imminent.

The amendment does not oblige disclosure of information but provides the framework for this to occur under the appropriate circumstances. The change in legislation is currently limited to health professionals working in the private sector only (National Privacy Principles); however, Australian states and territories may replicate the legislative changes in the public sector in the near future.
Box 1 Case study.

Nick, a 28-year-old male experiencing rectal bleeding was referred to a gastroenterologist working from a private clinic. The gastroenterologist asked Nick about any known health problems in his family. Nick revealed that his father had been diagnosed with familial adenomatous polyposis (FAP), an autosomal dominant form of colon cancer and subsequently died from that disorder.

The gastroenterologist considered it necessary to investigate Nick’s genetic status. He explained the process of DNA testing to Nick and advised of the implications that may arise as a result of having a DNA test. He then explained the relevance of identifying a genetic mutation with regard to the relative risk of developing colon cancer and hence the importance of ongoing monitoring. The gastroenterologist also highlighted the importance of sharing genetic information with family and explained that because the result might be of relevance to the health of other family members, the Commonwealth Privacy Act allows health professionals to disclose genetic information to genetic relatives without the consent of the patient in certain circumstances.

Nick agreed to have the DNA test and the results revealed that Nick had a mutation in the adenomatous polyposis coli (APC) gene which is the gene implicated in FAP.

Further discussion between Nick and the gastroenterologist revealed that Nick has three younger siblings but has not spoken with any of them since his mother died 2 years earlier. When asked whether he had considered contacting them to discuss the information he had learned about his genetic status, he said that he did not have a close relationship with his family and as such, did not feel comfortable discussing health information with them.

The gastroenterologist was hopeful that Nick would change his mind over time. On the next two subsequent follow-up visits, he reiterated the relevance of Nick’s health information to his siblings and asked Nick if he had given any further thought to contacting them reminding him again that in certain circumstances a health practitioner could pass on genetic health information without the patient’s consent. Nick was adamant about not contacting his siblings and told the gastroenterologist he did not want anyone else contacting them either.

The gastroenterologist decided to discuss the case with a senior colleague and also consulted a clinical geneticist.

Points for consideration

What factors support use or disclosure in these circumstances?
Because of the high risk and early onset of colon cancer (by age 40) in most individuals with an APC mutation, this situation represents a serious threat to the life, health or safety of genetic relatives that could be lessened by disclosure. Diagnosis before the development of cancer allows for preventive treatment, for example colectomy.

What factors weigh against use or disclosure?
Although a serious threat to genetic relatives exists, and this could be lessened or prevented by disclosure, consent has not been given and the case must be reviewed by experts in the area. Use or disclosure has the potential to compromise the relationship between the patient and the gastroenterologist, and to further compromise the relationship between the patient and his family. The privacy of family members must also be considered. The doctor’s legal obligation in terms of duty of care to family members is not clearly defined.

What information could be given to the patient?
The patient has been given the information needed to understand the implications of the diagnosis for his genetic relatives. If he continues to withhold consent, discussion of the possible use or disclosure without consent should be initiated. This should cover the provision in legislation for non-consensual disclosure to genetic relatives, the basis of the belief that release of the information is necessary to lessen a serious threat and the fact that the information would not directly identify the patient or the condition. The practitioner’s continued duty of care towards the patient and the continuing availability of genetic counselling for the patient should also be highlighted.

Who might be involved in decision-making about use or disclosure?
The gastroenterologist could make a decision regarding use or disclosure in consultation with his senior colleague and/or a clinical geneticist (ensuring the identity of the patient is not apparent or readily ascertainable where practicable). In doing so he would be acting in accordance with the guidelines and thus with the law. He may also choose to seek advice from his medical defence organization. If the gastroenterologist decides to use or disclose the information without consent, he should notify the patient of this decision.

How might disclosure take place?
If the gastroenterologist makes a decision to disclose, he could contact the siblings in writing advising them to make an appointment to discuss a familial disorder. However, the gastroenterologist is required to obtain the contact details of the patient’s relative(s) lawfully. Specific details on how and when a health practitioner may collect or use the contact details of a patient’s genetic relative, to inform the relative of the possible implications of the genetic information is available through the Office of the Australian Information Commissioner website. The opportunity for genetic counselling and DNA testing could then be provided. Cascade contact† could also be used to reach other genetic relatives. The value of having earlier consulted with a clinical geneticist would now be useful as identifying, counselling and testing family members is both time-consuming and logistically complex and might better be undertaken by the gastroenterologist working with the appropriate clinical genetics service. All communications with genetic relatives would need to be undertaken with consideration of the privacy of the patient and other relatives.

†The Guidelines define ‘cascade contact’ as a step-by-step process that can provide access to genetic information for a wider cross-section of a family, in which each genetic relative who is notified about their increased risk and makes contact with the disclosing health practitioner, is asked for consent to contact his or her genetic relatives. When additional genetic relatives make contact, the process is repeated.
Considerations

The patient
Use and disclosure of genetic information without the patient’s consent involves consciously acting against the patient’s expressed wishes. Patients may view such situations as a breach in confidentiality, and this may potentially create disruption to the patient–doctor relationship or family relationships.

The genetic relative
Genetic relatives may not want to be informed about their risk of inheriting a familial disease. They may also feel that receiving unsolicited information about a possible genetic risk is an invasion of privacy. Therefore, it is important to balance respect for an individual’s privacy and their right not to know, with the need to share genetic information that could be of significant importance to that person’s health. Informing genetic relatives of a genetic risk allows them to decide whether or not to learn their own genetic status through further assessment. This empowers them to make their own decisions about taking a proactive approach to maintaining their health.

The health practitioner
Health practitioners have a legal and ethical obligation to maintain confidentiality of information about their patients. With genetic conditions, an ethical responsibility can also be seen to extend to the wider family. Where a patient does not provide consent for the use or disclosure of his/her genetic information, there is likely to be conflict between the practitioner’s legal and ethical obligations to the patient and to his or her genetic relatives. The legislative change does not compel health practitioners to disclose genetic information to genetic relatives. However, failure to do so in the appropriate circumstances might raise issues if relatives become aggrieved because they have not been notified about a risk for a serious genetic condition.

Other factors
Communication, family, culture and lifestyle are fundamental to understanding the family dynamics involved in each situation. It is important to understand these aspects in the context of the patient in addition to understanding the diagnosis and nature of the genetic condition. Some patients may have impaired decision-making ability due to an illness or disability, and determining whether the patient can competently make a decision about the communication of his or her genetic information is another important consideration.

Guidelines
Making decisions about the use and disclosure of a patient’s genetic information without his or her consent requires consideration of a range of overarching issues. In accordance with legislation, the National Health and Medical Research Council (NHMRC) developed guidelines to assist health practitioners faced with the difficult task of making such decisions. The guidelines entitled ‘Use and disclosure of genetic information to a patient’s genetic relatives under Section 95AA of the Privacy Act 1988 (Cth) – Guidelines for health practitioners in the private sector’ (Guidelines) specify the requirements that must be met by health practitioners if they choose to use or disclose genetic information without patient consent.

Structure of the Guidelines
Information in the Guidelines is arranged in four parts.
PART A introduces nine principal guidelines (Box 2) which specify the requirements that must be met for disclosure to take place.
PART B includes a summary and practical guide, providing a more detailed overview of the nine principal guidelines. This section features guidance tools such as ‘key points for good practice’ and a flow chart to assist health practitioners to navigate their way through the decision-making process.
PART C explores the complex issues which need to be considered during the decision-making process. Understanding the family dynamics in situations where consent is withheld is imperative to good decision-making. This section discusses communication, cultural and lifestyle factors, diagnosis and understanding the nature of the genetic condition.
PART D comprises a number of scenarios. Many of the situations have been based on real life examples. The scenarios provide an illustration of the issues covered in the Guidelines, bringing together the issues and

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considerations which need to be understood by medical practitioners when making a decision about the use or disclosure of genetic information.

How to use the Guidelines

Health practitioners are encouraged to refer to the Guidelines early in the process. Ideally, information about the provisions created by the Privacy Act 1988 (Cth) should be communicated to the patient during pretest counselling when the implications of having a genetic test are discussed. Genetic testing is voluntary and it is necessary that patients understand the process and issues associated with having a genetic test to make an informed decision.

The ideal outcome for such situations is to counsel patients and obtain consent for the use and disclosure of their genetic information. By referring to the Guidelines early in the process, health practitioners can be made aware of the relevant issues, understand how to deal with them and involve other professionals, such as genetic counsellors to provide support and assistance throughout the process.

Disclosure without consent should be considered a last resort and should only occur after several unsuccessful attempts to obtain consent have been made and all other avenues have been exhausted. In the event the situation progresses and the medical practitioner has made a decision to use or disclose a patient’s genetic information to a genetic relative without patient consent, the Guidelines also provide advice on how to communicate this to the patient and how disclosure should take place. Specific tools designed to assist disclosure are included in the Guidelines, such as an example of a letter which could be sent to genetic relatives to inform them of their risk.

How to access the Guidelines

The Guidelines were developed by an NHMRC Working Committee and have been approved by the Australian Privacy Commissioner. They became effective on 15 December 2009. The Guidelines can be downloaded through the NHMRC website: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/e96.pdf.

Related Public Interest Determination

Where a decision has been made to use or disclose genetic information without the patient’s consent, the collection or use of the contact details of the patient’s genetic relatives would generally need the consent of the relative. The Australian Privacy Commissioner is satisfied that, in these circumstances, it is impractical to obtain consent for the collection of the genetic relative’s contact details and has issued a Public Interest Determination (PID) to allow the collection or use of contact details for
Transfusion-related acute lung injury in a neutropenic patient

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Key words
transfusion-associated acute lung injury, neutropenia, human leucocyte locus A.

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Received 2 October 2009; accepted 1 May 2010.
doi:10.1111/j.1445-5994.2010.02366.x

Transfusion-related acute lung injury (TRALI) is a leading cause of transfusion-related morbidity and mortality. Current concepts regarding the pathogenesis of this disorder imply a “two-hit” model in which neutrophils are sequestered in the pulmonary capillary bed, and subsequently activated by substances in the transfused blood product. We report a case of TRALI in a patient with neutropenia and discuss the possible factors contributing to the respiratory symptoms in this patient. We also emphasise the importance of recognising mild cases of TRALI in order to investigate the implicated donor/s appropriately, and to minimise the risk for more severe episodes in other patients.

Abstract
Transfusion-related acute lung injury (TRALI) is a leading cause of transfusion-related morbidity and mortality. The diagnosis is based on clinical assessment and radiographic findings, and consensus criteria have been proposed to assist in defining this entity for the purpose of comparison between haemovigilance programmes. However, identification of milder cases of TRALI is important in order to initiate appropriate investigation of the implicated donor/s, and limit the potential for more severe episodes in other patients.

Funding: None.
Conflict of interest: None.

We report a case of a 28-year-old woman treated for refractory acute promyelocytic leukaemia (APML), who developed respiratory distress shortly after a platelet transfusion. The diagnosis of APML was made in December 2005, and although the patient initially responded to conventional treatment she subsequently relapsed twice, 18 months and 24 months after the initial diagnosis. She was treated with differing regimens, including all-trans retinoic acid (ATRA), arsenic trioxide, idarubicin and gemtuzumab. A matched unrelated donor allogeneic stem cell transplant was planned, and the patient was admitted on 12 June 2008 for further salvage chemotherapy before the transplant. She was pancytopenic over this period; her white cell
count was consistently below $1.0 \times 10^9/L$, with an absolute neutrophil count between $0.03$ and $0.1 \times 10^9/L$. Transfusion support over this period included two units of leucodepleted red cells, a total of six units clinical fresh frozen plasma (FFP) and three apheresis platelet units, all given uneventfully with phenergan pre-medication.

On day 6 of therapy she was transfused with a 2-day-old single donor apheresis platelet unit. Thirty minutes after the transfusion, the patient developed extreme rigours and chills, with deep cyanosis and $O_2$ saturation of 81% on room air. She was tachycardic (pulse 166 b.p.m.) with a mildly reduced diastolic blood pressure (140/63 mm Hg). Her symptoms resolved rapidly following administration of i.v. hydrocortisone, pethidine and promethazine and 15 L/minute oxygen by face mask. Within 5 minutes, her $O_2$ saturation had increased to 100%, and routine observations had normalized. A transfusion reaction investigation was initiated based on the rigours and chills, but TRALI was not suspected clinically.

Two hours after the transfusion, the platelet count was $63 \times 10^9/L$, an increment of $30 \times 10^9/L$. At the time the patient had a leucocyte count of $0.7 \times 10^9/L$, with an absolute neutrophil count of $0.02 \times 10^9/L$ and lymphocyte count of $0.68 \times 10^9/L$. A gated cardiac study had been carried out the previous day and confirmed normal cardiac function with a LVEF of 62%. The most recent chest X-ray was from the 3 May and was reported as normal. Following the transfusion reaction, a chest X-ray was not carried out until 24 hours after the platelet transfusion at which point no evidence of bilateral infiltrates was found.

The patient sample collected immediately after the transfusion reaction demonstrated both Class I and Class II human leucocyte locus A (HLA) antibodies. Relatively strong antibody to the Class I allele HLA-A2 and weaker antibodies against other Class I antigens were demonstrated using a Single Bead Antigen assay. No Class I or Class II HLA antibodies were demonstrated in samples collected 2 weeks earlier and 3 weeks after the transfusion reaction (Table 1). HLA typing of the patient was HLA-A2, -A24, HLA-B44, -B51. No granulocyte antibodies could be demonstrated in the patient’s samples.

Human leucocyte locus A Class I antibodies were demonstrated in the serum of the male donor of the apheresis platelet unit, including reactivity with HLA-A2 and other Class I specificities detected in the patient. No granulocyte antibodies could be demonstrated (Table 2). The donor had a long history of regular donations and had not been implicated in any prior transfusion reactions. Cross-reference to the records of the Australian Red Cross Blood Service showed the following donation history: 13 apheresis platelet donations, 1 apheresis clinical FFP donation, 11 plasma donations for fractionation and 3 whole blood donations. The donor’s pre-donation questionnaire revealed no recent blood transfusion and further questioning during counselling determined no risk factors for HLA alloimmunization, no history of blood transfusion and no history of serious illness or operations. Current studies have shown that the prevalence of HLA antibodies is similar in both transfused and nontransfused males. The donor implicated in this case was deferred from subsequent donations.

### Table 1 Patient HLA antibody data

<table>
<thead>
<tr>
<th>Sample collection date</th>
<th>HLA Class I</th>
<th>HLA Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRA</td>
<td>SBA</td>
</tr>
<tr>
<td>3 June 2008</td>
<td>0%</td>
<td>Not tested</td>
</tr>
<tr>
<td>18 June 2008</td>
<td>45%</td>
<td>Positive</td>
</tr>
<tr>
<td>7 July 2008</td>
<td>0%</td>
<td>None detected</td>
</tr>
</tbody>
</table>

HLA, human leucocyte locus A; PRA, panel reactive antibody; SBA, single antigen bead analysis.

### Table 2 Donor HLA and granulocyte antibody data

<table>
<thead>
<tr>
<th>HLA Class I</th>
<th>HLA Class II</th>
<th>Granulocyte antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA</td>
<td>SBA</td>
<td>Specificity</td>
</tr>
<tr>
<td>56%</td>
<td>Positive</td>
<td>A2,A30,A31</td>
</tr>
<tr>
<td>Weak</td>
<td></td>
<td>A23,A24,A11,Cw14,B76,B38</td>
</tr>
</tbody>
</table>

HLA, human leucocyte locus A; PRA, panel reactive antibody; SBA, single antigen bead analysis.
Discussion

In the absence of a specific laboratory test, the diagnosis of TRALI depends on clinical assessment of the patient. In 2004, following a Consensus Conference convened in Toronto, Canada, clinical guidelines for the diagnosis of TRALI were published. The criteria include the development of acute onset hypoxaemia during or within 6 hours of transfusion, with the demonstration of bilateral infiltrates on chest X-ray. Circulatory overload should be excluded, as should pre-existing ALI or alternative risk factors for ALI. The authors acknowledge that the criteria exclude milder forms of TRALI, the rationale being that a clear definition for these cases is not available, and that including the mild cases would complicate comparative studies.

Although the true incidence of TRALI is unknown, it is considered a leading cause of transfusion-associated morbidity and mortality. Haemovigilance data suggest that mortality from TRALI is approximately 6% to 20%. It is therefore critical to identify mild cases in clinical practice as there are significant issues to address in management of the implicated donor/s. Appropriate management including donor deferral avoids the possibility of more severe reactions in other patients.

Davis et al. describe three cases in which the affected patients experienced respiratory symptoms which were mild and of short duration following transfusion of blood products, including FFP and leucodepleted red blood cells. None of the cases was referred to the transfusion unit as suspected cases of TRALI despite the presence of respiratory symptoms. In all three cases, donor antibodies with specificity for patient HLA antigens were identified, and granulocyte crossmatching was incompatible.

The presentation in our case was very similar. The patient experienced respiratory symptoms of acute onset within 30 minutes of receiving a platelet transfusion. The symptoms were of short duration, and neither fluid overload nor TRALI was suspected clinically. A chest X-ray was not requested; however, the combination of acute onset respiratory distress, documented hypoxia and the detection of donor antibodies to patient HLA antigens would be consistent with TRALI, albeit a mild presentation. Of note, HLA-specific antibodies, consistent with that found in the donor, could be detected in the patient serum shortly after the event. They were not present in previous samples and disappeared within a period of weeks. Crossmatching of platelet donor with patient granulocytes was not carried out for our case.

It is interesting to postulate the underlying mechanism for TRALI in this patient.

Current thinking regarding the pathogenesis of the ALI involves a ‘two-hit’ model. An initial requirement is that neutrophils are primed as a consequence of underlying comorbid conditions, such as surgery, infection, cardiovascular disease and haematologic malignancies. This priming augments the physiological sequestration of neutrophils in the pulmonary capillary bed. The primed neutrophils may then be fully activated by exogenous activating substances related to the transfusion, including neutrophil-binding antibodies, cytokines and bioactive lipids.

The neutrophil is therefore postulated as the effector cell in this two-hit model. However, in our patient, the neutrophil count was only $0.02 \times 10^9/L$ as a consequence of the chemotherapy. In a study by Silliman et al., patients with haematologic malignancy, in particular acute leukaemia undergoing induction chemotherapy, appeared to be at greater risk of developing TRALI. The authors do not comment on the neutrophil count in these patients.

An alternative hypothesis suggests that transfused HLA antibodies may induce TRALI by direct contact with susceptible endothelial cells of the lung capillaries. In their mouse model of TRALI, Looney et al. postulate that the transfused HLA Class I antibody binds to its cognate antigen present on the pulmonary endothelium, the first vascular bed encountered after infusion. The antibodies then sequester circulating neutrophils through Fcγ receptor interactions leading to neutrophil activation and lung injury. Some HLA antibodies, such as HLA-A2 induce neutrophil aggregation in vitro which suggests they have the capacity to prime and activate neutrophils.

The mechanisms in our patient are likely to be a combination of the above factors. We postulate that donor derived HLA-A2 antibodies binding to the pulmonary capillary endothelium may have facilitated the sequestration and activation of neutrophils despite the low white cell count, and that the short duration of the clinical episode may reflect the paucity of entrapped neutrophils. Additional mechanisms thought to contribute to TRALI in neutropenic patients include increased levels of vascular endothelial growth factor (VEGF) or antibodies to HLA Class II antigens in the transfused product. These directly affect the permeability of the pulmonary endothelial cells. We did not measure VEGF levels in our case, and there was no evidence for HLA Class II antibodies.

The relevant practice note is that clinicians should have a high index of suspicion for TRALI in any patient who experiences respiratory symptoms in relation to transfusion. Identification of mild cases of TRALI with appropriate donor management is critical in the prevention of future episodes, with the potential for severe and even life-threatening reactions.
References


Images in Medicine

**Aberrant right subclavian artery aneurysm**

Figure 1 Chest X-ray demonstrating a hyperdensity in the apical region of the right lung consistent with aberrant right subclavian artery aneurysm (arrow).

Aberrant right subclavian artery is one of the most common developmental anomalies arising from the aortic arch, with a reported incidence of 0.4–2.3%. We report a case of an aberrant right subclavian artery aneurysm.

An 86-year-old woman with a history of chronic obstructive pulmonary disease and atrial fibrillation presented to the hospital with acute onset shortness of breath. An X-ray of her chest revealed a hyperdensity in the apical portion of the right lung (Fig. 1). The differential diagnosis included substernal goitre, lymphoma, aneurysm and carcinoma. On further evaluation, computerised tomography scan and 3D reconstruction (maximum intensity projection display) of a computerised tomography angiogram of the neck showed a left-sided aortic arch with a 5.1-cm aberrant right subclavian artery aneurysm (Figs 2, 3). She refused surgical intervention for the aneurysm. One week following her initial presentation, she developed substernal chest pain and hypotension. An echocardiogram revealed new-onset,
severe aortic insufficiency. Laboratory tests demonstrated a decrease in haemoglobin from 94 to 76 g/L and an increase in creatine kinase from 42 to 958 U/L. She died 3 h later.

Commonly an incidental finding on chest X-ray, dysphagia is the most common symptom of aberrant right subclavian artery aneurysm; other complaints include chest pain, coughing and right arm discomfort. Acute dissection and rupture of the aneurysm may mimic an acute myocardial infarction, and thus should be considered in the differential diagnosis of acute onset chest pain. Clinical suspicion combined with prompt angiography and surgical intervention can be life-saving.

References


Black urine

A 91-year-old woman with a 7-year history of Parkinsonism and hypertension was treated with daily doses of levodopa 1200 mg and amlodipine 5 mg. She had undergone cystostomy due to recurrent urinary tract infection (UTI) 6 months previously, and had an indwelling catheter. She presented with fever and black-coloured urine in the drainage bag (Fig. 1). The urinalysis revealed alkaline urine (pH 7.8) without occult blood, protein, bilirubin or urobilinogen. Sediment analysis showed 10–20 white blood cells and no red blood cells per high power field. Urine culture yielded *Proteus mirabilis*. Intravenous cefazidime was given and the black urine resolved within 2 days.

*Proteus* species collectively cause 5% of cases of hospital-acquired UTI and are responsible for 20–45% of cases of complicated UTI associated with long-term catheterization. The high prevalence is partly due to production of urease, which hydrolyses urea into ammonia and results in alkaline urine.
in alkalinization of urine. Alkaline urine from patients receiving levodopa may turn black. Levodopa is a precursor of the biological pigment melanin. The enzyme tyrosinase catalyses the oxidation of levodopa to the reactive intermediate dopaquinone, which reacts further, eventually leading to melanin formation, especially in alkaline urine. Melanin formation in acidic urine is slow.\textsuperscript{1,2}

Black urine without myoglobin or bilirubin might be caused by ingestion of large amounts of rhubarb or fava beans. Some medications associated with black urine are methyldopa, chloroquine and primaquine, furazolidone, metronidazole and sorbitol. In addition, diseases, such as alkaptonuria, disorders of tyrosine metabolism and disseminated melanoma, might be associated with black urine.\textsuperscript{3}

Received 11 February 2010; accepted 2 March 2010.
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References

LETTERS TO THE EDITOR

Clinical-scientific note

Paradoxical ischaemic stroke in the setting of idiopathic thrombocytopenic purpura

Ischaemic stroke occurs rarely in the setting of idiopathic thrombocytopenic purpura (ITP),\textsuperscript{1} we report on a patient and a review of the literature.

A 64-year-old man, with dyslipidaemia, type II diabetes, hypertension and an ex-smoker, presented with acute coronary syndrome. Coronary artery computer tomography diagnosed significant stenosis of the proximal left anterior descending coronary artery. He was noted to have moderately severe thrombocytopenia on admission (Fig. 1). ITP was diagnosed following negative bone marrow aspirate, viral serology, serum protein electrophoresis and an autoimmune screen. As a result the patient was taken off all antiplatelet agents, because of the potential risk of haemorrhage. The platelets continued to decrease and reached $17 \times 10^9$/L 5 days later. He was treated with intravenous immunoglobulin (IVIG) and two units of pooled platelets.

Five days into the admission, prior to platelet transfusion and IVIG, there was new onset of global aphasia and right hemiparesis. Computed tomography (CT) of his brain was initially reported to show left intracerebral haemorrhage (Fig. 2). The diagnosis was revised to

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Platelet progression during treatment and significant events. ACS, acute coronary syndrome; IVIG, intravenous immunoglobulin. \(\bullet\) Platelet count.}
\end{figure}
haemorrhagic infarction after 1-carotid Doppler ultrasound and magnetic resonance angiography that demonstrated complete occlusion of the left internal carotid artery, and 2-Diffusion-weighted magnetic resonance imaging (MRI) of the brain illustrated embolic infarction in addition to haemorrhagic transformation in the distribution of the left middle cerebral artery territory infarct (Fig. 2). The patient was recommenced on antiplatelet agents with occlusion of the left carotid artery as the likely stroke mechanism. He did not experience any further infarction or haemorrhage following this event and his platelets returned to normal level.

Paradoxical thrombosis has been described in the setting of ITP\(^2,3\) with two case reports in the literature that specifically describe an association between chronic ITP and ischaemic stroke.\(^4,5\) In both case reports patient developed an acute stroke in the setting of a platelet count between 20 and 22, prior to treatment with IVIG or platelet transfusion. Both patients’ platelet counts stabilized with steroids and neither had further thromboembolic events. It has been postulated that ITP leads to platelet injury and release of platelet microparticles, which could result in a pro-thrombotic environment and consequently acute coronary syndrome and ischaemic stroke in this patient.\(^6\) We cannot discount the possibility that IVIG administration may have led to ‘increased blood viscosity, increased platelet numbers or due to vasospasm’.\(^7\)

In conclusion, there appears to be an association between chronic ITP and thromboembolic events, in particular ischaemic stroke. And the treatment for ITP is also a procoagulant.

Received 16 June 2010; accepted 11 April 2010.

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References
Beyond IV thrombolysis for acute ischaemic stroke

Syfret and colleagues are to be congratulated on their review of intra-arterial thrombolysis (IAT), which outlines the options available for ischaemic stroke therapies at leading stroke centres. Whilst it is acknowledged that these options are restricted to a small number of stroke patients, we believe it is essential that clinicians with access to such treatment continue to ‘push the boundaries’; simply giving intravenous thrombolysis (IVT) and hoping it works, is no longer enough. The review covers the evidence for IAT and thrombectomy, which is still evolving, and ongoing trials such as Interventional Management of Stroke III will provide further useful information. Thus far, much interest in these endovascular techniques has focussed around expanding the time window for therapy beyond that available for IVT, and for patients with contra-indications for IVT. We advocate more focus on a different paradigm, as also suggested in a recent editorial in Stroke; combining the rapidity of IVT with the recanalization (RC) advantages of IAT. A recently reported Spanish case series has shown some promising results in terms of RC, and clinical outcomes, albeit with a non-significant increase in haemorrhage rate. At our institution, we have adopted a ‘combination’ strategy, with an important point of difference; we don’t wait for the 1-h IV infusion to end and see what is happening (whilst 2 million brain cells per minute could be dying if there is no RC); we organize the cerebral angiography immediately as described below.

1 Acute stroke patients presenting <4.5 post-symptom onset are treated with IVT as per standard guidelines.

2 Multi-modal computed tomography (CT), including CT angiography and CT perfusion, is performed; but this does not typically impact on the decision for IVT.

3 Patients with a large proximal middle cerebral artery, internal carotid artery or major basilar occlusion, where an endovascular approach is technically feasible, are considered candidates for thrombectomy.

4 Whilst the IVT is ‘running’, the patient is consented, and then taken to the angiography suite.

5 Following the cerebral angiogram, if no significant RC has occurred, thrombectomy and other adjunctive endovascular techniques are performed.

Clinical, logistic and radiographic data are being prospectively collected. For our eight initial patients the mean time from onset of stroke symptoms to completion of the endovascular procedure is 3.6 h; recall that in PROACT II the average time from onset to initiating treatment was 5.3 h. If the mantra of ‘time is brain’ is true, then we believe we are making progress.

We believe this approach, which treats the stroke patients with the worst prognosis, provides a greater opportunity to demonstrate a benefit than the strategy to recruit more patients later in the time window.

Received 4 April 2011; accepted 28 April 2011.

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References


Evolving neurological terminology in the 21st century: ‘dystextia’ associated with complex migraine

Whilst advances in medical sciences are continuing to be made, the fundamentals of the neurological evaluation have remained largely unchanged. There is, however, modern evolution in neurological presentation and terminology, as illustrated by the following anecdote.

A 20-year-old man presented to the Emergency Department (ED) with a 5-day history of frontal headache, nausea and vomiting characteristic of migraine. He developed a sudden onset of expressive dysphasia and dressing apraxia associated with worsening of his headache. These symptoms lasted for 1 h before resolution. The expressive dysphasia manifested not only verbally, but also with written language – he described an inability to compose and send a text message on his mobile phone. He had no other comorbidities, but had experienced a similar episode of headache with dysphasia 2 years previously. At presentation to the ED, he had no residual neurological abnormalities. His computed tomography and magnetic resonance imaging brain scans and cerebrospinal fluid analysis were normal. The diagnosis of complex migraine was made.

Expressive dysphasia of the written word is well established in medical literature; however, difficulty with writing text messages, or ‘dystextia’, has only been described once. Cawood and others described dystextia in 2006 as the first manifestation of left-sided weakness in a patient with right-sided internal capsule lacunar infarct. Over time, they noted increases in texting speed with improvements in motor function and dexterity. Dystextia has not previously been described with any other neurological condition.

Formulating and sending a text message requires complex motor, visual and language skills and involves coordinated function of several areas of the brain and could be affected by stroke or transient neurological disturbance. Dystextia is therefore not a specific neurological impairment – a difficulty sending a text message could suggest a variety of underlying deficits. Despite this, the presence of dystextia is likely to be a sensitive indicator of abnormal cerebral function. In the 21st century, we rely heavily on fast and accurate modern communication. A patient may quickly become aware of a change in their ability to formulate a text message. As such, dystextia could well become a recognized neurological phenomenon, adding to the richness of neurological evaluation and diagnosis in the modern era.

Reference

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

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