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EDITORIAL

Using computed tomography coronary angiography to evaluate patients with acute chest pain: putting the horse before the cart

In order to justify widespread use and public reimbursement, any new diagnostic test should satisfy the following criteria: (1) it accurately detects the target disease in question (expressed as sensitivity, specificity and likelihood ratios), yields reliable and reproducible results in different patient populations and clinical settings independent of the person or laboratory doing the test, substitutes for tests more invasive or burdensome to patients, and is not overly resource-intense; (2) test results have the potential, in many subjects, to significantly alter the probability of disease, either up or down, compared to pretest estimates based on intuitive judgement or decision rules (expressed as predictive values); (3) changes in disease probability as a consequence of the test are of such magnitude that clinicians will alter their management intentions and (4) these ‘downstream’ changes in management will result in better patient outcomes than would otherwise have been the case after taking into account any harm incurred by performing the test itself or initiating actions on the basis of its results.

When evaluating tests, much attention is given to studying criteria 1 and 2, and deservedly so. Tests that are inaccurate, unreliable, non-reproducible, unacceptable to patients and clearly unaffordable will never make the grade. Unfortunately, the evaluation of test performance, compared to that of stress testing modalities whose sensitivity and specificity respectively stand at 70% and 75% for exercise electrocardiogram (ECG),8 86% and 81% for stress echocardiography,7 and 87% and 73% for stress myocardial perfusion imaging (MPI),9 Uninterpretable images are seen in only 3–5% of patients undergoing CTCA,3 and the test overcomes limitations of stress testing modalities (excepting pharmacological testing) owing to patient inability to exercise to threshold workloads, uninterpretable ECGs or clinical factors associated with higher false-positive rates. Moreover, many EDs have immediate access most of the time to CTCA, but not necessarily to stress testing facilities which incurs delayed outpatient referrals and greater loss to follow up.9

Observational studies confirm that, in patients with low to intermediate CAD risk (i.e. between 5% and 80%), CTCA is superior to stress tests in excluding CAD in between 50% and 70% of patients presenting with acute chest pain, with an average CTCA procedure time (including patient preparation) of 12 min and interpretation time of 10 min.10,11 A systematic review of prognostic studies revealed that a negative CTCA was associated with less than 0.2% risk of major adverse cardiovascular events (MACE) over the following 12 months, whereas a positive CTCA was associated with close to 9% risk of events.12

While these studies suggest CTCA is a very accurate test, most have been conducted in specialized academic centres with expert radiologists. In contrast, studies of diagnostic performance across multiple centres in real-world settings reveal a lower sensitivity (50–93%) which reduces the negative predictive value.13 A significant minority of patients has suboptimal coronary artery

Diagnostic accuracy and predictive value of CTCA

Recent systematic reviews of studies employing 64-slice CTCA in symptomatic patients across a wide spectrum of pretest disease risk4,5 reveal patient-level sensitivity of 98–99% and specificity of 85–88% in diagnosing CAD compared to invasive coronary angiography (ICA) as the reference standard. This diagnostic accuracy is superior to that of stress testing modalities whose sensitivity and specificity respectively stand at 70% and 75% for exercise electrocardiogram (ECG),6 86% and 81% for stress echocardiography,7 and 87% and 73% for stress myocardial perfusion imaging (MPI).9

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While these studies suggest CTCA is a very accurate test, most have been conducted in specialized academic centres with expert radiologists. In contrast, studies of diagnostic performance across multiple centres in real-world settings reveal a lower sensitivity (50–93%) which reduces the negative predictive value.13 A significant minority of patients has suboptimal coronary artery
visualization or coronary calcium that obscures vessels and results in overestimation of the presence and severity of CAD. Specificity as low as 64% and false-positive rates as high as 81% have been reported in selected subpopulations. Moreover, most studies involving symptomatic patients have been conducted in ambulatory referral settings, not EDs, and feature patients already scheduled for ICA who have a high prevalence of CAD (mean 59%; range 15–91%). This spectrum bias may inflate diagnostic accuracy and predictive value, especially in low-risk patients.

Of greater concern is the observation that, despite excellent accuracy in detecting anatomically apparent coronary lesions, CTCA, compared to dynamic stress imaging, is a rather poor predictor of functionally significant lesions which cause significant ischaemia and which in turn predicts the short-term risk of MACE. Quantifying the extent of inducible ischaemia is crucial to determining the need for coronary revascularization. In studies comparing CTCA with MPI, more than half of the lesions causing >50% stenosis on CTCA were not associated with perfusion abnormalities on MPI. In studies comparing CTCA with ICA, only 40–64% of vessels with >50% stenosis on CTCA were associated with abnormal fractional flow reserve on ICA—a marker of physiological impact now advocated as a determinant of the need for revascularization.

**Effects of CTCA on management decisions and patient outcomes**

To date, only four studies have assessed, in some way, the impact of CTCA on management and outcomes of patients presenting with acute chest pain to EDs. The first, a randomized trial, involved 197 patients who received CTCA plus a standard of care (SOC) protocol (serial ECG and enzymes with stress MPI as necessary) or SOC alone and were followed up to 6 months. There were no MACE in either group, but the CTCA strategy reduced diagnostic time compared with SOC (3.4 h vs 15 h, \( P < 0.001 \)) and lowered overall ED-related costs ($1586 vs $1872, \( P < 0.001 \)), due principally to a higher percentage of immediate discharges for negative tests. The second study, also randomized, assigned 268 patients to CTCA or SOC. CTCA use had no effect on the rate of final diagnosis of ACS (29% overall, as determined by independent cardiologists using all available data 1 month after discharge) or on rates of MACE, but was associated with fewer admissions deemed unnecessary in the intermediate risk group and a decreased hospital length of stay, principally among high-risk patients. The third trial involved 58 patients with or without known CAD, intermediate risk and negative enzyme and ECGs and followed up for 12 months after presentation. All patients underwent standard ED triage, including cardiology consultation, after which a preliminary diagnosis of ACS or non-ACS chest pain was made, along with recommendations for discharge home or hospitalization. CTCA was then performed in all patients and results used to adjust triage recommendations at the discretion of the treating physician. CTCA results led to a revised diagnosis (i.e. from ACS to non-ACS pain) in 18 of 41 (44%) patients, cancelled admissions in 21 of 47 (45%), and cancelled ICA in 20 of 32 patients (63%). Conversely, CTCA suggested the need for ICA in 5 of 26 (19%) patients for whom it was initially thought not required. None of the patients discharged after CTCA suffered any MACE during follow up. The fourth study involving 53 low-risk patients compared SOC (serial ECG, enzymes and stress testing) with two CTCA-based early discharge scenarios—CTCA and serial ECGs and enzyme tests to 12 h all negative, or CTCA plus enzyme tests and ECG on presentation all negative. The mean length of stay for the three strategies was 25.4, 14.3 and 5.0 h respectively (\( P < 0.001 \)) with mean charges of $7597, $6153 and $4251.

While these studies suggest promise for CTCA as an accurate and cost-saving approach to evaluating patients with chest pain in EDs, they are far from being definitive, and other concerns persist. CTCA does entail radiation risk (although less so with new generation dual source scanners and ECG-gated protocols) and up to 25% of patients may not be eligible for this technique because of obesity, contrast allergy, intolerance to \( b \)-blockers (required in some patients for heart rate control to allow sufficient temporal resolution for diagnostic quality images), arrhythmia or renal insufficiency. There is also the concern around what to do with extracardiac ‘incidentalomas’ detected in up to 20% of patients undergoing CTCA, many of whom might be subjected to needless investigation for benign lesions.

**The need for more evidence**

The existing research around use of CTCA in evaluating patients with chest pain in EDs demonstrates several limitations. Relatively few studies have assessed diagnostic accuracy of CTCA in such patients, only four have assessed impact on decision-making and patient outcomes, and, as yet, no formal cost-effectiveness study of CTCA in ED settings has been undertaken. Virtually all studies assess performance of first generation (64-slice) scanners rather than second (128-slice) and third (256-slice) generation scanners, which are being increasingly used. No randomized trials have directly compared CTCA with stress imaging in patients with low risk.
to intermediate risk in regards to downstream hard endpoints (such as MACE) following initial ED evaluation. No studies have studied CTC in combination with newly developed high-sensitivity troponin assays which, in contrast to existing assays,25 can detect myocardial necrosis within 3–4 h of symptom onset. These new assays might greatly alter the indications for CTC, especially if such assays increase the numbers of patients with a ‘detectable troponin’ who might then be referred for CTC.

The Cardiac Society of Australia and New Zealand acknowledges these limitations, stating in a recent position statement that ‘. . . while use of CTC in evaluating acute chest pain in the ED has been studied in a number of single-centre trials with encouraging results, multi-centre randomized trials and cost-effectiveness studies are required before recommending routine use.’26 In the USA, the unchecked growth in CTC (up to 26% per year in some estimates) in the absence of comparative efficacy data on alternative diagnostic strategies is causing concern.27 Before mass deployment of CTC as a new test with possible unchartered hazards, the ‘horse’ of rigorous evaluation must be placed before the ‘cart’ of implementing and funding it in routine practice.

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CLINICAL PERSPECTIVES

Practical guidelines for the acute emergency sedation of the severely agitated older patient

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Abstract
The vulnerability of older people to serious underlying medical illness and adverse effects of psychotropics means that the safe and effective treatment of severe agitation can be lifesaving, the primary management goals being to create a safe environment for the patient and others, and to facilitate assessment and treatment. We review the literature on acute sedation and provide practical guidelines for the management of this problem addressing a range of issues, including aetiology, assessment, pharmacological and non-pharmacological strategies, restraint and consent. The assessment of the agitated older patient must include concurrent assessment of the likely aetiology of, the risks posed by, and the risks/benefits of management options for, the agitation. A range of environmental modifications and non-pharmacological strategies might be implemented to maximize the safety of the patient and others. Physical restraints should only be considered after appropriate assessment and trial of alternative management and if the risk of restraint is less than the risk of the behaviour. Limited evidence supports a range of pharmacological options from traditional antipsychotics to atypical antipsychotics and benzodiazepines. It is advised to start low and go slow, using small increments of dose increase. Medical staff are frequently called to sedate agitated older patients in hospital settings, often after hours, with limited access to relevant medical information and history. Safe and effective management necessitates adequate assessment of the aetiology of the agitation, exhausting all non-pharmacological strategies, and resorting to pharmacological and/or physical restraint only when necessary, judiciously and for a short-term period, with frequent review and the obtaining of consent as soon as possible.

Introduction
Managing the acutely and severely agitated older patient is not easy. While delirium is a cause of agitation, there are significant other aetiologies that require consideration. Despite apparent frailty, older patients can still be extremely dangerous when aroused, posing significant risk to themselves and others, yet at the same time they can be extremely vulnerable to the adverse effects of sedation. Thus, the safe and effective treatment of an agitated older patient in the emergency department, general ward and occasionally, community setting, is critical. The two primary goals of management are to create a safe environment for the patient and others, and facilitate the assessment and treatment of the patient. Patients might be dehydrated, septic or in a metabolically altered state, and might have serious occult medical illnesses. Thus, rapid calming without excessive sedation can be lifesaving and facilitate medical and psychiatric evaluation and work-up. However, all agents currently used for the acute treatment of agitation have the potential for clinically important adverse events, including increased (‘paradoxical’) agitation. The challenge is to identify the cause of the agitation and to target management to the special needs of the older person. The following paper will provide practical guidelines for the management of this problem addressing a range of issues, including aetiology, assessment, pharmacological and non-pharmacological strategies, restraint and consent.
Common pitfalls: why is it important to get this right?

Common pitfalls in this situation include:
1. Treating the symptoms or behaviour and ignoring the underlying cause. Many of the underlying causes of severe agitation, such as delirium (see Aetiology), are associated with significant morbidity and mortality, particularly if left untreated. For example, delirium is associated with a two- to threefold increased risk of death.\(^2\)
2. Automatic and unreviewed charting of as needed or ‘prn’ antipsychotic regimens for agitated patients. This can be problematic because in such circumstances control of the dosage is often left to staff who may be unfamiliar with the patient.
3. Over-sedation leading to serious adverse effects, such as dehydration, falls, respiratory depression, pneumonia and death.

Aetiology: what causes agitation in the older patient?

Management of the agitated older patient must commence with consideration of the likely aetiology (Fig. 1). Acute agitation is encountered in the context of a range of situations and disorders, most commonly in association with delirium and/or dementia. While the setting will influence the likelihood of particular aetiologies (e.g. mental health or palliative care wards), the presence of delirium must be considered in any patient who develops an acute agitated state and the diagnosis should be presumed until proven otherwise. Delirium may occur in the context of normal premorbid cognitive function, or complicate a dementia. Delirium has a range of common causes, including: (i) metabolic (e.g. dehydration, hypoxia, electrolyte abnormalities); (ii) infective; (iii) structural (e.g. stroke, pulmonary embolus, constipation); (iv) toxic (therapeutic and illicit drug use and withdrawal) and (v) environmental.\(^3\)

Patients with dementia may develop acute agitation due to frank delirium, but additionally, agitation in dementia may communicate a range of possible physical or emotional discomforts, commonly fear, pain, disorientation, constipation, overstimulation or other unmet needs.\(^4\)

Other important aetiologies to consider include alcohol or benzodiazepine intoxication or withdrawal, agitated depression, primary psychotic illness, brain injury and an acute response to stressful events.

Assessment

The assessment of the agitated older patient must include concurrent assessment of:

- The likely aetiology of the agitation
- The risks posed by the agitation
- The risks and benefits of agitation management options for the individual patient

In distinguishing the aetiology of the agitation, it is important that a thorough history (particularly a collateral history) is taken, particularly to distinguish between delirium and dementia, where the duration of the symptoms is crucial to the diagnosis. Ascertain the presence of symptoms suggestive of dementia with Lewy bodies will necessitate particular caution in choice of pharmacological agents (see Fig. 1) and finally, past history of primary psychiatric illness will also influence management.

Medical evaluation and stabilization with full physical examination and organic screen (including, but not limited to full blood count and profile including electrolytes, blood sugar levels, C-reactive protein and urine examination) should occur in parallel with psychiatric assessment and management (Fig. 1). Pain assessment charts based on patient observation, rather than self-report, may aid detection of pain in non-verbal patients. A mental status evaluation documenting levels of consciousness and attention, extent of cognitive dysfunction and signs of psychosis is crucial in the diagnosis of delirium. The content of any delusions will impact upon the risk assessment, such that very frightened, paranoid patients may pose a particular risk to staff. It is important to note that while organic work-up for delirium is an essential part of the management plan, there is rarely time to carry this out in the setting of a behavioural emergency. Initial management may have to commence prior to completion of assessment, and must be associated with repeated reassessment. While it is essential that no presumptions are made regarding the implications of past presentations upon a current presentation, it is also essential to consider their relevance to assessment, risk assessment and management strategies. For example, if it is known that a particular patient has a past history of schizophrenia with severe psychotic relapses associated with aggressive behaviour, responding to particular doses of antipsychotic medications, then this might guide treatment choices. Conversely, such patients may still present with delirium, so that past history should not prejudice clinical management and lead to premature diagnostic closure.

Management

Prevention of delirium

The incidence of delirium can be decreased in hospital patients by multicomponent interventions which target...
Working diagnosis Delirium - suggested by acute onset (i.e. days or weeks), altered sensorium (attention & consciousness) & fluctuation

NB. May have dementia + delirium suggested by history of dementia + ↑ behavioural disturbance with onset over days/weeks rather than months

Working diagnosis Primary psychosis - suggested by history of primary psychosis such as bipolar disorder, schizophrenia or long history of delusions (usually systematised) or hallucinations; IN THE ABSENCE OF ALTERED SENSORIUM

ASSESS & MANAGE
Risk
Acute medical compromise
Harm to self or other

Delirium: consider sepsis, electrolyte disturbance/dehydration, stroke, environmental change, pain, pulmonary embolus, constipation, drug toxicity/withdrawal

BPSD: Unmet needs (pain, loneliness, constipation); stress threshold with over/understimulation, antecedents or triggers to behaviour using history or ‘ABC’ chart

Consider: using pain assessment chart

Obtain Relevant History, esp past agitation and response to interventions, key personal likes/dislikes

Non-pharmacological approach
Meet needs, remove triggers
Environmental modification
Keep safe/non-access to danger observe involve family falls prevention 1:1 nursing

If fails, or not feasible

Low-dose Pharmacotherapy (ORAL unless not possible: see Table 1 for doses)
Consider impact comorbid conditions, past response, current medications
In delirium avoid anticholinergic meds (e.g. olanzapine); consider haloperidol; risperidone ± benzodiazepines (e.g. lorazepam)
In DLB avoid antipsychotics except quetiapine, consider benzodiazepines
In primary psychosis use atypical antipsychotics ± benzodiazepines
In alcohol or benzodiazepine withdrawal use benzodiazepines (and thiamine)

Regular Review for positive or adverse effects
Obtain informed consent for restraint use and pharmacotherapy
Commence selected practices to reduce further agitation

Figure 1 Individualized decision-making tree for severe agitation in older patients. BPSD, behavioural and psychological symptoms of dementia.
immobility, dehydration, sleep deprivation and sensory impairments. Orthogeriatric services commencing prior to surgery have been shown to reduce delirium in older patients with hip fracture by addressing psychoactive drug use, fluid and electrolyte imbalance, immobility, hypoxia, pain and bowel and bladder function.

Consent issues

The principle or doctrine of necessity upholds the actions of doctors who are unable to get instructions from patients who are likely to be incapable only for a short period because, for example, they were unconscious or delirious and, with care and treatment, would soon regain capacity. In such circumstances, doctors can treat such patients by doing no more than is reasonably required. It is then incumbent upon the doctor who is continuing to treat the patient to obtain consent from the patient, or if they are incapable, from the patient’s proxy, as soon as is practical. In regards to patients unable to give consent, obtaining valid consent from either a person responsible, guardian or tribunal (depending on the state or jurisdiction and whether the patient is objecting or not) is particularly important for agents acting on the central nervous system and substances used to ‘control behaviour’.

Non-pharmacological strategies

Environmental modifications

A range of environmental modifications may be implemented to maximize the safety of patient and others, including: (i) involvement of family members in care or supervision of the patient (familiar faces can be reassuring to those who are very frightened or agitated); (ii) movement to a position of best observation, or placement in a purpose-built secure unit; (iii) preventing access to means of self-harm, such as open windows, balconies, internal stairwells, hand hoists over beds, cords and coat hangers; (iv) falls injury prevention strategies; (v) distraction devices or inaccessible placement (e.g. between scapulae) of cannulae to prevent removal of catheters or cannulae and (vi) consideration of one to one nursing. Such strategies can be useful regardless of the aetiology of the agitation (see references for reviews of delirium management). In particular, use of specialized units, or ‘delirium rooms’, for patients with acute agitation associated with hyperactive delirium, with access to both geriatric and psychiatric input and specialized, trained nursing staff, may be associated with lower physical and chemical restraint and improved function.

Physical restraint

Physical restraint is the intentional restriction of a person’s voluntary movement or behaviour by the use of a device and includes use of limb, wrist and vest restraints, mittens, bedrails, tray chairs and bucket chairs. Restraints may be used in the management of severe agitation, but care needs to be taken as their use can actually result in an increase in agitation and aggression, as well as abrasions, pressure areas and compressive neuropathies. Their use should only be considered after appropriate assessment and trial of alternative management methods and if the risk of restraint use is less than the risk of the behaviour. They should never be used as a replacement for nursing care or patient supervision, and consent must always be sought for their use.

Pharmacological strategies: what is the evidence?

Traditional antipsychotics

Acute sedation with traditional high-potency neuroleptics (e.g. haloperidol) can have significant side-effects, particularly dystonia and extrapyramidal symptoms. However, they have the potential benefit of reducing arousal with less sedation and have less impact on blood pressure and muscarinic receptors than some of the lower potency antipsychotics (e.g. chlorpromazine), which should not be used in older persons.

A recent Cochrane review of antipsychotic use in delirium found equal efficacy of low-dose haloperidol to the atypical antipsychotics olanzapine and risperidone and no greater frequency of adverse drug effects. The efficacy and safety of haloperidol in treating agitation in dementia have also been evaluated in a Cochrane Systematic Review of five randomized placebo-controlled trials that showed that demented subjects receiving haloperidol showed no significant improvement in overall agitation scores but an improvement in aggression compared with controls.

One of the major issues with regards to the use of traditional antipsychotics in acutely agitated patients with dementia is the neuroleptic hypersensitivity associated with dementia with Lewy bodies. Extreme caution is thus advised with using traditional antipsychotics to acutely sedate any patient with a history of dementia, parkinsonism, visual hallucinations and fluctuating consciousness.

Atypical antipsychotics

There are some limited data to support the use of olanzapine in the management of acute agitation in older
people. In a meta-analysis of three studies, Battaglia et al.\(^1\) found that acute agitation in patients with dementia (\(n = 206\)) in an emergency department setting was significantly reduced by intramuscular (IM) olanzapine (2.5 mg) (1–3 injections/24 h) when compared with placebo with no more sedation than lorazepam (1.0 mg). Similarly, in a double-blind randomized trial comparing the efficacy and safety of rapid-acting IM olanzapine (dosages of 2.5 and 5.0 mg) with lorazepam (1.0 mg) or placebo in 272 patients with agitation associated with Alzheimer’s disease and vascular dementia, Meehan et al.\(^20\) found that at 2 h, both olanzapine and lorazepam showed superiority over placebo in terms of reduced agitation. This was maintained at 24 h in the olanzapine, but not the lorazepam group. There were no significant differences in sedation, adverse events, extrapyramidal symptoms, QT interval or vital signs among all groups.

IM olanzapine reaches mean maximum plasma concentration 15–45 min after injection (vs 3–6 h for an equivalent oral dose) while maintaining a similar pharmacokinetic profile to oral olanzapine (half-life, clearance and volume of distribution) such that dose adjustments are not necessary when equating the two modes of administration. Hypotension and bradycardia have been observed during IM administration of olanzapine.\(^21\)

Risperidone has been studied for the longer-term management of agitation in the elderly, specifically for the management of psychosis and behavioural disturbances in patients with dementia;\(^22,23\) and to control agitation in delirium, where it has been found to have equal efficacy to haloperidol.\(^24\) However, the use of risperidone to control acute agitation immediately has not been studied. The only currently available parenteral formulation is an extended-acting slow release formulation that is dosed every 2 weeks and therefore not suitable for use in acute agitation. However, there is an available rapidly dissolving oral tablet (‘quicklet’), which may have practical advantages in this context.

Ziprasidone, another atypical antipsychotic available in rapid-acting IM formulation, might have a role in treating acutely agitated older patients. A retrospective study of the safety of IM ziprasidone in agitated elderly patients admitted to a neuropsychiatric service found no significant differences in QTC intervals of treated patients;\(^7\) and a study of older patients admitted to a psychiatric emergency service found equal efficacy to haloperidol and no adverse effects on electrocardiogram, heart rate or blood pressure, nor adverse cardiac events.\(^25\) A case series of five patients with Parkinson’s disease demonstrated no deterioration of motor function or other relevant side-effects in patients treated with IM ziprasidone for acute agitation.\(^26\)

Although there is no evidence supporting or refuting the use of quetiapine in the acute emergency sedation of older patients, patients with delirium treated with quetiapine improved more rapidly than a placebo group on a delirium severity scale.\(^27\)

**Benzodiazepines**

Equally efficacious to neuroleptics in producing sedation, benzodiazepines (e.g. lorazepam) are not associated with extrapyramidal symptoms and can be better tolerated in the rapid treatment of agitation. However, respiratory depression, excessive sedation (greater than seen with high-potency neuroleptics), and, rarely paradoxical disinhibition and increased agitation, can pose significant problems, particularly with agents such as midazolam and diazepam. There is a preference for benzodiazepines with shorter half-lives given the risk of accumulation and over-sedation, particularly in older people.

Combination treatment, such as haloperidol with lorazepam, appears superior in efficacy to either agent alone; however, sedative effects are at least as great as with benzodiazepines used as a single agent.\(^28,29\) In particular, combinations of olanzapine with parenteral benzodiazepine have not been studied, and it is recommended that parenteral benzodiazepine not be given until at least 2 h after olanzapine administration due to risk of respiratory depression.\(^30\) Parenteral benzodiazepines available in Australia include lorazepam,\(^30\) midazolam (used often to treat acute agitation in adult patients presenting to Australian emergency departments)\(^31\) and clonazepam, although, with the exception of lorazepam,\(^20\) there is no randomized controlled trial evidence for their use in older patients. IM diazepam is not recommended for use for acute sedation. Intravenous sedation is also best avoided in older patients with agitation.

**General principles for pharmacological treatment**

As with all antipsychotic use, start low and go slow, using small increments of dose increase (Table 1). Following oral or parenteral sedation, it is essential that appropriate advice is given to staff regarding appropriate levels of supervision, observation and frequency of review. This should be based on both the medication used and individual clinical situation, but should include consideration of the risks of falls, increased confusion, over-sedation and increased confusion. It should also aim to initiate strategies to reduce the risk of further episodes of agitation.
Use of ‘prn’ (or as needed) medications should be used with caution. They should not be prescribed routinely, but can be helpful when titrating medication dosages to meet clinical needs, thus intended as a short-term solution. They should be prescribed at a specific dose (rather than range of doses) and preferably by the usual treating team, for a specific indication or symptom and reviewed daily. It has been found that a significant reduction in the percentage of patients receiving psychotropic prn medications (53.4% to 23.1%) in an acute care geriatric psychiatry setting was achieved following the introduction of a multidisciplinary educational approach involving documentation of the indications for using prn medication and the steps that were taken before the prn medications were utilized (A. Burhan, unpubl. data).

Table 1 Medication options for acute sedation of older patients in general hospital wards

<table>
<thead>
<tr>
<th>Route</th>
<th>Drug class</th>
<th>Medications</th>
<th>Initial dose (mg)</th>
<th>Maximum dose in 24 h</th>
<th>Caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Benzodiazepine</td>
<td>Lorazepam (can be swallowed or used sublingually)</td>
<td>0.5–1.25</td>
<td>5 mg</td>
<td>Respiratory depression, confusion, ataxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diazepam for alcohol or benzodiazepine withdrawal</td>
<td>2–5</td>
<td>Three times daily as per Alcohol Withdrawal Scale</td>
<td>Respiratory depression, confusion, ataxia</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic</td>
<td>Olanzapine wafer</td>
<td>2.5–5</td>
<td>10 mg</td>
<td>Confusion, hypotension, bradycardia, ataxia</td>
</tr>
<tr>
<td>IMI</td>
<td>Antipsychotic</td>
<td>Risperidone quicklet</td>
<td>0.5–1</td>
<td>2 mg</td>
<td>Hypotension sedation, ataxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine</td>
<td>2.5</td>
<td>2.5 mg increments to max dose of 7.5 mg, at no closer than 30 min intervals</td>
<td>Confusion, hypotension, bradycardia, ataxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haloperidol</td>
<td>0.25–0.5</td>
<td>2 mg daily</td>
<td>Dystonia, extrapyramidal signs</td>
</tr>
</tbody>
</table>

Adapted from Mental Health and Drug and Alcohol Office. Individual clinical scenarios may require use of doses outside these ranges, or alternative medications, but this should only be with the supervision of a senior clinician with appropriate experience. If parkinsonism or suspicion of Lewy Body Dementia avoid antipsychotics initially and DO NOT use haloperidol. All antipsychotics, including both first-generation typical and second-generation atypical antipsychotics, have been associated with increased mortality. Pharmaceutical Benefits Scheme-approved indications of antipsychotic use are for schizophrenia and bipolar disorder; with the exception of risperidone which has PBS approval for use in dementia. IMI, intramuscular injection.

**Conclusion**

Medical staff are frequently called to sedate agitated older patients in hospital settings, often after hours, sometimes with limited access to relevant medical information and history. The vulnerability of older people to serious underlying medical illness and adverse effects of psychotropics means that safe and effective management necessitates adequate assessment and clarification of the aetiology of the agitation, exhausting all non-pharmacological strategies, resorting to pharmacological and/or physical restraint only when necessary, and doing so judiciously and for a short-term period, with frequent review and the obtaining of consent as soon as possible.

**References**

21 MIMS Full Prescribing information. [Olanzapine]. St Leonards: UBM Medica Australia Pty Ltd.
Low prevalence of significant carotid artery disease on ultrasound in patients proceeding to coronary artery bypass surgery

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Key words
carotid artery, screening, ultrasonography.

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Abstract
Background: Cardiothoracic surgery is associated with an increased risk of perioperative stroke. Preoperative carotid ultrasonography can identify significant stenosis, but there is debate about the value of screening. The aims of this study were to (i) determine the prevalence of significant carotid artery disease in screened patients undergoing cardiothoracic surgery and (ii) correlate their ultrasonographic findings with perioperative strokes.

Methods: Retrospective analysis of 166 patients (118 men, 48 women) who underwent a preoperative carotid ultrasound and coronary artery bypass graft surgery (CABG) from 2004 to 2007. Perioperative strokes were recorded and compared with ultrasonographic and clinical data. A separate cohort of 1423 patients (1064 men, 359 women) who underwent CABG over the same period was also evaluated.

Results: Only 11 screened patients (6.6%) had significant (>70%) carotid artery disease and two of these underwent simultaneous carotid endarterectomy. There were five perioperative strokes in screened patients, four of which occurred in individuals with <50% disease. Compared with the non-screened cohort, ultrasound screened patients were older and more likely to have a prior stroke or transient ischaemic attack, hypertension, hypercholesterolaemia, peripheral vascular disease and/or renal impairment than non-screened patients. There was no significant difference in perioperative strokes compared with non-screened patients (3% vs 1.2% respectively, P = NS).

Conclusion: There is a low prevalence of significant carotid artery disease in ultrasound screened patients. The risk of perioperative strokes in screened patients is low and not significantly different from non-screened patients.

Introduction
Coronary artery bypass graft surgery (CABG) is widely used and, in Australia, increasingly in patients who are older and sicker.1 Although the risk of stroke after general or non-vascular surgery is low, cardiac surgery has a higher risk, especially in patients >75 years of age.2,1 Recent Victorian data suggest that the risk of a perioperative stroke is 1–2%,1 but it could be as high as 9–15% depending on age, prior history of stroke and complexity of the cardiac surgery.2 Thus, there has been considerable interest in the evaluation of patients' risk of perioperative strokes before CABG.3–10 Selim has indicated that the risk of perioperative stroke increases with the grade of carotid stenosis, but has also acknowledged that the majority of strokes are related to atrial fibrillation, myocardial infarction and other factors.1 Although there are defined clinical factors predicting perioperative stroke,3,8 there is debate about the role of routine screening carotid ultrasonography, either because the prevalence of carotid artery disease is low9 or because the specificity of this approach is poor and therefore difficult to justify.6,7 As a consequence, some, but not all, clinicians at our...
institution refer patients for a carotid ultrasound before CABG. Accordingly, the aims of our study are to assess the: (i) prevalence of significant carotid artery disease in patients undergoing carotid ultrasonography before CABG and (ii) spectrum of ultrasonographic findings in screened patients who have perioperative strokes.

Methods

This is a retrospective review of prospectively acquired data, approved by the institutional ethics committee. Over a 3.5-year period from January 2004, 166 patients underwent a carotid ultrasound before CABG with or without valve surgery or repair; there were 118 men and 48 women, with mean age of 69 years (range 49–86 years). In order to assess for potential referral bias, we also reviewed data in 1423 patients (1064 men, 359 women; mean age = 64 years, range = 23–89 years), who underwent cardiothoracic surgery at our institution over the same time without a carotid ultrasound.

Prospectively collected data entered into a surgical database were used and medical records were evaluated by one of two authors (S. A. or J. Y. T.); patients’ age, gender, medical comorbidities and any perioperative strokes were recorded in a standard excel worksheet. Data were recorded according to medical history, results of physical examination, ECG and standard biochemical investigations and specifically included: a history of prior transient ischaemic attack (TIA) or stroke, diabetes, hypertension, hypercholesterolaemia, previous or current smoking, atrial fibrillation and peripheral vascular disease. Data were recorded in a binomial (either present or absent) or categorical fashion (for diabetes: 0 = absent, 1 = diet controlled, 2 = requires oral hypoglycaemic agents, 3 = requires insulin; for renal impairment: 0 = creatinine <120 μmol/L, 1 = 120–200 μmol/L, 2 = 200–300 μmol/L, 3 = 300–500 μmol/L, 4 = >500 μmol/L; for adverse neurovascular events: 0 = none, 1 = confirmed stroke, 2 = reversible neurological defect resolving within 72 h, 3 = reversible neurological defect resolving within 24 h). For data entry, we distinguished perioperative strokes and reversible neurological deficits according to classic time-based criteria,13 but for subsequent discussion refer to all of these as strokes.

Ultrasounds were acquired a mean of 21 days (range 1–187 days) before CABG (n = 154) alone or with valve repair (n = 12). At our institution, carotid ultrasound is carried out by qualified sonographers using modern duplex ultrasound equipment (Philips iU-22 with 7–4 MHz and 12–5 MHz transducers; Philips Ultrasound, Bothell, WA, USA). Studies are reported in conjunction with experienced sonologists who review real-time and soft-copy data and determine carotid artery status according to recently published criteria.12

Statistical analysis was undertaken using Fisher’s exact, Pearson Chi-squared and two-tailed t-tests and multivariate analysis. Statistical significance was set at a P-value of <0.05.

Results

The clinical characteristics of screened patients are listed in Table 1; for comparison, non-screened patients are also included. Screened patients were older and more likely to have had a prior stroke or TIA, hypercholesterolaemia, peripheral vascular disease and abnormal renal function than non-screened patients. There were no statistically significant differences between screened and non-screened patients in proportion or type of diabetes, in other clinical parameters or type of surgical procedure. In addition, there was no significant difference in the proportion of perioperative strokes between the two groups: five in screened patients, comprising one completed stroke and four transient reversible neurological events, which resolved after 24 h (n = 3) and 72 h (n = 1); and 17 in non-screened patients, comprising five completed strokes and 12 transient reversible neurological events, which resolved after 24 h (n = 8) and 72 h (n = 4). Only one of these 17 patients underwent a postoperative carotid ultrasound and this revealed an occluded left internal carotid artery and <50% disease on the right.

The spectrum of carotid ultrasonographic results in screened patients is listed in Table 2. There were 26 and 25 normal common and internal carotid arteries (15%...
and 16% respectively); most patients had <50% disease (109 right and 113 left; 66% and 68% respectively). Significant stenosis (>70%) or occlusions were present in 11 patients (6.6%), comprising five right and eight left common and internal carotid arteries (3% and 4.8% respectively). Of these, two patients (1.2% of the screened cohort) underwent simultaneous carotid endarterectomy (neither of these had a perioperative stroke). Irrespective of whether these two subjects were included or excluded from subsequent analysis, Fisher’s exact test shows no significant difference in the proportion of perioperative strokes (\(P = 0.068\)) between the two groups.

The relation between perioperative strokes and carotid ultrasound findings is shown in Table 3. As stated above, there were five perioperative strokes and three reversible neurological deficits occurred in patients with <50% disease on ultrasound; and one reversible neurological deficit occurred in a patient with 50–69% disease.

### Discussion

The major findings of our report are: (i) in ultrasound screened patients, the prevalence of significant (>70%) carotid artery disease is very low, (ii) the incidence of perioperative strokes is also low in screened patients (<3%) and there is no significant difference between those who are screened and those who are not and (iii) perioperative strokes can occur in patients with non-significant disease on carotid ultrasound, suggesting a role for other factors.

In our screened patients, 15–16% of carotid arteries were classified as entirely normal; furthermore, most patients (97% for the right and 95.2% for the left) had either normal arteries or <70% disease. Although the number of screened patients in our series is relatively small, our findings are similar to prior reports regarding larger patient cohorts from Iran, Turkey and the USA. A recent report showed that screening carotid ultrasonography is not of benefit to most patients and that <1% of screened patients had a stroke, which was thought to be related to their carotid disease.

 Accordingly, many investigators have attempted to refine their imaging approach by selecting patients according to risk factors. Our data show that this approach is occurring at least in a subliminal fashion in our institution, because screened patients were likely to be older and to have more renal impairment, peripheral vascular disease, hypercholesterolaemia and/or history of prior stroke or TIA. Despite this, however, the risk of a perioperative stroke did not differ significantly between screened and non-screened patients (3% and 1.2% respectively). Ascher and colleagues also failed to show any correlation between the risk of perioperative strokes and carotid ultrasonographic findings, although they did report an association between significant carotid artery disease, age, smoking and hypertension. To enhance the yield of preoperative carotid ultrasonography, Sheiman and d’Othee recently indicated that there should be at least two risk factors present. Gerraty and colleagues reported that symptomatic carotid artery disease is an important risk factor and should be one of the parameters used to select who receives a carotid ultrasound.

There are several potential limitations of our study: first, the number of perioperative strokes was small, thereby limiting the power of multivariate logistic regression analysis. We estimate that at least 50–100 adverse events are required to accurately assess what factors are associated with a perioperative stroke; however, it is uncertain whether this would have changed our findings. Second, the study is retrospective in nature and it is probable that the referring clinicians were not blinded to the results of the carotid ultrasound; indeed, two patients in the screened group underwent simultaneous carotid endarterectomy, but allowing for these two patients, there was still no significant difference in the proportion of perioperative strokes. Of interest, none of the 11 patients with significant carotid artery disease on ultrasound did not proceed to carotid endarterectomy, thus suggesting that the effect of post-test management bias was small. Third, the patients who underwent screening may not have been representative of most patients undergoing CABG; this seems likely, with screened

<table>
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<th>Carotid ultrasound results in screened patients</th>
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<tr>
<td><strong>Right</strong> (n = 166)</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>26</td>
</tr>
<tr>
<td>&lt;50%</td>
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<tr>
<td>109</td>
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<td>50–69%</td>
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<td>26</td>
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<tr>
<td>70–99%</td>
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<tr>
<td>3</td>
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<tr>
<td>Near-occlusion</td>
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<tr>
<td>0</td>
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<tr>
<td>Occluded</td>
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<td>2</td>
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<td><strong>Left</strong> (n = 166)</td>
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<td>20</td>
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<tr>
<td>70–99%</td>
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<tr>
<td>6</td>
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<tr>
<td>Near-occlusion</td>
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<td>Occluded</td>
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### Table 3

<table>
<thead>
<tr>
<th>Carotid ultrasound findings in patients with perioperative strokes</th>
</tr>
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<tbody>
<tr>
<td><strong>Right</strong></td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>TIA</td>
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<tr>
<td>TIA</td>
</tr>
<tr>
<td>TIA</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Reversible deficit &lt;72 h</td>
</tr>
</tbody>
</table>

TIA, transient ischaemic attack
patients being older and having a variety of other potential risk factors. Again, the lack of difference in outcome between the two groups suggests that the effect of this is small. Fourth, the retrospective nature of the research means that there was no clearly defined institutional policy for imaging of possible carotid artery disease; this could mean that our results may not readily apply elsewhere. However, our conclusions regarding the low prevalence of carotid artery disease in screened patients and the contribution of other factors to perioperative strokes agree with other publications. Finally, we could not assess the impact of carotid bruits on our findings, because their presence was difficult to determine on review of at least some medical records.

**Conclusion**

We have shown that screening carotid ultrasound usually reveals non-significant disease in patients proceeding to CABG. The risk of perioperative strokes appears low and might be related to factors other than ultrasonographically demonstrable carotid artery disease.

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**References**


Continuity of care: when do patients visit community healthcare providers after leaving hospital?

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Key words
continuity of patient care, patient discharge, discharge planning, physicians, family, community pharmacy.

Abstract

Background/Aims: Enhanced communication and transfer of information between healthcare providers and healthcare settings can reduce medication and healthcare errors post-hospital discharge. The timeframes within which patients access community healthcare providers post-hospital discharge are not well studied. This study aimed to determine length of time from hospital discharge until a general practice, pharmacy or specialist visit, or care planning service.

Methods: We conducted a retrospective analysis of Department of Veterans’ Affairs health claims data. All 109 860 veterans hospitalized in 2006 were included. Main outcome measures were time from first hospital discharge to first claim for a general practice, pharmacy, specialist visit and/or care planning service.

Results: Within 30 days of hospital discharge 71% of subjects visited a general practitioner (GP), 86% had medicines dispensed from a community pharmacy and 44% saw a specialist. Median time to first pharmacy visit was 6 days (interquartile range 2–14) and 12 days for a GP visit (interquartile range 4–31). Less than 2% of the cohort received a discharge plan, case conference or medication review in the month after discharge.

Conclusions: With 25% of patients having a claim for a GP service within 4 days of discharge, discharge summaries need to reach community-based health professionals within this time. Most patients visited their community pharmacy within 2 weeks of hospital discharge and before they saw their GP. Pharmacists are not routinely advised of hospitalization or provided with discharge summaries. More active engagement of this professional group in the continuum of care might improve care after hospital discharge.

Introduction

As patients move between healthcare settings and providers, for example between hospital and the community, there is potential for poor quality use of medicines and adverse events to occur.¹-³ Enhanced communication and transfer of information between healthcare providers, consumers and different healthcare settings can reduce the potential for medication and healthcare errors to occur post-hospital discharge.³ Several strategies have been introduced by the Australian government in an effort to improve continuity of care. These include the development of guiding principles to achieve continuity in medication management⁴ and the introduction of the Enhanced Primary Care package.⁵

The Australian Pharmaceutical Advisory Council (APAC) guiding principles to achieve continuity in medication management outline the steps and activities required to achieve continuity in care when patients move between healthcare settings and providers.³ A clear message of the guiding principles is that effective and timely transfer of information between episodes of care is essential to achieve continuity in medication management.³ Implementation of the APAC guiding principles is a key requirement of access to Pharmaceutical Benefits Scheme (PBS) medicines for patients discharged from public hospitals,⁷ which is currently implemented in participating public hospitals in five Australian states. Prior
to PBS access in public hospitals, patients received up to a week’s supply of medicine at discharge and had to visit community healthcare providers for further supply. It was envisaged that access to the PBS at hospital discharge could improve continuity of care and would be more convenient for patients, removing the need to see community healthcare providers soon after discharge for further medicine supply. It is unclear whether supply of medicine in PBS quantities (generally one month’s supply) at the time of hospital discharge has increased the time within which patients present to community healthcare providers post-hospital discharge.

The Enhanced Primary Care package was introduced by the Australian government in 1999 to improve the prevention and management of chronic conditions and to assist coordinating the care of patients discharged from hospital. The Enhanced Primary Care package provides funding through Medicare for general practitioner (GP) health assessments of patients with chronic conditions, development of healthcare plans for patients with multiple healthcare providers and case conferences between GPs and two or more other healthcare providers. Multidisciplinary case conferences have been found to be useful in communicating medication changes during hospital admission to community care providers and the reasons behind them, and might lead to better patient satisfaction with the discharge process and better patient understanding of their post-discharge care plan. Case conferences at the time of discharge have also been shown to enhance communication between hospital and community health providers, thereby contributing to improved continuity of care. However, since their introduction uptake of care plans has been low, and no studies have investigated the frequency with which discharge plans are conducted.

In order to be of maximum benefit, and to minimize the potential for medication errors and adverse events to occur, transfer of information between healthcare providers should occur as soon as possible as patients move between healthcare settings and providers. In a small sample of 147 selected elderly patients, GPs reported that 80% visited them within a week of hospital discharge. In another study of 180 patients discharged from a single hospital, the average time reported for GP presentation was 10 days post-discharge. We located no representative studies that provide evidence of the time frame within which patients access GPs or other health professionals post-discharge. This information could help inform the timelines for information transfer and identify the community healthcare providers to whom discharge summaries should be provided. Our study aimed to determine the time from hospital discharge until a general practice, pharmacy or specialist visit, or care planning service.

**Methods**

Data for this study were sourced from the Department of Veterans’ Affairs (DVA) claims databases. The DVA claims databases contain details of all prescription medicines, medical and allied health services and hospitalizations provided to veterans for which DVA pay a subsidy. The data file contains 80 million pharmacy records, 200 million medical and allied health service records and over 6 million hospital records. DVA maintain a client file, which includes data on gender, date of birth and date of death.

Subjects for this study were DVA gold card holders, who are eligible for all DVA-funded health services and who were hospitalized in 2006. We extracted data on the time from first hospital discharge in 2006 to the first service claim for a general practice visit, pharmacy claim, specialist visit, medication review service or care planning service, including healthcare plan, GP plan or medication review service. We also extracted the first claim for service for a discharge plan or case conference after the date of hospital admission.

For those who accessed GP, pharmacy and specialist services in the 12 months post-discharge, the median time in days to first claim post-discharge was obtained from Kaplan–Meier estimates to allow for censoring of subjects. To identify the proportion of veterans who received each health service in the first month post-discharge, failure probabilities and 95% confidence intervals by 30 days were obtained from Kaplan–Meier estimates. Subgroup analysis was undertaken by Australian state, type of hospital (public or private) and major diagnostic group for the hospital admission, based on the WHO International Classification of Diseases (ICD) code. All analyses were undertaken using SAS, V9.1 (SAS institute, Cary, NC, USA).

**Results**

The study population consisted of 109,860 veterans of which 60% were male and 40% female. The mean age was 80.3 years (standard deviation 9 years) and 8% of study subjects lived in an aged-care facility at the time of discharge from hospital. For two-thirds of subjects, their first admission in 2006 was to a private hospital, with the remaining 34% admitted to public hospitals.

Within 30 days of discharge from hospital, 71% of subjects had visited a GP, 86% had prescriptions dispensed from a community pharmacy and 44% had seen a specialist (Table 1). For those who received the service, the median time to a general practice service was 12 days (interquartile range 4–31), 6 days (interquartile range 2–14) for a pharmacy claim and 35 days (interquartile range 11–117) for a specialist service (Table 1).
Subjects whose primary diagnosis for the hospital admission involved infections, circulatory, blood or respiratory systems had the shortest median time to a general practice claim; 9 days or less (Table 1). Subjects with a primary diagnosis for their hospital admission, which involved the sensory system (eyes, ears), had the longest median duration to a general practice claim of 21 days. For all diagnostic categories the median time to a pharmacy claim was 8 days or less (Table 1).

For patients discharged from private hospitals the median time to the first general practice visit was between 12 and 32 days, and between 6 and 28 days for public hospital patients (Table 2). Time to first presentation at a pharmacy post-discharge was similar for patients discharged from private and public hospitals in each state (Table 2).

The probability of receiving a care plan service within 30 days of discharge was small, with less than 2% of the cohort having claims for discharge plans, less than 2% having claims for case conferences and less than 2% having claims for medication review services (Table 3). Discharge plans and case conferences were most common within 30 days of discharge for those hospitalized for a musculoskeletal disorder or injury; however, this represented 6% or less of these populations for each plan (Table 3).

| Table 1 | Proportion of veterans with a claim for service and median time in days (interquartile range) to first claim for service following discharge from hospital by major diagnostic category of hospital admission |
|---|---|---|
| | General practice service | Pharmacy service† | Specialist service |
| Number of subjects who received service during follow up | 104 426 | 104 818 | 96 354 |
| Number with at least one claim during first month of follow up (%) | 78 468 (71%) | 94 817 (86%) | 47 887 (44%) |
| Median time to claim by major diagnostic category of admission: | | | |
| All diagnoses | 12 (4–31) | 6 (2–14) | 35 (11–117) |
| Infections | 7 (2–23) | 5 (2–14) | 40 (8–155) |
| Neoplasms | 15 (6–36) | 7 (3–16) | 36 (12–103) |
| Blood disorders | 9 (3–22) | 6 (2–12) | 26 (9–85) |
| Endocrine diseases | 12 (4–31) | 6 (2–13) | 34 (13–95) |
| Mental and behavioural disorders | 13 (4–39) | 8 (3–20) | 118 (27–365) |
| Nervous system | 13 (4–33) | 7 (3–16) | 37 (12–134) |
| Diseases of the eye, ear | 21 (9–48) | 7 (3–15) | 39 (23–96) |
| Circulatory system | 8 (3–21) | 5 (1–13) | 23 (5–66) |
| Respiratory system | 7 (2–20) | 4 (1–11) | 36 (9–147) |
| Digestive system | 11 (4–29) | 7 (2–15) | 38 (12–149) |
| Skin and subcutaneous tissue | 10 (3–28) | 6 (2–13) | 50 (14–166) |
| Musculoskeletal system and connective tissue | 14 (5–34) | 6 (2–15) | 42 (10–121) |
| Genitourinary system | 12 (4–31) | 6 (2–16) | 37 (13–111) |
| Symptoms, signs not elsewhere classified | 8 (3–23) | 6 (2–14) | 32 (9–125) |
| Injury | 10 (3–32) | 6 (2–16) | 39 (4–194) |

†Excludes pharmacy services on day of discharge.

| Table 2 | Median time in days (interquartile range) to first claim for general practice or pharmacy service following discharge from hospital by state and type (public or private) of hospital admission |
|---|---|---|---|---|
| | Private | Public | Private | Public |
| | General practice service | Pharmacy service† | General practice service | Pharmacy service† |
| ACT | 15 (6–43) | 7 (2–16) | 8 (3–24) | 5 (1–15) |
| NSW | 14 (6–35) | 6 (2–14) | 6 (2–20) | 4 (1–13) |
| NT | 32 (10–83) | 12 (4–23) | 28 (9–81) | 8 (2–20) |
| QLD | 14 (5–34) | 6 (2–15) | 9 (3–26) | 5 (1–14) |
| SA | 16 (6–35) | 7 (2–15) | 10 (3–29) | 6 (2–16) |
| TAS | 13 (5–33) | 6 (2–13) | 7 (2–26) | 5 (2–15) |
| VIC | 14 (5–34) | 6 (2–14) | 8 (3–25) | 6 (2–16) |
| WA | 15 (5–40) | 7 (3–17) | 12 (4–37) | 7 (2–18) |

†Excludes pharmacy services on day of discharge.
Our study identifies the timelines within which patients visit community healthcare providers post-hospital discharge. Over 70% of patients visit their GP and community pharmacy in the month after discharge, with at least a quarter presenting in the first 4 days. This suggests that transfer information needs to reach community healthcare providers within 4 days of discharge to ensure continuity of care for patients.

The timeliness of communication between Australian hospital physicians and GPs has not been widely studied. In one small survey, 68% of GPs reported receiving discharge summaries a week or more after the patient had been discharged from hospital.13 Another small Australian survey reported that only 44% of discharge summaries were received by GPs in the 2 weeks following patient discharge.14 GPs might not receive hospital discharge summaries for their patients at all, with 23%13 and 33%14 of the GPs in these respective surveys reporting they did not receive discharge summaries for their patients. These findings are reflected in international studies. A systematic review found that only 75% of discharge summaries were received by GPs, and only 15% were received within a week of patient discharge.15 Between 66% and 88% of patients visited their GP before the hospital discharge summary arrived.15 This suggests that not only is timely delivery of discharge summaries to GPs an issue, receipt of a discharge summary at all is not guaranteed. Our results suggest that discharge summaries should be received by GPs within 4 days of patient discharge so that they are available at the first consultation post-discharge.

The consequences of poor communication between hospital and community healthcare providers have been highlighted in numerous studies.15 In one study, 31 of 78 adverse events were attributed to inadequate communication between healthcare providers.15 Among inappropriate or no patient follow-up found that 40% had a medical error that contributed to poor communication. In our study, 31 of 78 adverse events were associated with inappropriate or no follow-up post-discharge. Another study involving required medicines not being prescribed post-discharge found that 40% had a medical error attributable to poor communication. In our study, 86 patients followed-up found that 40% had a medical error attributable to poor communication.

Of the eligible patients in our study, only a small proportion received a care plan or medication review. The majority of these errors were medication-related and involved required medicines not being prescribed post-discharge. Twelve per cent of patients visited their GP before the hospital discharge summary arrived.15 Systematic review is reflected in international studies. A systematic review found that only 75% of discharge summaries were received by GPs, and only 15% were received within a week of patient discharge.15 Between 66% and 88% of patients visited their GP before the hospital discharge summary arrived.15 This suggests that not only is timely delivery of discharge summaries to GPs an issue, receipt of a discharge summary at all is not guaranteed.

Our study identifies the timelines within which patients visit their GP and community pharmacy post-hospital discharge. Over 70% of patients visit their GP and community pharmacy in the month after discharge, with at least a quarter presenting in the first 4 days. This suggests that transfer information needs to reach community healthcare providers within 4 days of discharge to ensure continuity of care for patients.

Table 3 Percentage of veterans (95% confidence interval) receiving a claim for a care plan or medicine review within 30 days of first discharge by major diagnostic category of hospitalization

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>Healthcare plan</th>
<th>General practitioner plan</th>
<th>Discharge plan</th>
<th>Case conference</th>
<th>HMR†</th>
<th>RMR‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>All diagnoses</td>
<td>109783</td>
<td>2.1 (2.0, 2.2)</td>
<td>2.1 (2.1, 2.2)</td>
<td>1.7 (1.6, 1.8)</td>
<td>1.6 (1.6, 1.7)</td>
<td>0.2 (0.1, 0.2)</td>
<td>1.2 (1.1, 1.4)</td>
</tr>
<tr>
<td>Infections</td>
<td>1145</td>
<td>2.2 (1.4, 3.3)</td>
<td>1.8 (1.2, 2.8)</td>
<td>2.0 (1.3, 3.0)</td>
<td>2.7 (1.9, 3.9)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.8 (0.1, 1.5)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>15325</td>
<td>2.0 (1.7, 2.2)</td>
<td>1.9 (1.7, 2.1)</td>
<td>0.5 (0.4, 0.7)</td>
<td>0.6 (0.5, 0.7)</td>
<td>0.0 (0.0, 0.1)</td>
<td>1.1 (0.6, 2.0)</td>
</tr>
<tr>
<td>Blood disorders</td>
<td>1881</td>
<td>2.0 (1.5, 2.8)</td>
<td>2.2 (1.6, 3.0)</td>
<td>0.7 (0.4, 1.2)</td>
<td>0.6 (0.3, 1.1)</td>
<td>0.1 (0.0, 0.5)</td>
<td>1.1 (0.4, 3.4)</td>
</tr>
<tr>
<td>Endocrine diseases</td>
<td>3161</td>
<td>2.4 (1.9, 3.0)</td>
<td>3.2 (2.6, 3.8)</td>
<td>1.0 (0.7, 1.4)</td>
<td>0.8 (0.5, 1.2)</td>
<td>0.3 (0.1, 0.5)</td>
<td>1.7 (0.7, 4.1)</td>
</tr>
<tr>
<td>Mental and behavioural disorders</td>
<td>2131</td>
<td>2.0 (1.4, 2.7)</td>
<td>1.4 (1.0, 2.0)</td>
<td>0.9 (0.6, 1.4)</td>
<td>1.0 (0.6, 1.5)</td>
<td>0.3 (0.1, 0.6)</td>
<td>0.5 (0.1, 1.2)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>3652</td>
<td>2.5 (1.8, 2.4)</td>
<td>2.5 (2.0, 3.0)</td>
<td>0.8 (0.6, 1.2)</td>
<td>1.1 (0.8, 1.6)</td>
<td>0.1 (0.1, 0.4)</td>
<td>0.9 (0.2, 3.3)</td>
</tr>
<tr>
<td>Diseases of the eye, ear</td>
<td>11051</td>
<td>2.1 (1.8, 2.4)</td>
<td>1.8 (1.6, 2.1)</td>
<td>0.1 (0.0, 0.2)</td>
<td>0.1 (0.1, 0.2)</td>
<td>0.1 (0.1, 0.2)</td>
<td>0.8 (0.2, 2.3)</td>
</tr>
<tr>
<td>Circulatory system</td>
<td>15325</td>
<td>2.4 (2.2, 2.7)</td>
<td>2.9 (2.6, 3.2)</td>
<td>2.1 (1.9, 2.4)</td>
<td>2.0 (1.8, 2.3)</td>
<td>0.3 (0.2, 0.4)</td>
<td>0.9 (0.5, 1.7)</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>6849</td>
<td>2.4 (2.1, 2.8)</td>
<td>2.3 (1.9, 2.7)</td>
<td>1.6 (1.3, 1.9)</td>
<td>1.3 (1.1, 1.6)</td>
<td>0.2 (0.1, 0.3)</td>
<td>1.2 (0.7, 2.1)</td>
</tr>
<tr>
<td>Digestive system</td>
<td>13547</td>
<td>1.8 (1.6, 2.0)</td>
<td>2.0 (1.8, 2.2)</td>
<td>0.5 (0.4, 0.7)</td>
<td>0.6 (0.5, 0.7)</td>
<td>0.1 (0.0, 0.2)</td>
<td>1.8 (1.1, 3.0)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>2449</td>
<td>2.4 (1.8, 3.0)</td>
<td>1.8 (1.4, 2.5)</td>
<td>0.7 (0.4, 1.1)</td>
<td>0.9 (0.6, 1.4)</td>
<td>0.2 (0.1, 0.6)</td>
<td>1.0 (0.3, 3.1)</td>
</tr>
<tr>
<td>Musculoskeletal system and connective tissue</td>
<td>9158</td>
<td>1.5 (1.3, 1.8)</td>
<td>1.9 (1.6, 2.2)</td>
<td>5.0 (4.6, 5.5)</td>
<td>4.2 (3.8, 4.7)</td>
<td>0.1 (0.1, 0.2)</td>
<td>1.5 (0.6, 3.6)</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>5394</td>
<td>2.0 (1.7, 2.4)</td>
<td>2.1 (1.7, 2.5)</td>
<td>1.1 (0.8, 1.4)</td>
<td>0.8 (0.6, 1.1)</td>
<td>0.1 (0.1, 0.3)</td>
<td>1.7 (0.9, 3.2)</td>
</tr>
<tr>
<td>Symptoms, signs not elsewhere classified</td>
<td>10172</td>
<td>2.1 (1.8, 2.4)</td>
<td>2.2 (1.9, 2.5)</td>
<td>1.3 (1.1, 1.5)</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.3 (0.2, 0.4)</td>
<td>1.5 (0.9, 2.5)</td>
</tr>
<tr>
<td>Injury</td>
<td>8543</td>
<td>2.5 (2.2, 2.8)</td>
<td>2.0 (1.7, 2.3)</td>
<td>5.9 (5.4, 6.5)</td>
<td>6.2 (5.7, 6.8)</td>
<td>0.2 (0.1, 0.4)</td>
<td>0.9 (0.5, 1.5)</td>
</tr>
</tbody>
</table>

†Home Medicines Review – includes patients not in residential care at discharge. ‡Residential Medication Management Review – includes patients discharged to residential care.
service after discharge, suggesting under-utilization of these services. Patients recently discharged from hospital are likely to benefit from these types of interventions. Multidisciplinary case conferences are useful in communicating medication changes during admission and the reasons behind them, and may lead to better patient satisfaction with the discharge process and better patient understanding of their post-discharge care plan. Case conferences at the time of discharge can also contribute to improved continuity of care by enhancing communication between hospital and community health providers. Medicine reviews conducted in the week post-hospital discharge have been shown to reduce the risk of death and readmissions to hospital in the 3–18 months post-discharge, particularly among patients likely to have multiple readmissions in the future. Given that medication misadventure is most likely to occur soon after hospital discharge, medicine review and care plan services conducted soon after discharge might be of greater benefit than if conducted later. This might particularly be the case for patients who have multiple healthcare providers, where enhanced communication between the different providers is likely to improve the continuity of care.

For the majority of subjects in this study, the first community healthcare provider consulted post-discharge was a community pharmacist, accessed within 2 days of discharge for a quarter of the patients studied. Early presentation of patients to a community pharmacy post-discharge does not appear to be related to the amount of medicine supplied. Access to PBS medicines for patients admitted to public hospitals was proposed in the 1998–2003 Australian Health Care Agreements; prior to this patients discharged from public hospitals only received up to a week’s supply of medicine. In contrast, patients discharged from private hospitals had access to medicines subsidized on the PBS and could receive the standard PBS quantity (usually a month’s supply). By June 2004 patients admitted to 55 public hospitals in Victoria, Western Australia and Queensland had access to PBS medicines at discharge. In our study, the median time to visiting a community pharmacy post-discharge was similar for public and private hospital patients in these states. However, time to presentation at community pharmacies was also similar for patients discharged from private hospitals and public hospitals in states without PBS access during the study period. Access to PBS medicines in public hospitals does not appear to extend the time to presentation at a pharmacy post-discharge, even though increased quantities of medicine are supplied.

Although many Australian public hospitals routinely transfer discharge summaries to the patient’s nominated GP, transfer of medication discharge summaries to community pharmacies occurs on a less routine basis. If community pharmacists are unaware of medication changes during admission, there is potential for continued dispensing of discontinued or dose-changed medicines. International research has shown that when community pharmacists are provided with transfer summaries at hospital discharge, medication errors may be reduced. Given the timeliness with which patients consult pharmacists post-discharge, more active engagement of this professional group in the continuum of care might improve care after discharge. There is potential for hospital pharmacists to play an active role in this information transfer by preparing medication transfer summaries for community pharmacists. In order to be of maximum benefit, these summaries should be forwarded to the patient’s nominated community pharmacy within 2 days of discharge, the time frame within which 25% of study subjects first visited their pharmacy post-discharge.

A limitation of our study is that we only considered continuity of care after the first hospital admission for subjects. Patients with multiple hospital admissions each year are likely to be sicker than others, and this might have implications for the timelines within which they are able to access community healthcare providers. The data in our analysis were limited to DVA treatment card holders. A comparison of the DVA population with the wider Australian population has shown that DVA card holders have slightly more GP visits (rate ratio 1.17) and hospitalizations (rate ratio 1.21) per year than other Australians. Continuity of care issues are likely to be relevant in the veteran population because of their higher rate of hospital admission; however, the influence of this and the higher rate of GP visits among veterans on the generalizability of our results is unknown.

**Conclusion**

Our study highlights that the median time to a general practice visit was 12 days after discharge and 25% of subjects visited their GP within 4 days, suggesting that discharge summaries must reach community-based health professionals within 4 days. This study also highlights the lack of use of care plans soon after discharge. This is an area of practice suitable for considerable enhancement of activity, particularly for patients who visit multiple service providers. A quarter of veterans visit a community pharmacy within 2 days of discharge from hospital; however, pharmacists are not necessarily routinely advised of hospitalization or provided with discharge summaries. More active engagement of this professional group in the continuum of care might considerably improve care after hospital discharge.
References


Continuity of care after leaving hospital

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Outpatient parenteral antimicrobial therapy-treated bone and joint infections in a tropical setting

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Key words
outpatient parenteral antibiotic therapy, Hospital in the Home, osteoarticular infection, bone and joint infection.

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Abstract

Background: Osteoarticular infections are a primary indication for outpatient parenteral antimicrobial therapy (OPAT). The climate and geographical diversity of tropical Australia, together with the prevalence of melioidosis, disseminated gonococcal disease and community-acquired methicillin-resistant Staphylococcus aureus renders this a challenging environment in which to manage such infections. We evaluated patients managed by the Royal Darwin Hospital Hospital in the Home service for bone and joint infections.

Methods: A retrospective analysis of the therapeutic outcomes at the end of intravenous therapy was carried out for patients treated between 1 January 2006 and 15 September 2007.

Results: Fifty-five patients were treated, including 21 (38%) indigenous Australians and 18 (33%) from remote communities. Baseline characteristics were similar to other published data, but there were two cases each of gonococcal septic arthritis and melioidosis. During treatment, 39 (71%) lived at home, with five (9%) of these receiving treatment at community clinics. Thirteen (24%) resided in self-care units in the hospital grounds. Three (5%) were managed at hostels or in prison. Median duration of parenteral therapy was 42 days, with a median of 22 days outside hospital, providing a total saving of 1307 bed-days. Clinical success at end of therapy was 84%, with no significant difference between indigenous and non-indigenous cohorts.

Conclusion: OPAT for osteoarticular infections is both feasible and effective in a tropical environment, including for indigenous patients. Extension of treatment to remote-dwelling patients is facilitated by the innovative use of self-care units and administration of treatment at remote clinics.

Introduction

Outpatient, or ambulatory, parenteral antimicrobial therapy has been used since the 1970s as an alternative to hospitalization for patients with a variety of infections, and is known variably as outpatient parenteral antimicrobial therapy (OPAT) or Hospital in the Home (HITH). Benefits include a reduction in nosocomial infections, greater freedom for patients to return to work or educational facilities, and reductions in hospital inpatient bed-days.1–3 It has been consistently proven to be cost-effective in the management of a variety of infections.3

The treatment of bone and joint infections, including prosthetic device-related osteomyelitis, usually necessitates a prolonged course of antibiotic therapy, making outpatient treatment an ideal management choice for those who are otherwise medically fit. International OPAT registries list osteomyelitis as a primary indication for OPAT therapy,1,2 although there are virtually no published data on the outcomes of osteoarticular infections treated with outpatient therapy in tropical environments.

The ‘Top End’ refers to the tropical top third of the Northern Territory of Australia. The Royal Darwin Hospital (RDH) is a referral hospital for a catchment population of 170,000, of whom 27% are indigenous. Approximately one-third live in remote areas, often necessitating hospital retrieval through aeromedical services.4–6 Treating patients from such diverse backgrounds, across a geographical area extending for half a million
square kilometres, provides a real challenge in terms of logistics and provision of equality of healthcare. This study aimed to evaluate therapeutic outcomes in those receiving OPAT for bone and joint infections in the Top End.

**Methods**

We carried out a retrospective analysis of the clinical outcomes of therapy in patients who received ambulatory antimicrobial therapy for bone and joint infections, coordinated by the HITH service at RDH. Patients were included if they commenced therapy between 1 January 2006 and 15 September 2007. We reviewed medical notes and the hospital pathology database for patient demographics, medical comorbidities and clinical and microbiological details of infection.

The RDH HITH service is a collaboration between specialist nurses, infectious diseases physicians and infectious diseases registrars. In most cases, intravenous therapy was initiated during hospital admission, and continued as an outpatient under the supervision of the HITH service. Antimicrobials were administered through percutaneously inserted central venous catheters (PICC), as 24-h infusions using elastomeric infusion devices (Baxter Healthcare, Sydney, NSW, Australia). Care was provided by HITH staff at the hospital, if patients were well enough to travel daily, or at their home or alternative accommodation (hostel, prison). A number of patients in remote locations (as defined by the Accessibility/Remoteness Index of Australia4) had care for their PICC lines, and infusors were changed on a daily basis by nursing staff. Patients residing in the hospital self-care units, Darwin hostels/prison or their own homes in Darwin all received identical treatment: daily review by HITH nurses and weekly clinical review at RDH outpatients by the infectious diseases team with regular monitoring of haematological, biochemical and inflammatory markers. Those treated at remote community clinics lived in their own homes and were assessed daily by remote nurses, with change of antibiotic infusors. Blood tests and clinical review were carried out weekly by remote nurses and the results were discussed with the HITH team in Darwin. Antibiotic infusors were sent in thermally insulated containers from RDH every 1–2 weeks through regular small aircraft flights.

Therapeutic outcome at the end of OPAT was defined as follows:

1. **Success = a cure or major improvement as shown by improvement in clinical and radiological appearances, and significant decrease in C-reactive protein.** Although some patients continued oral antibiotics beyond the end of intravenous therapy, monitoring of this was not included in this study.

2. **Therapeutic failure = where the prescribed course of OPAT was not successful in eliciting either a cure or major improvement as defined by one or more of the following criteria:**
   
   i. There was a need to continue intravenous therapy beyond the originally prescribed course
   
   ii. Relapse or lack of improvement according to clinical assessment
   
   iii. There was a need for unanticipated surgery to control the infection (e.g. surgical debridements, amputation)
   
   iv. The OPAT course was interrupted for any other reason

   Continuous variables were compared using Student’s t-test or Mann–Whitney U-test for normal and non-normal variables respectively. Categorical variables were compared using Fisher’s exact test. A P-value of <0.05 was considered significant.

   Ethics approval for the study was granted by the Human Research Ethics Committee of the NT Department of Health and Community Services and Menzies School of Health Research.

**Results**

**Baseline demographics**

Fifty-five patients received OPAT for osteoarticular infections between 1 January 2006 and 15 September 2007. Thirty-six (65%) were male, and 21 (38%) were indigenous Australians (Aboriginal or Torres Strait Islander). The age range was 16–93 years, with a mean (standard deviation) of 50 (16) years. Mean (standard deviation) age in the indigenous patients was 43.2 years (12.5) in comparison with 54.1 years (16.6) in the non-indigenous patients (P = 0.01). Bone and joint infections represented 6.2% of the 885 patients treated by HITH over the study period.

**Location of treatment**

Of the 55 patients, 37 (67%) were from the urban or rural suburbs of Darwin, and 18 (33%) were from remote areas of the Northern Territory (Fig. 1).

Of those treated in Darwin, 34 (62%) lived at home for the duration of treatment, with a further three (5%) in hostel accommodation, or prison. Thirteen patients (24%) resided in the self-care facilities in the hospital grounds; 12 of these were indigenous and 12 were from...
remote communities. These patients either lacked suitable accommodation for home treatment, or had medical or social comorbidities, which made close monitoring particularly desirable, including alcohol misuse (6/13), diabetes (7/13) or renal disease (6/13). The remaining five (9%) were treated at community clinics, four (7%) of whom were in remote communities.

### Diagnostic groups

Patients were categorized into one of four diagnostic groups. The osteomyelitis cohort was further subcategorized according to the site of infection and the proportion of patients who were diabetic for each of these locations (Fig. 2). Diabetic foot infections were the predominant category (Table 1).

### Causative organisms

Causative organisms were isolated from surgical specimens, wound or blood cultures. Eleven (20%) patients were recorded as having ‘no growth’ from cultures. Of note were two patients with melioidosis, one of whom had both an infected elbow joint and paravertebral abscess, and the other patient who had septic arthritis of the hip with associated femoral osteomyelitis. Two patients had disseminated gonococcal infection, both presented with gonococcal septic arthritis of the knee. Of the nine patients with methicillin-resistant \textit{Staphylococcus aureus} (MRSA) infection, seven were multi-resistant MRSA and two were non-multi-resistant MRSA, with both of the latter isolates sensitive to sulphamethoxazole-trimethoprim (Table 2).

Many patients had more than one organism isolated, and their antimicrobial therapy was adjusted to reflect the need to cover a variety of potentially causative pathogens.

### Antimicrobial therapy

All patients received intravenous antibiotics, and 44 (80%) were prescribed concomitant oral antibiotics. Of these, 38 (69%) were requested to continue oral therapy after completion of intravenous treatment. The usual management was a further 2–4 weeks of oral antibiotics, although one patient received lifelong suppression for ongoing and surgically inoperable infection of a prosthetic knee replacement.

The commonest intravenous antibiotics used were flucloxacillin (18, 33%), ticarcillin-clavulanic acid (15, 27%) and vancomycin (10, 18%). The commonest oral antibiotics were dicloxacillin (15, 27%) and amoxicillin-clavulanic acid (11, 20%).

---

**Table 1** Categorization of bone and joint infections

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Number of patients (total = 55)</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomyelitis</td>
<td>28</td>
<td>51</td>
</tr>
<tr>
<td>Native joint septic arthritis</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Prosthetic joint or device infection</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Mixed osteomyelitis and septic arthritis</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Forty-two (76%) patients had had surgical procedures directed at the amelioration of infection prior to the instigation of HITH therapy. These procedures included surgical debridement, joint washouts and removal of infected surgical hardware.
The total number of inpatient bed-days saved because of administration of intravenous therapy outside hospital was 1307. The range of total duration of intravenous therapy (including time spent as an inpatient) was 4–79 days (median 42) while the range of length of OPAT therapy was 3–56 days (median 22).

Patients receiving continuous vancomycin infusions had levels carried out at regular intervals with a median level calculated. Overall, the median level was 16.0 mg/L (range 9.4–21.2).

Adverse events

Forty-eight patients tolerated therapy well, but seven (13%) experienced adverse drug events. Intravenous antibiotics were responsible for adverse events in three (5%) patients; one developed rashes with both teicoplanin and vancomycin, one developed thrombocytopenia attributed to flucloxacin, and one had deranged liver enzymes from ceftriaxone. Among oral antibiotics, sulphamethoxazole caused thrombocytopenia in one patient and worsening renal function in another. One patient experienced diarrhoea after taking clindamycin, and another was unable to tolerate dicloxacillin because of nausea. There were no complications related to intravenous access and, in particular, the PICC lines were well tolerated and maintained despite the potential difficulties of the tropical environment.

The incidence of adverse events was significantly lower in indigenous patients (0/21) compared with non-indigenous patients (7/34, \( P = 0.03 \)).

### Table 2: Causative organisms

<table>
<thead>
<tr>
<th>Isolated pathogens</th>
<th>Total number of isolates</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-sensitive Staphylococcus aureus†</td>
<td>13</td>
<td>13 (24)</td>
</tr>
<tr>
<td>Methicillin-resistant Staphylococcus aureus†</td>
<td>9</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Streptococcus spp.†</td>
<td>4</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Enterococcus spp.†</td>
<td>3</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci†</td>
<td>3</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Other Gram positives†</td>
<td>5</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae†</td>
<td>2</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Burkholderia pseudomallei†</td>
<td>2</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa†</td>
<td>5</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Enterobacter cloacae†</td>
<td>3</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae†</td>
<td>2</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other Gram negatives†</td>
<td>9</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Anaerobes†</td>
<td>4</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Patients with one isolate</td>
<td>–</td>
<td>28 (51)</td>
</tr>
<tr>
<td>Patients with two isolates</td>
<td>–</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Patients with three isolates</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Patients with four isolates</td>
<td>–</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

†Categories not mutually exclusive.

Outcome results

Of the 55 patients treated, 46 (84%), of which 18 were indigenous, were considered to have had a successful outcome at completion of intravenous OPAT therapy. There were similar outcomes for the indigenous patients in comparison with non-indigenous patients (\( P = \text{not significant} \)).

Nine patients were deemed to have had an unsuccessful outcome from OPAT therapy. Two (4%) required unplanned surgical intervention (further debridement, amputation) in order to control infection. Three (6%) were deemed to require further treatment, either medical or surgical, in order to elicit a cure, but these patients declined further intervention. Two (4%) failed intravenous therapy because of adverse drug reactions, one of whom required hospital admission. One (2%) was admitted to hospital during his OPAT course in order to have chemotherapy for a malignant condition and this was considered a treatment failure. One further patient (2%) required long-term antibiotic suppression as mentioned previously.

Analysis for predictors of success or failure revealed no statistically significant correlations for gender, medical comorbidity, causative organism or substance misuse. There was a non-significant association between length of treatment and a successful outcome. Patients achieving a successful outcome had a median length of treatment of 42 days, compared with those who failed treatment receiving a median of 27 days of therapy (\( P = 0.09 \)).

Discussion

To our knowledge, this is the first study to examine the use of ambulatory parenteral antibiotic therapy for osteoarticular infections in a tropical environment as geographically diverse as the Top End of Australia. It is also the first to include indigenous Australians treated with this technique.

The baseline characteristics of our patients were similar to those of other studies examining the use of OPAT for bone and joint infections, in terms of age and gender, but the indigenous patients tended to be younger and had more diabetic foot infections than the non-indigenous cohort. This may reflect the fact that indigenous Australians often have multiple medical comorbidities and present with complications of diabetes earlier than non-indigenous individuals.

Of the total duration of intravenous therapy, approximately half was administered outside hospital through the HITH programme, representing a significant saving in terms of actual bed-days and financial cost. The self-care units in the hospital grounds are an invaluable resource,
particularly for those who live in remote rural communities, where a full range of medical services is unavailable, particularly during the wet season, when many access roads are flooded. Self-care accommodation also enables those with difficult social circumstances, such as poor housing or substance addiction, to receive treatment outside the ward environment, while still remaining close to the physical location of the HITH team. Almost a quarter of our cohort made use of these facilities, and nearly all were Aboriginal. Many indigenous patients find staying in a hospital environment difficult, and this facility may improve compliance with therapy by allowing them a greater degree of independence.

In keeping with most major studies reporting on the use of OPAT for osteoarticular infections, S. aureus was the most common organism isolated in our cohort, with methicillin resistance (MRSA) noted in 41% of these isolates. Rates of MRSA vary considerably in different studies, although good outcomes have been achieved even in groups with high rates of infection.3 There is a global increase in community-acquired MRSA infections, which is also impacting on tropical northern Australia.10,11 The majority of community-acquired MRSA isolates are non-multi-resistant, being susceptible to sulphamethoxazole-trimethoprim and usually to tetracyclines. Oral therapy is being increasingly recommended and used, especially for skin and soft tissue infections.11,12 However, although sulphamethoxazole-trimethoprim and tetracyclines have good bone penetration, clinical studies are required to determine optimal therapy for non-multi-resistant MRSA osteoarticular infections, and in particular whether there are circumstances where such oral therapy can potentially replace intravenous vancomycin completely or after defined time periods.

Of interest, and pertinent to the tropical location of northern Australia, were two cases of melioidosis bone and joint infection, both of whom had successful outcomes following prolonged OPAT cefazidime combined with sulphamethoxazole-trimethoprim. This organism is endemic to northern Australia and south-east Asia,13 with septic arthritis and osteomyelitis being not infrequent primary presentations and also occurring secondary to the more common melioidosis pneumonia.14 We have previously described our extensive and successful use of HITH in the management of this infection.15

Due to the high numbers of infections caused by S. aureus, the two most common antibiotics used were flucloxacillin and vancomycin, both of which can be administered through a 24-h constant infusion through a PICC line. Vancomycin levels were within the range of acceptability for serious resistant staphylococcal infections at RDH. Ticarcillin-clavulanic acid is used predominantly to cover the polymicrobial infections common in diabetes-related foot infections. An adverse drug reaction rate of 13% is consistent with other OPAT cohorts.

Patients with bone infections related to diabetes have a high rate of relapse, even after apparent cure.1,16 Multi-disciplinary involvement in the management of diabetes-related osteomyelitis, with attention to glycaemic control, vascular risk factors and foot care, is of paramount importance in this group. One potential disadvantage of the use of OPAT for diabetes-related lower limb infection is that the removal of the patient from the hospital environment may isolate them from access to these services. Such considerations may be relevant in all communities, but perhaps is of particular importance in tropically located, geographically isolated, rural communities. The ability to review and follow up these patients is especially difficult and requires extraordinary commitment by the health service in order to try and prevent relapses. A longer follow-up study, with a concentration on diabetic individuals, would be useful to assess more fully the benefits of providing OPAT to these patients.

The small numbers of patients involved in this study limit the usefulness of statistical analysis of outcomes in individual subgroups. Important questions for future studies include whether indigenous patients have the same outcomes as non-indigenous Australians, and whether those treated in isolated rural community clinics, with remote liaison with HITH staff, can still achieve the same outcomes as those who are treated nearer to the hospital and physical location of the team. A further limitation is that this study has not examined outcomes of OPAT for bone and joint infections beyond the end of intravenous therapy. A repeat analysis looking at 6- or 12-monthly outcomes would be beneficial. Ideally, all patients should have had a microbiological diagnosis based on invasive sampling either from bone, or from blood cultures; however, in most of our cases, such samples were not taken and diagnosis was based on wound swab cultures alone.

**Conclusion**

An apparent cure or significant improvement was noted in 84% of our patients at the end of OPAT treatment. There was a non-significant association between outcome and length of intravenous treatment, which could be examined in greater detail in a larger study. Our results are consistent with other outcome studies, showing the comparative effectiveness of providing such a service to patients in this area of Australia. Almost all previous studies come from the northern hemisphere, but the similarity of these results in terms of baseline demographics, causative pathogens and end of therapy outcomes makes comparison with data and extrapolation...
of guidelines from Europe and the USA appropriate. The results of this small study suggest that tropical environments, and inclusion of indigenous patients, often with challenging social backgrounds, are not barriers to the successful implementation of an ambulatory antibiotic programme for osteoarticular infections. The innovative use of self-care accommodation close to hospital services enables extension of outpatient therapy to those for whom treatment in their own homes is impracticable, for either geographical or social reasons.

Acknowledgements

The authors would like to thank the HITH staff for their assistance in the management of patients and in identifying study patients from their database.

References

Clinical heterogeneity and prognostic features of South Australian patients with anti-synthetase autoantibodies

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Key words
anti-synthetase syndrome, inflammatory myopathy, autoantibody, interstitial lung disease, Ro-52 antigen.

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Abstract

Aim: To determine the clinical, serological and prognostic features of patients with autoantibodies against three aminoacyl-transfer RNA synthetases (ARS), namely Jo-1 (histidyl-tRNA synthetase), PL-7 (threonyl-tRNA synthetase) and PL-12 (alanyl-tRNA synthetase) in South Australia.

Methods: Patients with autoantibodies against ARS detected by line immunoassay (anti-Jo1, anti-PL7, anti-PL12) or enzyme-linked immunosorbent assay (anti-Jo1) were identified from existing laboratory databases for the period 1994–2009. Demographic, clinical and serological data were obtained by retrospective review of patients’ medical records and laboratory databases.

Results: Forty-two patients with autoantibodies were identified (anti-Jo1 = 37, anti-PL7 = 4, anti-PL12 = 1). Females were more commonly affected than males (M : F = 12:30). Twenty-one patients had polymyositis (anti-Jo1 = 17, anti-PL7 = 4), seven dermatomyositis (anti-Jo1 = 6, anti-PL12 = 1), 10 overlap syndrome (anti-Jo1 = 10; lupus = 4, scleroderma = 3, Sjögren’s syndrome = 2 and rheumatoid arthritis = 2) and four had interstitial lung disease (ILD) only (anti-Jo1 = 4). ILD was present in 69%, polyarthritis in 59% and positive anti-nuclear antibody (ANA) in 43% of patients. Concurrence of autoantibodies against Ro-52 with Jo-1 was seen in 12 patients. The mean follow-up period was 8.3 years (95% CI 5.8–10.8) with 12 deaths. Poor prognostic indicators were age of onset > 60 years (P = 0.001), cancer (P = 0.002), negative ANA (P = 0.006) and negative autoantibodies to extractable nuclear antigens (P = 0.02).

Conclusion: Patients with autoantibodies against ARS present with varied clinical features and occasionally with isolated lung involvement (amyopathic ILD). Older age of onset, malignancy and negative immunologic tests are predictors of poor prognosis. Concurrence of autoantibodies against Jo-1 and Ro-52 may reflect a coupling effect during generation of autoimmunity.

Introduction

Anti-synthetase syndrome (ASS) is characterized by the presence of autoantibodies against aminoacyl-transfer RNA synthetase (ARS) enzymes accompanied by a constellation of organ manifestations, including myositis, synovitis, interstitial lung disease (ILD) and skin rashes.1 The clinical heterogeneity of ASS emphasizes the importance of cross-speciality consultation in the diagnosis and management of this chronic immune-mediated condition. Anti-Jo1 or anti-histidyl-tRNA synthetase is the commonest myositis-specific autoantibody (MSA) found in 20–30% of patients with idiopathic inflammatory myopathy (IIM).1–4 To date autoantibodies against seven other ARS antigens – PL-7 (threonyl), PL-12 (alanyl), EJ (glycyll), OJ (isoleucyl), KS (asparaginyl), Ha (tyrosyl) and Zo (phenylalanyl) – have been described.7–15 Notably, there are minor clinical variations in ASS associated with the distinct synthetases like the presence of milder muscle disease in patients with anti-PL710 and the predominance of ILD in patients with anti-PL12, anti-KS and anti-OJ.12,15,17

However, questions regarding Jo-1 being the commonest antigenic target among ARS,1–6 concurrence of autoantibodies against ARS and Ro-522,6 and the varied clinical presentation of ASS remain unanswered.1 The
availability of a commercial assay as recently reported to detect autoantibodies against Jo-1, PL-7 and PL-12 may lead to an increased identification and recognition of the ASS and facilitate further studies. This may help to uncover the pathogenic mechanisms involved and have implications in terms of management and prognostication. The aims of this study were to determine the clinical, serological and prognostic features of patients with autoantibodies against Jo-1, PL-7 and PL-12 in South Australia.

Materials and methods
Patients with autoantibodies directed against ARS as detected by line immunoassay (LIA (anti-Jo1, anti-PL7 and anti-PL12); Euroline myositis antigen profile assay, Euroimmun AG, Luebeck, Germany) or enzyme-linked immunosorbent assay (ELISA (anti-Jo1); RELISA, Diagnostic solutions) were identified from existing laboratory databases for the period 1994–2009. The Euroline myositis antigen profile LIA detects IgG antibodies against Mi-2, Ku, Pm-Scl, Jo-1, PL-7, PL-12 and Ro-52 and has been used in our laboratory since 2007. Stored serum samples from patients with IM (myositis registry) were also analysed by the myositis antigen profile LIA and included in the study. Patients were recruited into the myositis registry by identifying positive muscle biopsies carried out at all public hospitals of South Australia, which are reported at a single centre. Demographic, clinical and serological features were obtained by retrospective review of patients’ medical records and laboratory databases. Ethics approval was obtained from the Research Ethics Committee, Royal Adelaide Hospital. The diagnosis of autoimmune conditions was confirmed in accordance with the current classification criteria being used. Myositis was further defined by the presence of symmetrical muscle weakness, elevated creatine kinase (CK), myopathic changes on electromyography and a diagnostic muscle biopsy as definite (three criteria), probable (two criteria) and suspected (one criterion). The presence of distinctive skin changes was needed in addition to the above criteria for the diagnosis of dermatomyositis (DM). The diagnosis of ILD was considered to be present if interstitial infiltrates were seen on chest radiography or high-resolution computed tomography or if the disease was confirmed by histopathology. Poor prognosis was defined as death of the patient. The survival of patients was calculated from the date of diagnosis to the date of death or last follow up. The normal laboratory value for CK was 0–180 U/L, while a positive antinuclear antibody (ANA) and rheumatoid factor (RF) were defined as a titre above 1:40 dilution and more than 20 kIU/L respectively. Qualitative nailfold capillaroscopy was carried out by a single observer (PJRT), using a dissecting microscope as described before to assess the presence of capillary dilatation, dropouts, distortion or asymmetry, and microvascular haemorrhage in selected patients.

Data were entered on Excel worksheet and analysed by GraphPad Prism 5.0 software (GraphPad Software Inc., San Diego, CA, USA). The survival analysis was carried out by Log-rank analysis of the Kaplan–Meier survival curves and hazard ratios (HR) provided with 95% confidence intervals (CI).

Results
Forty-two patients with autoantibodies against ARS were identified (anti-Jo1 = 37, anti-PL7 = 4, anti-PL12 = 1). Twenty-five of these were from the myositis registry (n = 128). Females were more commonly affected than males (M : F = 12:30); however, the difference in mean age of onset of disease was not statistically significant (M = 56.7 years (95% CI 45–68.4); F = 49 years (95% CI 43.4–54.6); p = 0.35). Fourteen patients had definite polymyositis (anti-Jo1 = 12, anti-PL7 = 2), six had probable polymyositis (anti-Jo1 = 4, anti-PL7 = 2), one suspected polymyositis (anti-Jo1 = 1, anti-PL7 = 1), five DM (anti-Jo1 = 5), two DM sine myositis (anti-Jo1 = 1, anti-PL12 = 1), 10 overlap syndrome (anti-Jo1 = 10; lupus = 4, scleroderma = 3, Sjögren’s syndrome = 2 and rheumatoid arthritis = 2) and four had I LD only with no muscle weakness or elevated CK (anti-Jo1 = 4). The clinical and serological features (summarized according to the autoantibodies detected: anti-Jo1, anti-PL7 and anti-PL12 in Table 1) observed were as follows: fever (16, 38%), current or ex-smokers (17, 40%), Raynaud’s phenomenon (13, 31%), mechanic’s hands (9, 21%), muscle weakness (28, 67%), polymyalgia (25, 59%), deforming arthropathy (7, 17%), I LD (29, 69%), positive ANA (18, 43%) and positive RF (12, 29%). Seven patients had history of cancer: melanoma, 2; basal cell carcinoma, 1; colon cancer, 1; non-Hodgkin lymphoma, 1; thyroid cancer, 1; and squamous cell lung cancer, 1. A muscle biopsy was carried out in 23 patients (55%); four patients who had presented with I LD only (amyopathic I LD) did not undergo a muscle biopsy as they had normal muscle power and normal CK levels. Nailfold capillaroscopy abnormalities were detected in nine out of 11 (82%) patients studied. The morphological changes consisted of distortion of the capillary arcades, capillary dilatation, capillary dropouts and the presence of microhaemorrhages.

The concurrence of autoantibodies (summarized in Table 2) against Ro-52 with ARS was detected in 15 patients (15/42, 36%): Ro-52 with Jo-1 in 12 patients (12/37, 32%), Ro-52 with PL-7 in two (2/4, 50%) and
Ro-52 with PL-12 in one patient (1/1, 100%) respectively. Autoantibodies against Ro-60 and La were detected mostly in patients with overlap syndrome (8/10 and 4/5 respectively, Table 2), but also in one patient with amyopathic ILD who had no other features of lupus or Sjögren’s syndrome.

The mean follow-up period was 8.3 years (95% CI 5.8–10.8) with 12 deaths (M : F = 3:9, ILD = 11). The cause of death was known in five patients and attributed to progression of ILD in two patients, community-acquired pneumonia in one patient and cancer (metastatic melanoma and squamous cell lung cancer respectively) in two patients. Treatment options used either alone or in combination included: prednisolone (41, 98%), methotrexate (17, 40%), azathioprine (11, 26%), cyclophosphamide (5, 12%), hydroxychloroquine (4, 10%), intravenous immunoglobulin (3, 7%), cyclosporine (2, 5%) and plasmapheresis (1, 2%). Poor prognostic indicators (summarized in Table 3) were age of onset > 60 years (P = 0.001, HR 4.96; 95% CI 2.46–43.4) and cancer (P = 0.002, HR 4.47; 95% CI 2.61–61.60). Positive ANA (P = 0.006, HR 0.10; 95% CI 0.05–0.60) and presence of autoantibodies against other extractable nuclear antigens (ENA; P = 0.02, HR 0.22; 95% CI 0.07–0.81) were associated with better survival outcomes. Patients with ILD also had a poor prognosis, but this was statistically not significant (P = 0.06, HR 5.09; 95% CI 0.92–11.87).

Discussion

We have reviewed the clinical and laboratory features of South Australian patients with autoantibodies against ARS and report an array of interesting findings. Our study confirms the diverse spectrum of clinical manifestations associated with ASS. The prevalence of mechanic’s hands (21%), deforming arthropathy (17%), ILD (69%), positive ANA (43%) and positive RF (29%) observed herein is comparable to that previously reported by Schmidt et al. in their review of 231 patients with anti-Jo1-associated ASS. However, the frequency of polyarthritis observed in three-fifths, Raynaud’s phenomenon in one-third and myositis in two-thirds of our patients is lower compared with published literature, possibly explained by the varied nature of ASS and population selection bias of our cohort. Notably, more than half of our patients had a negative ANA test, a commonly used screening test for autoimmune conditions, which

Table 1 Clinical and serological characteristics according to autoantibody profile in patients with anti-synthetase syndrome

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Anti-Jo1</th>
<th>Anti-PL7</th>
<th>Anti-PL12</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>25</td>
<td>4</td>
<td>1</td>
<td>30 (71)</td>
</tr>
<tr>
<td>Fever</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>16 (38)</td>
</tr>
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<td>Raynaud’s phenomenon</td>
<td>10</td>
<td>2</td>
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<td>13 (31)</td>
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<td>History of cancer</td>
<td>7</td>
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<tr>
<td>Mechanics’ hands</td>
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<td>9 (21)</td>
</tr>
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<tr>
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<td>2</td>
<td>1</td>
<td>9 (21)</td>
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</tbody>
</table>

Table 2 Profile of autoantibodies detected in patients with anti-synthetase syndrome

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Definite PM</th>
<th>Probable PM</th>
<th>Suspected PM</th>
<th>DM</th>
<th>Amyopathic ILD</th>
<th>Overlap syndrome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>4</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>Anti-Jo1</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Anti-PL7</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Anti-PL12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anti-Ro52</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>15</td>
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<tr>
<td>Anti-Mi2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anti-Ku</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Anti-PmScI</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Anti-Ro60</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>10</td>
<td>10</td>
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<td>Anti-La</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Anti-u1RNP</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

DM, dermatomyositis; ILD, interstitial lung disease; PM, polymyositis.
could provide false reassurance of the absence of autoimmune and potentially delay the recognition of this syndrome in patients with subtle clinical manifestations. Furthermore, only antibodies against Jo-1 (and not other ARS) are routinely sought on routine ENA testing. It could be speculated that earlier recognition, diagnosis and treatment in patients with positive autoantibodies accounts for their survival advantage as observed in our study. The new Euroline myositis antigen profile LIA detects antibodies against Jo-1, PL-7, PL-12, OJ and EJ and is available in our laboratory on specific request. Occasionally, these patients can present with isolated ILD with no muscle or joint symptoms (amyopathic ILD) as reported in our study and a recent publication.28 Consequently, patients with autoantibodies against non-Jo1 ARS may have previously been labelled as idiopathic ILD or inflammatory myopathies. In our experience, qualitative nailfold capillaroscopy assessment,26 which was abnormal in four-fifths of all patients studied (9/11, 82%), can be a useful diagnostic tool in evaluating these patients with subtle clinical presentations.

The co-occurrence of autoantibodies against Ro-52 and ARS as reported earlier2,6,29–31 was observed in one-third of our study patients. The concurrence of these autoantibodies is difficult to explain in the absence of demonstrable molecular cross-reactivity or mimicry between these antigens.29,31 However, it has been proposed that these antigens might be co-expressed in apoptosis or inflamed tissues31 and a coupling effect (pairing of autoantibody generation for Jo-1 and Ro-52 antigens) during generation of autoimmunity may explain their concordance. Jo-1 is the commonest antigenic target among the eight ARS identified so far and multiple autoantibodies against different ARS in a single patient have never been observed.4,6 This was also observed in our study with every patient having autoantibodies to only one ARS (Jo-1, PL-7 or PL-12), but autoantibodies against other ENAs (Ro-52, Ku, Mi-2, Pm-Scl) were present as reported earlier.2,6 This suggests that autoantibodies against ARS do not cross-react with each other and are mutually exclusive.

The Euroline myositis antigen profile LIA is a valuable tool in the detection of autoantibodies in patients with IIM. This assay is easier to carry out than the more demanding immune precipitation techniques. As reported recently, the Euroline myositis antigen profile LIA has a sensitivity and specificity of 45% and 62%, respectively, for the detection of any one autoantibody in a cohort of 153 patients with IIM and 77 disease controls.20 However, it should be understood that this assay has seven different antigens, each of which has its own sensitivity and specificity in IIM. Further studies are needed to validate this commercial assay before it can be recommended for routine laboratory use in the evaluation of patients with autoimmune diseases.

The management of patients with ASS is challenging and requires cross-speciality collaboration as these patients may present with isolated clinical manifestations, recruiting additional organ involvement as the disease progresses. Recent reports have shown promise in the use of rituximab in refractory cases32 and mycophenolate mofetil in ILD.27 Patients with ASS have a poor prognosis compared with non-ARS-related inflammatory myositis owing to the increased frequency and severity of steroid resistant ILD.3,33 In our study, patients with ILD showed a trend towards poor prognosis (P = 0.06), failing to reach statistical significance because of small numbers. Patients with older age of onset, history of malignancy and negative ANA and ENA were associated with a poor prognosis in our study. Limitations of our study include retrospective assessment, missing data and inability to carry out LIA on all patients to assess for concordance with anti-Ro52 as there were no stored sera for 17 patients.

Table 3 Prognostic indicators in patients with anti-synthetase syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alive (n = 30)</th>
<th>Dead (n = 12)</th>
<th>P-value</th>
<th>Hazard ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset &gt;60 years</td>
<td>5</td>
<td>7</td>
<td>0.001*</td>
<td>4.96 (2.46–43.4)</td>
</tr>
<tr>
<td>History of cancer</td>
<td>1</td>
<td>6</td>
<td>0.002*</td>
<td>4.47 (2.61–61.60)</td>
</tr>
<tr>
<td>Positive ANA†</td>
<td>13</td>
<td>11</td>
<td>0.006*</td>
<td>0.10 (0.05–0.60)</td>
</tr>
<tr>
<td>Presence of other ENAs</td>
<td>19</td>
<td>3</td>
<td>0.02*</td>
<td>0.22 (0.07–0.68)</td>
</tr>
<tr>
<td>Presence of ILD</td>
<td>18</td>
<td>11</td>
<td>0.06</td>
<td>5.09 (1.92–11.87)</td>
</tr>
<tr>
<td>Gender M : F</td>
<td>9.21</td>
<td>3.9</td>
<td>0.52</td>
<td>1.4 (0.40–6.02)</td>
</tr>
<tr>
<td>Fever</td>
<td>9</td>
<td>7</td>
<td>0.18</td>
<td>2.19 (0.57–7.97)</td>
</tr>
<tr>
<td>Polyaarthites</td>
<td>19</td>
<td>6</td>
<td>0.08</td>
<td>0.39 (0.08–1.12)</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>8</td>
<td>5</td>
<td>0.67</td>
<td>0.77 (0.22–2.66)</td>
</tr>
<tr>
<td>CK &gt;1000 U/L</td>
<td>13</td>
<td>5</td>
<td>0.32</td>
<td>1.73 (0.51–7.85)</td>
</tr>
<tr>
<td>Elevated CK (&gt;180 U/L)†</td>
<td>22</td>
<td>7</td>
<td>0.74</td>
<td>0.84 (0.20–3.21)</td>
</tr>
</tbody>
</table>

*Statistically significant difference. †Titre above 1:40 dilution. ‡Normal laboratory values 0–180 U/L. ANA, anti-nuclear antibody; CI, confidence interval; CK, creatine kinase; ENA, extractable nuclear antigen; F, female; ILD, interstitial lung disease; M, male.
Conclusion

To our knowledge, we have described the clinical, serological and prognostic profile of the second largest cohort of patients with ASS, adding to the limited literature available. Clinicians should meticulously explore for subtle signs and request specific testing for autoantibodies against ARS (if available) when evaluating patients with undifferentiated autoimmune conditions involving the lungs, muscles and joints in isolation or in combination. Inter-speciality collaboration between pulmonologists and rheumatologists through combined clinics and commercially available assays to detect autoantibodies against ARS may lead to a better recognition and management of this syndrome.

Acknowledgement

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References

Measurement properties of the 6-min walk test in individuals with exercise-induced pulmonary arterial hypertension

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Key words
6-minute walk test, exercise-induced pulmonary arterial hypertension, aerobic capacity, cardiac output.

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Abstract

Background: Exercise-induced pulmonary arterial hypertension (EIPAH) is associated with reduced peak exercise cardiac output (CO) and aerobic capacity (peak VO2). We investigated the validity of the encouraged 6-min walk test (6MWT) to identify exercise limitation and estimate aerobic capacity in subjects with EIPAH.

Methods: Seventeen subjects with EIPAH (56 ± 14 years, 15 women) and 20 healthy controls (57 ± 13 years, 19 women) underwent two encouraged 6MWTs and a symptom-limited cardiopulmonary exercise test (CPET). To measure central hemodynamics, subjects with EIPAH performed the CPET with a pulmonary artery catheter in situ.

Results: Compared with controls, subjects with EIPAH had reduced peak VO2 (1.2 ± 0.4 vs 1.7 ± 0.5 L/min, P < 0.01), 6-min walk distance (6MWD) (575 ± 86 vs 669 ± 76 m, P < 0.001) and 6-min walk work (6MWW) (39 ± 11 vs 45 ± 7 km.kg, P < 0.01). In subjects with EIPAH, there was a moderate correlation between 6MWD and peak VO2 (r = 0.72, P < 0.01) and a strong correlation between 6MWW and peak VO2 (r = 0.86, P < 0.001). There were significant correlations between 6MWD and peak CO (r = 0.59, P < 0.05), and between peak VO2 and peak CO (r = 0.55, P < 0.05). Peak heart rate was similar in the CPET and 6MWT in subjects with EIPAH (133 ± 15 vs 133 ± 19 beats/min, P = 0.8).

Conclusions: The encouraged 6MWT identifies reduced exercise capacity and provides a valid estimate of aerobic capacity in EIPAH.
Introduction

Pulmonary arterial hypertension (PAH) is a progressive condition characterized by elevated pulmonary vascular resistance, reduced pulmonary blood flow and an attenuated increase in cardiac output (CO) during exercise. The hallmark of PAH is exertional intolerance with symptoms that include dyspnoea, fatigue and light-headedness. The diagnosis of PAH is based on abnormal resting haemodynamics. However, recent studies demonstrate that individuals have normal haemodynamics at rest but a higher than expected mean pulmonary artery pressure (mPAP), in the presence of a normal pulmonary artery wedge pressure and reduced cardiac output at peak exercise, in association with reduced exercise capacity and symptoms typical of PAH. This elevation in pulmonary pressure on exercise has been called exercise-induced PAH (EIPAH) and has been proposed to be part of the spectrum of pulmonary vascular diseases.

The capacity of the cardiovascular, respiratory and skeletal muscle systems to transport and utilize oxygen for aerobic metabolism is quantified by measuring peak oxygen consumption (peak VO2) during a cardiopulmonary exercise test (CPET). While peak VO2 reflects disease severity and prognosis in PAH, a CPET requires specialist knowledge and equipment. In contrast, the 6-min walk test (6MWT) requires minimal equipment, is easy to administer and is widely available. Measures derived from the 6MWT include the 6-min walk distance (6MWD) and 6-min walk work (6MWW), the product of 6MWD and body weight. 6MWD, which quantifies functional exercise impairment, has been shown to provide a valid estimate of peak VO2 in individuals with PAH and is more sensitive to change with pharmaceutical therapy in PAH than peak VO2. Accordingly, 6MWD has been employed as the primary outcome measure for clinical trials of pharmaceutical therapy in PAH. However, in subjects with chronic obstructive pulmonary disease (COPD), 6MWW has been shown to correlate more strongly with disease severity and to have greater sensitivity and specificity for low exercise capacity than 6MWD.

The 6MWT can be administered with or without encouragement. Clinical trials in PAH have mostly utilized a protocol devoid of encouragement to better reflect the subjects’ ability to perform activities of daily living. However, the American Thoracic Society recommends a 6MWT protocol with standardized encouragement, to measure maximal walking capacity. Investigations reporting physiological responses to a 6MWT in PAH have typically utilized an encouraged 6MWT given that it is more likely to identify a physiological limitation to exercise than an unencouraged test. However, in individuals with mild-moderate impairment in aerobic capacity, such as EIPAH, mechanical constraints that limit maximum walking speed, rather than physiological dysfunction, may influence 6MWD. This ‘ceiling effect’ has been reported in patients with chronic heart failure (CHF) and PAH with mild functional limitation (World Health Organisation Functional Class II (WHO FC II)).

The aims of this study, in subjects with EIPAH, were to: (i) compare physiologic and symptomatic responses between the 6MWT and CPET, and (ii) determine whether the 6MWT can identify functional exercise limitation and accurately estimate aerobic capacity.

Methods

Participants

Forty-nine adults were recruited from the Pulmonary Hypertension Unit at Royal Perth Hospital (Perth, Western Australia). All subjects had been referred for investigation of dyspnoea of unknown aetiology, were in WHO FC II or III, and were investigated for PAH as defined by the 2004 European Society of Cardiology Guidelines, that is, mPAP > 25 mmHg and pulmonary artery wedge pressure ≤15 mmHg at rest. Based upon historically accepted upper limits of normal, subjects were identified as having EIPAH if mPAP was ≥30 mmHg and pulmonary artery wedge pressure was <20 mmHg, on exercise. As determined prior to commencement of the study, subjects were excluded or withdrawn from the study if they had a body mass index (BMI) > 35 kg/m² (n = 4), ischaemic heart disease (n = 1), a history or evidence of pulmonary parenchymal or airway disease on high resolution computed tomography or lung function testing (n = 5), a musculoskeletal condition limiting exercise performance (n = 1), anaemia (n = 1), PAH at rest (mPAP > 25 mmHg at rest, n = 6), normal mPAP at rest or on exercise (n = 10), or a pulmonary artery wedge...
pressure >15 mmHg at rest or >20 mmHg on exercise (n = 4). Data from the remaining 17 subjects were used in the analyses.

A population-based sample of 20 healthy control subjects was recruited from a database of research volunteers maintained by the Lung Institute of Western Australia (Perth, Western Australia). Controls were matched to subjects with EIPAH for gender, age (±5 years) and BMI (±3 kg/m², provided BMI was ≤35 kg/m²). All controls underwent medical examination and a series of screening tests (medical history, echocardiogram, electrocardiogram, lung function tests and haematology) to confirm their healthy status.

The study was approved by the Human Research Ethics Committees of Royal Perth Hospital and Curtin University. Written informed consent was obtained from all subjects prior to enrolment. This work was performed at Royal Perth Hospital, Perth, Western Australia.

**Study design**

The study used a prospective cross-sectional design. All subjects completed two encouraged 6MWTs on 1 day, separated by at least 30-min rest. A symptom-limited incremental CPET was performed between 1 and 32 (mean of 5) days following the 6MWTs. Subjects recruited from the Pulmonary Hypertension Unit had a pulmonary artery catheter in situ during the CPET, for the measurement of central haemodynamics. All tests were supervised by the same investigator (RF).

**Exercise protocols**

**Six-minute walk test**

The 6MWT was performed over a 45-m course in an enclosed corridor according to the American Thoracic Society guidelines.10 Heart rate (Polar Electro Oy; Kempele, Finland) was monitored throughout the test. Sensations of dyspnoea and leg fatigue were assessed immediately following test cessation using the Borg Category Ratio Scale.16

**Cardiopulmonary exercise test**

The CPET was performed using an electronically braked cycle ergometer attached to a customized imaging table (Lode BV, Groningen, the Netherlands) with the subject in a semi-recumbent position (torso at 50° from the horizontal). An incremental symptom-limited protocol was employed, which involved a 3-min baseline period followed by 15-W increments in workload every 3 min. The initial workload was individualized based upon gender, age and 6MWD. Standardized instructions and encouragement were provided to promote a maximum effort. Breath by breath ventilation, oxygen and carbon dioxide concentrations and the derived minute ventilation, \( V_{O_2} \) and carbon dioxide output were determined using the Vmax metabolic analysis system (Sensormedics, Yorba Linda, CA, USA). Heart rate (12 lead electrocardiogram; Cardiosoft, Version 4.2, GE Medical Systems, Milwaukee, WI, USA) and SpO2 (Oxypleth pulse oximeter and ear sensor, Novemetrics, Wallingford, CT, USA) were monitored continuously throughout the test.

The method of haemodynamic monitoring and data collection employed in the assessment of the subjects with EIPAH has previously been reported.3 In brief, pulmonary artery pressure was continuously monitored (Compact, Datex Engstrom, Helsinki, Finland). Cardiac output was determined using thermal filament thermodilution, updated every 60 s (Vigilance, Baxter, CA, USA). Pulmonary artery wedge pressure was recorded at rest and every 3 min, immediately prior to an increase in workload, and in the final minute of the test. If a subject performed less than 30 s of the final workload attempted, the mPAP, pulmonary artery wedge pressure and CO responses were taken as the values measured within the last 60 s of the previous workload. Systolic arterial pressure was measured manually, at the brachial artery, at rest and every 3 min, immediately prior to an increase in workload and in the final minute of the test.

Ratings of dyspnoea and leg fatigue were recorded during the last 60 s of each workload and immediately following test cessation. The maximum workload was defined as the highest workload maintained for >30 s and peak \( V_{O_2} \) was defined as the 30 s average measured at the maximum workload within the last 30 s prior to test termination. Minute ventilation, \( V_{O_2} \), carbon dioxide output and respiratory exchange ratio were calculated.

The demographic, 6MWD and peak \( V_{O_2} \) data for both EIPAH and control groups have previously been reported.3

**Statistical analyses**

The effect of test repetition on 6MWD was examined using a general linear model for repeated measures. For each group, the magnitude of change in 6MWD between tests 1 and 2 was compared using the paired t-test. The greater 6MWD was used in all subsequent analyses. The coefficient of repeatability was determined as twice the SD of the difference in 6MWD measured on the two tests. Comparisons of responses to the 6MWT and CPET for the EIPAH group and control group were performed for each group separately using paired t-tests (heart rate (HR)) and Wilcoxon signed rank tests (peak dyspnoea...
and rate of perceived exertion). Differences between the EIPAH and control groups were analysed using unpaired t-tests (continuous variables) and the Mann–Whitney U-test (peak dyspnoea and rate of perceived exertion).

Relationships between 6MWD and 6MWW with peak values of \(\dot{V}_{O_2}\) and CO were assessed using Pearson correlation coefficients and linear regression analysis. Data were analysed using SPSS software Version 18 (SPSS, Chicago, IL, USA). A P-value of < 0.05 was considered to be statistically significant. Data are presented as mean ± SD unless otherwise stated.

### Results

Subject characteristics are presented in Table 1. The subjects with EIPAH had a lower forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC), per cent predicted, than the controls (\(P < 0.001\) for both). However, all lung function test results for subjects in the EIPAH group were within the reference range and FEV₁/FVC was the same in both groups indicating there was no evidence of airflow obstruction in the EIPAH subjects. The diffusing capacity for carbon monoxide was reduced in the EIPAH group when compared with the controls and the reference range.

### Exercise responses

There were no adverse events associated with the exercise tests. In the EIPAH subjects, dyspnoea or leg fatigue was the most common symptom limiting performance on both tests. In the controls, the most common factors limiting performance on the 6MWT and CPET were an inability to walk faster and leg fatigue respectively (Table 2).

### Physiological and symptomatic responses during 6MWT and CPET

Peak HR was similar in the CPET and 6MWT in the EIPAH group (\(P = 0.8\)), but higher in the CPET than the control group.

### Table 1

Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EIPAH</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women/men</td>
<td>15/2</td>
<td>19/1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 14 (35–81)</td>
<td>57 ± 13 (33–77)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 ± 0.8</td>
<td>1.65 ± 0.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67 ± 12</td>
<td>68 ± 9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 ± 5</td>
<td>25 ± 4</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>93 ± 11**</td>
<td>112 ± 11</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>97 ± 13**</td>
<td>116 ± 13</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>74 ± 18*</td>
<td>87 ± 13</td>
</tr>
<tr>
<td>WHO functional class II</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>WHO functional class III</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.01, **p < 0.001, EIPAH versus control. Data are mean ± SD (range) or number of subjects. BMI, body mass index; CO, cardiac output; DLCO, diffusing capacity for carbon monoxide; EIPAH, exercise-induced pulmonary arterial hypertension; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; kg, kilograms; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; \(\dot{S}pO_2\), oxygen saturation; WHO, World Health Organisation.

### Table 2

Comparison of heart rate and symptomatic responses to 6MWT and CPET

<table>
<thead>
<tr>
<th></th>
<th>EIPAH</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT</td>
<td>CPET</td>
<td>6MWT</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>133 ± 19</td>
<td>133 ± 15**</td>
</tr>
<tr>
<td>% predicted HR max</td>
<td>76 ± 13</td>
<td>77 ± 8**</td>
</tr>
<tr>
<td>Peak dyspnoea</td>
<td>3.4 ± 1.5*‡</td>
<td>4.8 ± 1.2</td>
</tr>
<tr>
<td>Peak RPE</td>
<td>4.6 ± 2*†</td>
<td>6.0 ± 2.4*</td>
</tr>
<tr>
<td>Limiting factor:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>9 (43%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Leg fatigue</td>
<td>8 (38%)</td>
<td>6 (35%)</td>
</tr>
<tr>
<td>Mechanics</td>
<td>2 (9.5%)</td>
<td>0</td>
</tr>
<tr>
<td>General fatigue</td>
<td>0</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (9.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, EIPAH versus control. †p < 0.05, ‡p < 0.01, §p < 0.001 6MWT versus CPET. ¶Mechanical constraints of walking limiting maximum distance. Data are mean ± SD (percentage of subjects). 6MWT, 6-min walk test; bpm, beats per minute; CPET, cardiopulmonary exercise test; EIPAH, exercise-induced pulmonary arterial hypertension; RPE, rate of perceived exertion.
6MWT in the control group \( (P < 0.05) \) (Table 2). Peak HR was higher in the control group than the EIPAH group during the CPET \( (P < 0.01) \) (Table 2). The peak dyspnoea score was higher in the CPET than the 6MWT in both groups \( (EIPAH P < 0.01, \text{control } P < 0.001) \) and higher in the EIPAH group than the control group at the end of the 6MWT \( (P < 0.05) \). There was no difference in the peak dyspnoea score between groups at the end of the CPET \( (P = 0.8) \).

**Exercise capacity**

6MWD, 6MWW and peak \( \dot{V}_{O_2} \) were all significantly reduced in the EIPAH group, compared with the controls \( (P < 0.01) \) (Table 3).

**Effect of test repetition on 6MWD**

Fifteen subjects (88%) in the EIPAH group and 16 (80%) subjects in the control group increased their 6MWD on the second test. There was a significant difference in 6MWD between test 1 and test 2 in both the EIPAH \( (556 \pm 86 \text{ m vs } 574 \pm 85 \text{ m}, P < 0.001) \) and control \( (655 \pm 66 \text{ m vs } 668 \pm 77 \text{ m}, P < 0.01) \) groups. Test repetition was associated with marked individual variation in the magnitude of change in 6MWD in the EIPAH \( (+18 \pm 15 \text{ m}, \text{range } -16 \text{ to } +39 \text{ m}, (3 \pm 3\%)) \) and control \( (+9 \pm 11 \text{ m}, \text{range } -10 \text{ to } +29 \text{ m}, (1 \pm 2\%)) \) groups. There was no difference in the magnitude of change in 6MWD on the second test between the EIPAH and control groups \( (P = 0.08) \). The coefficient of repeatability for the EIPAH and control groups was 31 m and 22 m respectively. The variability between 6MWTs 1 and 2 is demonstrated in Figure 1.

**Relationship between 6MWT results, peak \( \dot{V}_{O_2} \) and peak CO**

Figure 2 illustrates the relationships between 6MWW and 6MWD with peak \( \dot{V}_{O_2} \) in subjects with EIPAH. There was a strong correlation between 6MWW and peak \( \dot{V}_{O_2} \) \( (L/\text{min}) \) for subjects with EIPAH \( (r = 0.86, P < 0.001) \) and a moderate correlation for the control group \( (r = 0.74, P < 0.001) \). Peak \( \dot{V}_{O_2} \) accounted for 73% and 55% of the

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**Table 3 6MWT and CPET results**

<table>
<thead>
<tr>
<th>6MWT</th>
<th>EIPAH</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD, m (% predicted)***</td>
<td>575 ± 86 (88 ± 11)</td>
<td>669 ± 76 (102 ± 9)</td>
</tr>
<tr>
<td>6MWW, kg.km</td>
<td>39 ± 11**</td>
<td>45 ± 7</td>
</tr>
<tr>
<td>Peak ( \dot{V}_{O_2} ), L/min (% predicted)</td>
<td>1.2 ± 0.4 [64 ± 18]**</td>
<td>1.7 ± 0.5 [90 ± 19]</td>
</tr>
<tr>
<td>Peak ( \dot{V}_{O_2} ), mL/min.kg(^{-1})</td>
<td>18 ± 4**</td>
<td>25 ± 7</td>
</tr>
<tr>
<td>Initial workload, W</td>
<td>18 ± 13 (0–30)</td>
<td>43 ± 21 [15–75]</td>
</tr>
<tr>
<td>Maximum workload, W</td>
<td>62 ± 20 (30–90)</td>
<td>104 ± 39 [60–195]</td>
</tr>
<tr>
<td>( \dot{V}<em>{O_2}/\dot{V}</em>{CO_2} ) at AT</td>
<td>41 ± 7.3***</td>
<td>31 ± 2.9</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>1.05 ± 0.06*</td>
<td>1.11 ± 0.06</td>
</tr>
</tbody>
</table>

*\( P < 0.05, **P < 0.01, ***P < 0.001, \) EIPAH versus control. Data are mean ± SD (per cent predicted, or range). 6MWD, 6-min walk distance; 6MWT, 6-min walk test; 6MWW, 6-min walk work; CPET, cardiopulmonary exercise test; EIPAH, exercise-induced pulmonary arterial hypertension; kg.km, kilogram times kilometre; peak \( \dot{V}_{O_2} \), peak oxygen consumption; \( \dot{V}_{O_2}/\dot{V}_{CO_2} \) at AT, ventilatory equivalent for carbon dioxide at the anaerobic threshold.
variance in 6MWW in the EIPAH (Fig. 2) and control groups respectively. There were moderate correlations between 6MWD and peak $V_O_2$ in the EIPAH ($r = 0.72, P < 0.01$) and the control groups ($r = 0.61, P < 0.01$).

In the EIPAH group, there was a significant correlation between 6MWD and peak exercise CO ($r = 0.59, P < 0.05$), but not between 6MWW and peak exercise CO ($r = 0.46, P = 0.07$). A significant correlation was evident between peak $V_O_2$ (L/min) and CO ($r = 0.55, P < 0.05$). Peak exercise CO accounted for 21% of the variance in 6MWW, 36% of the variance in 6MWD and 30% of the variance in $V_O_2$ (L/min).

**Discussion**

The principal findings from this study are that 6MWD and 6MWW, derived from an encouraged 6MWT, identify reduced exercise capacity and correlate significantly with peak $V_O_2$ in subjects with EIPAH. These findings suggest that the encouraged 6MWT is a valid test of exercise capacity in this cohort. While 6MWD, 6MWW and peak $V_O_2$ all correlated with peak exercise CO, only a small proportion of the impairment in exercise capacity was explained by peak exercise CO. This finding suggests that factors other than cardiac output during an acute bout of exercise contribute to exercise limitation in EIPAH.

The significant difference in 6MWD observed between the EIPAH and control groups demonstrates the capacity of the encouraged 6MWT to detect reduced functional exercise capacity in subjects with EIPAH who have mild-moderate functional limitation (WHO FC II and III). Furthermore, the moderate (6MWD) to strong (6MWW) correlations with peak $V_O_2$ suggests that the 6MWT is a valid method of estimating aerobic capacity in the absence of a CPET in EIPAH, although the wide prediction intervals highlight that the relationship was not strong in some individuals, a finding that is consistent with other studies. This result demonstrates that the 6MWT cannot be used to accurately predict peak $V_O_2$ in an individual with EIPAH.

The similar peak HR elicited during the 6MWT and CPET in subjects with EIPAH suggest that the encouraged 6MWT represents high intensity exercise for this cohort. This is consistent with reports in other patient populations in which the encouraged 6MWT and CPET have been shown to elicit similar HR and peak $V_O_2$ responses. This finding is in contrast to a report that found a significantly higher peak HR during a CPET (employing cycle ergometry) compared with an unencouraged 6MWT in PAH. This disparity is likely to reflect the difference in 6MWT protocol between studies. An encouraged 6MWT has been shown to elicit a greater physical effort than an unencouraged 6MWT in COPD and CHF. Our findings suggest that an encouraged 6MWT, in subjects with EIPAH in WHO functional classes II and III, is not subject to a ceiling effect and reflects physiological limitation and aerobic capacity in this cohort.

In contrast to the subjects with EIPAH, the control subjects had lower peak HR and dyspnoea scores during...
the 6MWT than the CPET and, at best, moderate correlations between peak $V_{O2}$, 6MWD and 6MWW, suggesting that a ceiling effect limited the capacity of the 6MWT to accurately estimate aerobic capacity in the healthy individuals.

Subjects from both groups reported higher dyspnoea scores during the CPET than the 6MWT. In the EIPAH group, in whom the maximum HR in each test were similar, this might be due to the higher levels of local muscle acidosis,26 serum lactate27 and consequently $V_e$28,27,28 that occurs during a cycling test compared with a walking test, contributing to increased ventilatory work and an increased sensation of dyspnoea.29

In previous studies of subjects with pulmonary vascular disease, reduced CO on exercise has been associated with impaired oxygen uptake kinetics30 and reduced peak $V_{O2}$.1,31 In our study, reduced CO during an acute bout of exercise appeared to have a limited role in the exercise limitation identified in subjects with EIPAH. There is increasing evidence that PAH is a systemic condition32 with features similar to CHF and COPD. Inflammation, increased sympathetic nerve activity, a heightened ergoreflex response, skeletal muscle dysfunction and systemic endothelial dysfunction contribute to exercise limitation in CHF13–36 and COPD.15,17–39 These systemic abnormalities, with the exception of ergoreflex upregulation, have also been described in PAH12,40–42 and are potential contributors to exertional symptoms and exercise limitation in EIPAH. This is an important area for future research.

Previous studies in cohorts with chronic lung conditions,19,43–45 cardiovascular disease25 and healthy adults46–48 have reported that test repetition (familiarization to the 6MWT protocol) results in a small but significant increase in 6MWD on the second test. Our study extends this observation to subjects with EIPAH. While the mean increase in 6MWD with test repetition was small there was a large variability among individuals, with the magnitude of increase being as great as 39 m. The coefficient of repeatability, of 31 m, for 6MWD in our group, in whom the maximum HR in each test were similar, this might be due to the higher levels of local muscle acidosis,26 serum lactate27 and consequently $V_e$28,27,28 that occurs during a cycling test compared with a walking test, contributing to increased ventilatory work and an increased sensation of dyspnoea.29

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Limitations of the study

The sample size of this study was relatively small and further prospective studies are required to confirm these findings. The high proportion of women in our study reflects the higher proportion of women to men in PAH populations;49 however, we cannot be certain that the results of this study translate to male subjects with EIPAH. Measurement of gas exchange (peak $V_{O2}$ and minute ventilation) during the 6MWT would have strengthened this study and has previously been shown to be feasible and useful in PAH.24 The respiratory exchange ratio of 1.05 ± 0.06 observed in the EIPAH group suggests that a maximum $V_{O2}$ was not achieved in some subjects, most likely because of early test termination due to intolerable symptoms.

Conclusions

An encouraged 6MWT identified reduced exercise capacity and provided a valid estimate of peak $V_{O2}$ in subjects with EIPAH, although wide prediction intervals demonstrated that peak $V_{O2}$ cannot be accurately predicted from a 6MWT in an individual with EIPAH. Peak exercise cardiac output in EIPAH accounted for a small proportion of the reduction in exercise capacity, suggesting that factors other than cardiac output on an acute bout of exercise are likely to contribute significantly to exercise limitation in this population.

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Combined catheter thrombus fragmentation and fibrinolysis for acute pulmonary embolism

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Key words
pulmonary embolism, catheterization, urokinase, warfarin, right ventricular dysfunction.

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Abstract

Aims: The aim of this study is to evaluate the effectiveness and safety of combined catheter thrombus fragmentation and fibrinolysis for acute pulmonary embolism (PE).

Methods: Forty-six patients (19 men and 27 women, average age 52.3 ± 13.4 years) with acute PE and right ventricular dysfunction were treated by mechanical thrombus fragmentation with a percutaneous transluminal coronary angioplasty guide catheter. Urokinase was injected into the culprit pulmonary artery after catheter thrombus fragmentation in all patients.

Result: Clinical success was achieved in all patients. After the treatment, the average pulmonary artery pressure was decreased from 57.2 ± 6.2 to 36.3 ± 4.1 mmHg (P < 0.01). The oxygen saturation rate was raised from 81.4 ± 4.3% to 97.0 ± 2.0% (P < 0.01), and the right ventricular function was improved. There was no in-hospital mortality and there were no major complications, such as haemorrhage. Patients were treated with warfarin for 6 months with no signs of PE recurrence during the follow up.

Conclusion: In PE patients with right ventricular dysfunction and unstable haemodynamics, combined catheter thrombus fragmentation and thrombolysis appears to be a useful therapeutic strategy. In PE patients with right ventricular dysfunction and stable haemodynamics, randomized trials are still required to show that combination of catheter-directed thrombus fragmentation and thrombolysis is superior to standard anticoagulation.

Introduction

Pulmonary embolism (PE) is a life-threatening condition with a high mortality rate because of acute right ventricular failure and cardiogenic shock.1 The major treatment options include anticoagulation, systemic thrombolysis.
and surgical thrombectomy.\textsuperscript{1} Anticoagulant therapy is the current standard of care for the patients with uncomplicated PE.\textsuperscript{2} Thrombolytic therapy followed by anticoagulation is the treatment of choice for patients with massive PE associated with shock or circulatory compromise because of the high mortality rate in patients receiving anticoagulation alone.\textsuperscript{2} The role of thrombolytic therapy or other ‘invasive’ therapy in patients with right ventricular dysfunction who are haemodynamically stable remains unclear. This is due to the lack of conclusive evidence from randomized studies that more aggressive therapy results in improved clinical outcomes than standard anticoagulation.\textsuperscript{3,4} If patients are contraindicated to thrombolysis because of an increased bleeding risk, surgical embolectomy can be used to reverse right ventricular failure.\textsuperscript{5} Catheter-directed thrombectomy or thrombus fragmentation techniques have also been introduced to treat patients with massive PE.\textsuperscript{5,6} These catheter techniques appear to be particularly useful if surgical thrombectomy is not available, or the patient has contraindications to surgery.\textsuperscript{7} Some recent studies have shown that catheter thrombectomy or thrombus fragmentation has a high clinical success rate.\textsuperscript{7–9} The catheter-based treatment for PE is constantly evolving, and a recent report showed that combination of catheter thrombectomy and thrombolysis with monteplase was safe and effective in treating acute massive PE.\textsuperscript{10} The primary purpose of this study is to describe our experience in catheter fragmentation and aspiration combined with thrombolysis to treat patients with massive PE and right ventricular dysfunction.

\textbf{Patients and methods}

\textbf{Patient selection}

This prospective study was approved by the institution review board of Liaocheng People’s Hospital. Written informed consent was obtained from all participants. Between August 2003 and June 2007, 46 patients with massive PE and right ventricular dysfunction were recruited to this study. There were 19 men and 27 women, with an average age of 52.3 ± 13.4 years (Table 1). With the five female patients, the PE occurred shortly after giving birth to a child.

Massive PE was defined as the presence of cardiogenic shock or hypotension. Cardiogenic shock was defined as systemic systolic blood pressure <90 mmHg, or a pressure drop ≥40 mmHg for >15 min not caused by arrhythmia, hypovolaemia or sepsis.\textsuperscript{8} This diagnosis was confirmed by pulmonary angiography during the procedure, showing a compromise of a main pulmonary artery or of two or more lobar arteries (Fig. 1).

The diagnosis of right ventricular dysfunction was based on one or more of the following echocardiographical findings\textsuperscript{9,11}: (i) a diastolic diameter of the right ventricle >30 mm; (ii) a right ventricular diastolic diameter/ left ventricular diastolic diameter ratio >1; (iii) paradoxical septal movement, hypokinesia of the right ventricular free wall; (iv) loss of inspiratory collapse of the inferior vena cava (IVC) and (v) tricuspid regurgitation at a velocity >2.8 m/s.

\textbf{Catherization procedures}

Under local anaesthesia, a 6-French pigtail catheter was inserted into the right femoral vein through an 8-French sheath. After the procedure, 8000 units of heparin were injected intravenously through the venous sheath. The pigtail catheter was advanced to the pulmonary artery, and angiograms were performed for both left and the right pulmonary artery. Pulmonary arterial pressure was also measured with this catheter.

After the thrombus was located, a percutaneous transluminal coronary angioplasty (PTCA) guide catheter was advanced to the area of the obstruction. The distal end of
the catheter was placed in the site of the thrombus, and manual aspiration was attempted with a 50 mL syringe attached to the operator end of the PTCA guide catheter. If the thrombus was hard and could not be aspirated in the first attempt, the PTCA guide catheter was rotated to allow the distal end of the catheter to fragment the thrombus. The fragmented blood clots were manually aspirated with the large syringe. For smaller thrombus that lodged distal to the lobar branches of the pulmonary artery and could not be reached by the angioplasty catheter, a 0.035-inch guidewire was used to fragment the thrombus.

After the catheter fragmentation and manual aspiration of thrombus, urokinase (500 000–750 000 units) was injected into the central pulmonary artery. This dose was approximately half of the recommended intravenous dose used for PE. Angiograms were repeated and pulmonary arterial pressure was measured approximately 20 min after the final angiogram.

The procedure was considered successful when the occluded pulmonary artery was re-opened, together with improvement in arterial oxygen saturation rate as well as an increase in systolic blood pressure to more than 90 mmHg, or an improvement of more than 10 mmHg.

The venous sheath was removed 4 h after the completion of the procedure. This was immediately followed by warfarin (commencing dose 3 mg, daily) for long-term PE prevention. As warfarin has a delayed onset of action, enoxaparin (5000 units) was subcutaneously administered every 12 h for 3–4 days until the international normalization ratio (INR) from warfarin reached 2–3, when the low molecular weight heparin was ceased.

**Statistical analysis**

Data were presented as means ± SD. Differences in numerical data were analysed by a Student’s t-test. Categorical data were analysed with a chi-squared test. A P-value of < 0.05 was considered to be statistically significant. All data analysis was performed with a SPSS Statistical Package (SPSS 11.0, SPSS Inc., Chicago, IL, USA).

**Results**

All patients had echocardiographical evidence of right ventricular hypokinesia and dilatation (Table 1). Cardiogenic shock was present in 11 patients before the pulmonary catheterization, whereas the remainder had a drop in systolic blood pressure of more than 10 mmHg on admission (Table 1). The location of the obstructed pulmonary arteries in the 46 patients is summarized in Table 1, with the right inferior pulmonary artery being the most commonly affected. In 63% of the patients, two or more of the pulmonary arteries were obstructed (Table 1).

Pulmonary angiography was performed before and after the combined urokinase and catheter intervention. All obstructed pulmonary arteries were re-opened by the catheterization and thrombolysis treatment (Fig. 1). Clinical success was also achieved in all patients. Aspiration of the pulmonary thrombus and urokinase injection was first attempted and successful in 23 (50%) patients, as evidenced by obtaining clots and re-opening of the obstructed pulmonary artery on angiogram following the aspiration (Fig. 1). In the other 23 patients, after unsuccessful aspiration, catheter fragmentation of the thrombus was successfully attempted, which was followed by thrombus aspiration and urokinase injection.

Twenty minutes after the re-opening of these arteries, the average pulmonary pressure was reduced from 57.2 ± 6.2 to 36.3 ± 4.1 mmHg (P < 0.01), whereas the arterial oxygen saturation was increased from 81.4 ± 4.3% to 97.0 ± 2.0% (P < 0.01). A significant increase of
systolic blood pressure was observed (76.4 ± 10.1 mmHg vs 87.9 ± 9.6 mmHg, P < 0.001).

There were no major complications, such as major bleeding complications, perforation of the pulmonary artery, perforation of the right ventricle or tamponade. No myocardial infarctions or sudden deaths were documented during the hospitalization phase.

Warfarin was continued after hospital discharge. All patients were followed up for at least 6 months at our hospital clinics and showed no symptoms or signs of PE.

Discussion
The major findings of this study are: (i) it is feasible to use conventional PTCA guide catheter for thrombus fragmentation and aspiration; (ii) the combined catheter-based treatment and thrombolysis with urokinase are safe and effective in treating acute PE.

All patients in the present study had clinical or echocardiographical evidence of right ventricular dysfunction. Eleven patients also had cardiogenic shock, and the remaining patients had a reduction in systolic blood pressure. The reported mortality rate among the patients with right ventricular dysfunction and unstable haemodynamics is high, ranging from 25% to 65%.12,13 The mortality rate in patients with right ventricular dysfunction, but relatively stable blood pressure is reported to be 5–10%.12,13 Although thrombolytic therapy has been recommended for massive PE by several clinical guidelines,13,14 the absolute clinical benefit with thrombolysis is still uncertain.15 Catheter-directed thrombus fragmentation in these patients is able to rapidly re-open the obstructed pulmonary arteries and to restore pulmonary perfusion.7–9 This mechanical treatment is associated with a rapid reduction in pulmonary pressure and increase in systolic blood pressure and oxygenation saturate rate.5–9 It is also associated with a low-in-hospital mortality rate.7–9

Although catheter thrombus fragmentation can alleviate main pulmonary obstruction, the fragmented clots may migrate to the distal branches of the pulmonary arteries and cause distal embolization, increasing the mean pulmonary arterial pressure.7 In the present study, a relatively large PTCA guide catheter was used, enabling manual aspiration of the thrombus before its fragmentation. In addition, urokinase was locally injected to help to dissolve any remaining blood clots in the arterial system. The combination of catheter thrombus fragmentation and thrombolysis is expected to minimize the risk of embolization in the distal arterial branches. This therapeutic approach is clearly associated with a short- and medium-term clinical benefit, manifested as rapid improvement in haemodynamic parameters and right ventricular function following the treatment, and symptom free during 6-month follow up.

The limitation of this study is that the effect of catheter thrombus fragmentation and aspiration was not compared with the combined catheter treatment and thrombolysis. A randomized and controlled trial might be required to clarify this issue. We did not routinely perform pulmonary angiogram before urokinase injection. Therefore, the additional benefit of the thrombolytic therapy to the catheter intervention is uncertain, although the present study did show that the combination use of catheter aspiration/fragmentation and urokinase is effective. Moreover, the combined use of catheter invention and urokinase is not associated with major bleeding complications, such as stroke or haematoma at the site of sheath insertion. This might be related to the relative small urokinase dose, but it might be also due to the smaller study sample size.

Conclusion
The combination of catheter-directed thrombus fragmentation and thrombolysis is safe and effective in treating PE patients with right ventricular dysfunction and unstable haemodynamics. In selected patients, this therapeutic approach is associated with a rapid improvement in systemic blood pressure and oxygen saturation rate. With continued administration of warfarin, the clinical benefits can be maintained for at least 6 months. In PE patients with right ventricular dysfunction but stable haemodynamics, randomized trials are required to show that combination of catheter-directed thrombus fragmentation and thrombolysis is superior to standard anticoagulation.

References
2 Dalen J.E., Alpert J.S., Hirsch J. Thrombolytic therapy for pulmonary embolism: is it effective? Is it safe?
Hypertension is an independent predictor of mean platelet volume in patients with acute ischaemic stroke

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mean platelet volume, hypertension, acute ischaemic stroke.

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Abstract

Introduction: Mean platelet volume (MPV) was shown to be significantly increased in patients with acute ischaemic stroke, especially in non-lacunar strokes. Moreover, some studies concluded that increased MPV is related to poor functional outcome after ischaemic stroke, although this association is still controversial. However, the determinants of MPV in patients with acute ischaemic stroke have never been investigated.

Subjects and methods: We recorded the main demographic, clinical and laboratory data of consecutive patients with acute (admitted within 24 h after stroke onset) ischaemic stroke admitted in our Neurology Service between January 2003 and December 2008. MPV was generated at admission by the Sysmex XE-2100 automated cell counter (Sysmex Corporation, Kobe, Japan) from ethylenediaminetetraacetic acid blood samples stored at room temperature until measurement. The association of these parameters with MPV was investigated in univariate and multivariate analysis.

Results: A total of 636 patients was included in our study. The median MPV was 10.4 ± 0.82 fL. In univariate analysis, glucose (β = 0.03, P = 0.05), serum creatinine (β = 0.002, P = 0.02), haemoglobin (β = 0.009, P < 0.001), platelet count (β = -0.002, P < 0.001) and history of arterial hypertension (β = 0.21, P = 0.005) were found to be significantly associated with MPV. In multivariate robust regression analysis, only hypertension and platelet count remained as independent determinants of MPV.

Conclusions: In patients with acute ischaemic stroke, platelet count and history of hypertension are the only determinants of MPV.
Introduction

Mean platelet volume (MPV) is a platelet index which is readily generated by automated cell counters and aids in the differential diagnosis of thrombocytopenic disorders.\(^1\) During ischaemia, platelets tend to increase in size, become more reactive and produce more thromboxane A2.\(^2\) In the recent years, MPV has been associated with ischaemic complications, such as myocardial infarction and ischaemic stroke.\(^2\) MPV has been shown to be significantly increased in patients with acute ischaemic stroke compared with controls, especially in non-lacunar strokes.\(^3,4\) Moreover, some studies concluded that increased MPV is related to poor functional outcome after ischaemic stroke.\(^4,6\) although this association is still controversial.\(^7,8\) The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial found that patients with elevated MPV have higher risk of stroke recurrence.\(^9\) Recently, it has been shown that increased MPV is an independent predictor of risk of stroke recurrence.\(^9\) Against Recurrent Stroke Study (PROGRESS) trial found that patients with elevated MPV have higher risk of stroke recurrence.\(^9\) Recently, it has been shown that increased MPV is an independent predictor of risk of stroke recurrence.\(^9\) The level of significance was set at 95% (\(P = 0.05\)).

The aim of the present study is to identify the predictors of MPV in acute ischaemic stroke patients analysing a wide range of demographic, laboratory and clinical parameters.

Subjects and methods

We recorded the main demographic (age, gender), laboratory (haemoglobin, red cell distribution width, white cell count, platelet count, MPV, serum glucose, creatinine, cholesterol) and clinical (skin temperature, heart rate, blood pressure, National Institutes of Health Stroke Scale (NIHSS), stroke subtype) data of all consecutive acute stroke patients admitted in our Neurology Service between 1 January 2003 and 31 December 2008. NIHSS was recorded by NIHSS certified examiners. We also recorded patients’ medical history, including prehospital Rankin, previous treatment and brain CT (non-contrast CT and CT-angiography) findings. Exclusion criteria included transient ischaemic attack (TIA), intracerebral haemorrhage, subarachnoidal haemorrhage, cerebral sinus venous thrombosis and late admission (\(>24\) h after stroke onset). MPV was generated at admission by the Sysmex XE-2100 automated cell counter (Sysmex Corporation, Kobe, Japan) from ethylenediaminetetraacetic acid blood samples stored at room temperature until measurement.

The JNC-7 definitions were used for the diagnosis of arterial hypertension.\(^10\) Diabetes mellitus was defined according to the American Diabetes Association criteria.\(^11\) Any associated past medical history, such as strokes, TIsAs or amauroses, as well as prior medication, was also recorded. Silent strokes and leucoaraiosis (defined as a Blenow grade of \(\geq 1\)) were recorded. On acute arterial imaging (mostly CT-angiography), arterial occlusion, stenosis \(\geq 50\%\) and/or signs of acute dissection within the ischaemic territory were considered significant arterial pathology. For the classification of stroke, we used the Trial of Org 10172 in Acute Stroke Treatment (TOAST) definitions,\(^12\) adding dissections, patent foramen ovale in patients without other significant risk factors, and combining atherosclerotic causes of TOAST with ‘likely atherosclerotic causes’ of the Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Tetrobron in Patients with a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM) study.\(^13\)

Statistical analysis

Continuous parameters with Gaussian distribution are reported as mean \(\pm\) standard deviation (SD) and those without normal distribution are reported as median \(\pm\) SD. The association of all parameters presented in Table 1 with MPV was tested in univariate analysis. The parameters that were found to be of statistical significance were included in multivariate (robust regression) analysis in order to identify which ones were independently associated with MPV. The level of significance was set at 95% (\(P = 0.05\)).

Results

Our study included 636 patients with acute ischaemic stroke admitted within 24 h after stroke onset. The general characteristics of our sample, including acute arterial imaging (CT-angiography, Doppler or MR-angiography) findings and stroke classification, are summarized in Table 1. A previous stroke or TIA was reported in 26.4% of patients. The most frequent subtype was cardioembolic strokes and 86.8% were non-lacunar. The median MPV was 10.4 \(\pm\) 0.82 fL.

In univariate analysis, the only variables found to be significant predictors of MPV were glucose (\(\beta = 0.03, P = 0.05\)), serum creatinine (\(\beta = 0.002, P = 0.02\)), haemoglobin...
Hypertension predicts MPV in stroke patients

(β = 0.009, P < 0.001), platelet count (β = -0.002, P < 0.001) and history of arterial hypertension (β = 0.21, P = 0.005). When all these parameters were included in multivariate robust regression analysis, only platelet count (β = –0.003, P < 0.001) and history of hypertension (β = 0.26, P < 0.01) remained as independent determinants of MPV.

Discussion

The present study is the first to investigate the determinants of MPV in patients with acute ischaemic stroke, analysing a wide range of demographic, laboratory and clinical data. Among them, MPV was found to be independently associated only with platelet count and hypertension.

The inverse relation between platelet count and MPV, which was shown in our study, illustrates the physiology of platelet production. The human organism tends to keep constant the platelet mass, which is the mathematical product of platelet count and platelet volume. As a result, reductions of the platelet count are compensated by increase of MPV. Several studies reported decreased platelet count in acute ischaemic stroke, as well as in other ischaemic complications such as acute coronary events.

We showed that hypertensive disease is a significant determinant of MPV in ischaemic stroke patients. This conclusion is in line with previous studies which showed that MPV is increased in hypertensive patients. Interestingly, platelet count was not compensatory decreased for the MPV increase, and as a result platelet mass was also increased. Perhaps, this hypertension-induced increase of platelet mass could play a role in the pathogenesis of hypertensive complications. Indeed, MPV was shown to be associated with left ventricular mass and interventricular septum thickness, target organ damage, hypertensive retinopathy in hypertensive patients. Similarly, MPV was associated with increasing severity of the hypertensive disease. The association between MPV and hypertensive complications supports the use of MPV as a surrogate marker in trials of antihypertensive drugs.

Serum creatinine and haemoglobin were found to be significant predictors in univariate analysis but not in multivariate. The univariate effect of these two parameters may just represent the impact of hypertensive

---

**Table 1** General characteristics of our study population

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>73 ± 15.8</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>269 (42.3%)</td>
</tr>
<tr>
<td>Laboratory measurements</td>
<td></td>
</tr>
<tr>
<td>MPV, fL</td>
<td>10.4 ± 0.82</td>
</tr>
<tr>
<td>Platelet count, x10^12/L</td>
<td>22 ± 107</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>140 ± 55.2</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>13.6 ± 1.4</td>
</tr>
<tr>
<td>White blood cell count (x10^12/L)</td>
<td>7.8 ± 4.6</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>6.5 ± 4.2</td>
</tr>
<tr>
<td>Serum creatinine (mmol/L)</td>
<td>81.5 ± 58.7</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.1 ± 3.1</td>
</tr>
<tr>
<td>Vital signs – clinical examination</td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>36.4 ± 14.1</td>
</tr>
<tr>
<td>Heart rate (min)</td>
<td>77 ± 34.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>157 ± 65.1</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>89 ± 37.1</td>
</tr>
<tr>
<td>NIHSS ≤ 4</td>
<td>266 (41.8%)</td>
</tr>
<tr>
<td>Medical history – previous treatment</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>414 (65.1)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>154 (24.2)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>125 (19.7)</td>
</tr>
<tr>
<td>Valvulopathy, n (%)</td>
<td>22 (3.5)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>110 (17.3)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>142 (22.5)</td>
</tr>
<tr>
<td>Previous stroke(s)/TIAs, n (%)</td>
<td>168 (26.4)</td>
</tr>
<tr>
<td>Antiplatelet treatment, n (%)</td>
<td>250 (39.3)</td>
</tr>
<tr>
<td>Antihypertensives, n (%)</td>
<td>342 (53.7)</td>
</tr>
<tr>
<td>Oral hypoglycaemic agents, n (%)</td>
<td>59 (9.3)</td>
</tr>
<tr>
<td>Insulin, n (%)</td>
<td>18 (2.8)</td>
</tr>
<tr>
<td>Anticoagulant, n (%)</td>
<td>55 (8.6)</td>
</tr>
<tr>
<td>Lipid-lowering drugs, n (%)</td>
<td>155 (24.4)</td>
</tr>
<tr>
<td>Prehospital Rankin = 0</td>
<td>373 (58.6)</td>
</tr>
<tr>
<td>Previous ocular ischaemia</td>
<td>9 (1.4)</td>
</tr>
</tbody>
</table>

Findings in imaging studies

| Silent lesions in brain CT, n (%) | 178 (28.0) |
| Early ischaemic changes in brain CT, n (%) | 191 (30.0) |
| Leukoaraiosis, n (%) | 93 (14.6) |
| Significant pathology in arterial imaging, n (%) | 289 (45.4) |

Stroke subtypes, n (%) | 166 (26.1) |

Atherosclerotic, n (%) | 174 (27.3) |

Dissection, n (%) | 24 (3.8) |

Lacunar/microangiopathy, n (%) | 84 (13.2) |

Other, n (%) | 23 (3.6) |

Unknown, n (%) | 63 (9.9) |

Patent foramen ovale, n (%) | 25 (3.9) |

Continuous variables are reported as median ± standard deviation. Categorical variables are reported as absolute number (n). CT, computed tomography; MPV, mean platelet volume; NIHSS, National Institutes of Health Stroke Scale; RDW, red-cell distribution width, TIA, transient ischaemic attack.
complications on MPV (chronic kidney disease and the subsequent anaemia) and perhaps, this is the reason that their effect was not significant in multivariate analysis when adjusted for hypertension. We also found no association between previous hypolipidaemic treatment and MPV. On the contrary, Coban et al. recently reported a significant decrease in MPV after 12 weeks of rosuvastatin treatment. This inconsistency between the two studies may be explained by the fact that in our analysis, we studied hypolipidaemic drugs as a single category and did not differentiate between different categories. The same explanation may account for the lack of any significant association between previous antihypertensive treatment and MPV in the present study. Finally, our results also showed that stroke subtype is not associated with MPV levels and did not confirm previous studies which concluded that MPV levels in ischaemic stroke patients were related to stroke subtype, being higher in cortical strokes compared with lacunar.

The main limitation of our study is the lack of data for other parameters like electrocardiogram ischaemic changes and proportion of body fat, which were shown to be associated with MPV in unselected elderly population. Another limitation is that we did not analyse separately the effect of different antihypertensives, lipid-lowering drugs, antiplatelets and oral hypoglycaemic agents on MPV.

Conclusion
This is the first study to study the determinants of MPV in patients with acute ischaemic stroke. Platelet count and hypertension were identified as the only predictors of MPV. Further studies are warranted to investigate whether antihypertensive treatment can decrease MPV and whether such an effect constitutes an independent protective mechanism against cardiovascular complications of hypertension.

Acknowledgements
We would like to thank the patients and their families, the nursing and medical staff of the stroke unit (Neurology Service), the intensive care unit, and the emergency service of CHUV.

References

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BRIEF COMMUNICATION

Metastatic parathyroid carcinoma initially misdiagnosed as parathyroid adenoma: the role of parafibromin in increasing diagnostic accuracy

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Key words
parathyroid carcinoma, parathyroid adenoma, parafibromin, HRPT2 (CDC73).

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Abstract
Parathyroid carcinoma, although a rare cause of primary hyperparathyroidism, carries a significant morbidity and mortality from severe symptomatic hypercalcaemia and related complications. We report a case where the diagnosis was not considered from the outset and review the current clinical and histopathological markers available to assist in the diagnosis of parathyroid carcinoma.

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A 42-year-old woman presented in 2007 with symptomatic hypercalcaemia. She initially presented 10 years earlier to another service with general malaise associated with severe hypercalcaemia (serum Ca\(^{2+}\) 4.21 mmol/L (reference range (RR): 2.11–2.55 mmol/L)) and a markedly elevated parathyroid hormone (PTH) level of >1400 pmol/L (RR: 1.6–6.2 pmol/L). She had mild renal impairment with a creatinine clearance of 56 mL/min per 1.73 m\(^2\) and bilateral nephrocalcinosis. There was no history of fracture, but she had an elevated alkaline phosphatase of 1372 U/L (RR: 40–100 U/L), widespread subperiosteal bone resorption on X-ray of the hands and generalized increased uptake on isotope bone scan consistent with metabolic bone disease. A diagnosis of primary hyperparathyroidism was made. There was no family history of hypercalcaemia or primary hyperparathyroidism. A neck exploration and a right inferior parathyroidectomy were performed. The frozen section and final histology were reported as being consistent with a parathyroid adenoma (weight 5 g). Notably, her postoperative Ca\(^{2+}\) remained elevated at 2.84 mmol/L with a markedly elevated PTH level of 280 pmol/L.

She was lost to follow up and re-presented in July 2007 with low back pain. Her serum Ca\(^{2+}\) was 4.0 mmol/L and PTH level was 90 pmol/L. Serum Ca\(^{2+}\) remained elevated despite intravenous fluid and pamidronate. The previously normal chest X-ray now revealed a well-circumscribed right upper lobe mass, which was confirmed on computed tomography scan. She had a 10+ pack-years smoking history and reported unintentional weight loss of 10 kg over the preceding months. A Technetium 99m-sestamibi scan revealed normal uptake in the neck but increased uptake in the lung mass.

A right upper lobectomy revealed a well-circumscribed 2.9-cm tumour. The lung mass was confirmed to be metastatic parathyroid carcinoma with positive immunohistochemistry for PTH and absent parafibromin staining (Fig. 1). Transient hypocalcaemia and suppression of PTH were observed postoperatively. After 2 years of follow up, her serum Ca\(^{2+}\) and PTH levels have remained normal. Parathyroid carcinoma is frequently associated with

![Figure 1](image1.jpg)

(A) Normal parathyroid tissue demonstrated diffuse positive nuclear staining for parafibromin (external positive control ×40). (B) Bronchial epithelium (arrows) demonstrated positive nuclear staining for parafibromin (internal positive control ×40). (C) High-power view (×400) of normal parathyroid cells with positive nuclear parafibromin staining. (D) High-power view (×400) of the lung mass with negative staining for parafibromin.
HRPT2 mutation, and rarely with MEN1 mutation; however, germline testing for both HRPT2 and MEN1 mutation was negative in this patient. On review of slides from primary surgery, vascular space invasion, trabecular architecture, a high mitotic rate and fibrous bands were observed. Although the other features are less specific, the presence of vascular space invasion alone would have been sufficient for the diagnosis of parathyroid carcinoma based on the current World Health Organisation criteria.1

This case highlighted three major points: (i) despite its rarity, parathyroid carcinoma should always be considered in primary hyperparathyroidism, particularly in the presence of atypical clinical and biochemical features; (ii) parafibromin immunohistochemistry and mutational analysis of HRPT2 are important adjuncts to the diagnosis of parathyroid carcinoma based on the current World Health Organisation criteria.1

Discussion

Parathyroid carcinoma is rare and accounts for <1% of all cases of primary hyperparathyroidism in most series.2 Although it can be difficult to differentiate from benign conditions, including parathyroid adenoma, hyperplasia and atypical adenoma, it is important to consider this diagnosis from the outset as improved outcome, including survival, can be achieved with en bloc resection at initial operation.1,3 Several series have attempted to identify factors, which help to distinguish parathyroid carcinoma from its benign counterpart.1,4 A summary of these features is outlined in Table 1. Although not pathognomonic, the presence of severe symptoms with end-organ involvement, markedly elevated Ca2+ and PTH levels and increased tumour weight (>1.9 g) should raise the suspicion of parathyroid carcinoma.6 The patient described here had severe symptomatic hypercalcaemia with renal and skeletal complications in conjunction with a markedly elevated PTH level (>1400 pmol/L) at initial presentation. These features were highly suggestive of a malignant process. The lack of hypocalcaemia/eucalcaemia and persistently raised PTH level after initial surgery also suggested an ongoing PTH-dependent hypercalcaemic process secondary to incomplete tumour resection or the presence of metastatic disease.

Conventional histopathological analysis is a poor predictor of parathyroid carcinoma. For example in one multinational study less than 50% of cases that actually metastasized were correctly diagnosed histologically as carcinoma at first presentation.7 Furthermore perhaps as few as 15% of all cases diagnosed histopathologically as carcinoma (36% if rigid criteria for malignancy are applied by a specialist endocrine pathologist) will actually go on to behave in a malignant manner.8 Whether these cases represent carcinoma cured by surgery or are benign lesions ‘overdiagnosed’ by poorly specific pathological criteria is impossible to know. Because of the poor specificity and sensitivity of traditional histological analysis, many markers have been proposed to separate benign and malignant parathyroid tumours. These markers include immunohistochemistry for Ki-67, cyclin D1, p27kip1, Rb, bcl2, mdm-2, CaSR, and galectin-3, and high levels of allelic loss across a panel of tumour-suppressor genes.9 However, because parathyroid

<table>
<thead>
<tr>
<th>Features</th>
<th>Parathyroid carcinoma</th>
<th>Benign primary hyperparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>More typical and severe</td>
<td>Usually mild or asymptomatic</td>
</tr>
<tr>
<td>Palpable neck mass</td>
<td>Up to 40% of patients</td>
<td>Usually absent or &lt;10%</td>
</tr>
<tr>
<td>Recurrent laryngeal nerve palsy</td>
<td>Suggest malignancy in the absence of neck surgery</td>
<td>Rarely affected</td>
</tr>
<tr>
<td>End-organ involvement</td>
<td>More common (especially renal and skeletal complications)</td>
<td>Less common</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Serum Ca²⁺</td>
<td>Usually &gt;3.5 mmol/L.</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>Markedly elevated, usually three to ten times upper limit of normal</td>
<td>Usually mildly elevated</td>
</tr>
<tr>
<td>Serum ALP</td>
<td>Much higher</td>
<td>Usually mild</td>
</tr>
<tr>
<td>α- and β-subunit of HCG</td>
<td>May be elevated</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Pathology</td>
<td>Tumour weight</td>
<td>Usually &gt;1.9 g (up to 5 g)</td>
</tr>
<tr>
<td>Macroscopic description</td>
<td>Grayish, lobulated, firm, stony hard</td>
<td>Reddish brown, soft, round, oval</td>
</tr>
<tr>
<td>Microscopic description</td>
<td>Unequivocal invasive growth (WHO 2004 criteria)</td>
<td>Invasive growth absent</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; HCG, human chorionic gonadotropin; PTH, parathyroid hormone.
carcinoma is rare and false positives with these techniques are relatively common, none has been considered definitive or is particularly useful in individual cases.

A breakthrough came in 2002 when the gene responsible for hyperparathyroidism-jaw tumour (HPT-JT; OMIM #145001) syndrome (a rare syndrome with a striking 15% lifetime risk of parathyroid carcinoma) was identified as ‘Hyperparathyroidism 2’ (HRPT2). HRPT2 (also known as CDC73 due to its similarity to a yeast protein involved in RNA polymerase II based transcription) contains 17 exons and encodes a 531-amino-acid protein known as parafibromin. Three major international studies subsequently demonstrated that 77% of all parathyroid carcinomas (defined on the basis of proven metastasis rather than histopathological criteria) harbour inactivating mutations of HRPT2/CDC73. These mutations are found in less than 1% of unselected parathyroid adenomas and therefore may be considered specific for carcinoma. Although the absence of HRPT2/CDC73 mutation cannot be used to exclude carcinoma, its presence can be considered definitive for the diagnosis of parathyroid carcinoma. It has therefore been recommended that all individuals with a diagnosis of parathyroid carcinoma should be offered genetic testing for HRPT2/CDC73.

As sequencing for HRPT2/CDC73 in all atypical or suspicious lesions is beyond the means of most clinical services, immunohistochemistry for parafibromin has been developed as a simple and cheap de facto marker of HRPT2/CDC73 mutation. Because most HRPT2/CDC73 mutations are truncation or deletion in nature, tumours with double hit inactivation of HRPT2/CDC73 show loss of nuclear parafibromin staining. It has recently been suggested that positive staining for protein product 9.5 (PGP 9.5) might be used in combination with negative staining for parafibromin to increase further diagnostic sensitivity and specificity. It has therefore been recommended that immunohistochemistry for parafibromin and PGP 9.5 should be performed in atypical or unusual parathyroid tumours. Not only could abnormal staining provide a definitive diagnosis of malignancy, it can also triage genetic testing for HRPT2/CDC73 mutations on the basis that testing may only be offered to individuals with abnormal staining patterns.

The patient described here had negative immunohistochemical staining for PGP 9.5 in the original parathyroid tumour and the lung mass, weak/local staining for parafibromin in the original tumour but negative parafibromin staining in the lung mass. The significance of weak/local staining for parafibromin is uncertain, but it is found more commonly in parathyroid carcinoma than benign sporadic adenoma and is sometimes identified in cases with point mutations of HRPT2/CDC73. Given that a germline HRPT2/CDC73 mutation was not identified by sequence analysis, it is likely that somatic HRPT2/CDC73 mutations are present in the tumour tissue, and that this case is one of the sporadic metastatic parathyroid carcinoma.

Active communication between clinicians and pathologists is vital in delivering optimal patient care. A thorough clinical history should be provided to the pathologists to assist in the histological diagnosis. When the diagnosis does not match the clinical impression, such as in this case, clinicians and pathologists should review the pathology and further testing with additional immunohistochemical stains may be necessary. Regular clinicoradiopathological meetings are an effective way to complement this process in optimizing patient care and management.

In conclusion, parathyroid carcinoma is rare. However, this diagnosis needs to be considered early, particularly in a patient, such as this, who has severe symptomatic hypercalcaemia with a markedly elevated PTH level. Although HRPT2/CDC73 germline mutation testing was negative in this patient, loss of parafibromin staining has conclusively been shown to be a specific marker for the diagnosis of parathyroid carcinoma (essentially definitively so). It is likely therefore that the parathyroid carcinoma in this patient is sporadic. Immunohistochemical testing for parafibromin should be used as an additional diagnostic marker in combination with the clinical features to both definitively confirm a diagnosis of parathyroid carcinoma and to triage genetic testing for HRPT2/CDC73.

References
Immune reconstitution inflammatory syndrome manifesting as development of multiple autoimmune disorders and skin cancer progression

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Key words
immune reconstitution inflammatory syndrome, rheumatoid arthritis, hypothyroidism, thyrotoxicosis, human immunodeficiency virus.

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Abstract
We report the case of a 56-year-old man with the rare autoimmune pathologies of alternating hypothyroidism and hyperthyroidism due to thyroid-stimulating hormone receptor antibodies, and rheumatoid arthritis as manifestations of a human immunodeficiency virus-related immune reconstitution inflammatory syndrome. The patient also developed overt progression of a pre-existing skin malignancy that may also be related. This case highlights immune reconstitution syndrome as an important differential diagnosis following antiretroviral therapy commencement, and that a high index of suspicion should be maintained for this rare but important cluster of conditions. Furthermore, the patient’s genetic predisposition to autoimmunity provides helpful insights into the pathogenesis of these disorders.
Immune reconstitution inflammatory syndrome (IRIS) is an important differential diagnosis following commencement of antiretroviral therapy. We report a rare case of alternating hypothyroidism and hyperthyroidism due to thyroid-stimulating hormone (TSH) receptor antibodies, and rheumatoid arthritis (RA), together with apparent aggressive progression of a pre-existing skin malignancy.

Our patient was initially diagnosed with human immunodeficiency virus (HIV) in 1984 and hepatitis C virus (HCV) co-infection in 1990. Antiretroviral therapy was commenced in 1991 and resistance to multiple agents ensued resulting in a CD4+ T-cell count of <20/μL (2%) by October 2005. Complications over time included intractable severe drug-resistant oesophageal candidiasis present from 1995, peripheral neuropathy, lipodystrophy, Mycobacterium avium complex associated diarrhoea and hepatosplenomegaly. A skin lesion was removed from the posterior scalp in December 2006. Histology was reported as solar keratosis with focal intra-epidermal carcinoma.

A new antiviral regimen was commenced in March 2007 consisting of raltegravir, emtricitabine, zidovudine, etravirine, darunavir and tenofovir. CD4+ cells were first detected 18 days later and steadily climbed to 350 CD4+ T-cells/μL (18%) in December 2009 (Table 1). The previously intractable oesophageal candidiasis was eradicated within 5 months in the absence of antifungal agents.

Table 1 | Laboratory results following highly active retroviral therapy commencement

<table>
<thead>
<tr>
<th>Time in months post successful therapy commencement</th>
<th>0</th>
<th>5</th>
<th>7</th>
<th>11</th>
<th>17</th>
<th>21</th>
<th>23</th>
<th>27</th>
<th>29</th>
<th>30</th>
<th>31</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ T-cell count (cells/μL)</td>
<td>0</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>80</td>
<td>310</td>
<td>—</td>
<td>210</td>
<td>290</td>
<td>—</td>
<td>—</td>
<td>350</td>
</tr>
<tr>
<td>CD4+ T-cell per cent</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>18</td>
<td>—</td>
<td>15</td>
<td>16</td>
<td>—</td>
<td>—</td>
<td>18</td>
</tr>
<tr>
<td>Viral load (IU/mL; NR 0.3–4.5)</td>
<td>12 900</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>—</td>
<td>15</td>
<td>15</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Free T4 (pmol/L; NR 7–17)</td>
<td>—</td>
<td>—</td>
<td>8.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6.0</td>
<td>6.2</td>
<td>4.8</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Free T3 (pmol/L; NR 3.5–6.0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>TSH (mU/L; NR 0.3–4.5)</td>
<td>—</td>
<td>2.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>130</td>
<td>21</td>
<td>0.3</td>
<td>0.07</td>
<td>0.05</td>
<td>0.06</td>
<td>&lt;0.05</td>
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<tr>
<td>TRAb (IU/L; NR &gt;1.0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>210</td>
<td>220</td>
<td>—</td>
<td>210</td>
<td>190</td>
<td>—</td>
<td>140</td>
</tr>
<tr>
<td>RF (IU/mL; NR &lt;20)</td>
<td>—</td>
<td>86</td>
<td>121</td>
<td>—</td>
<td>182</td>
<td>162</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1:40</td>
<td>1:160</td>
<td>—</td>
<td>1:40</td>
<td>Neg</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anti-cardiolipin (IU/mL; NR &lt;6)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>21</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Funding: None.
Conflict of interest: None.

Approximately 14 days following commencement of the new regimen a recurrence of squamous cell carcinoma (SCC) of the scalp was diagnosed. Clinically the lesions floridly increased in size over the subsequent 10 days until operation, at which time the cancer was found to be invading his skull. A total of 57 Gy of high-energy electron beam radiotherapy followed. Currently the patient is free of malignancy, although a chronic scalp wound persists.

In December 2008 he complained of 4 months of lethargy, generalized oedema, voice change and 17 kg weight gain. Hypothyroidism was confirmed with an undetectable free levothyroxine and TSH level of 130 mU/L (normal range (NR) 0.3–4.5). TSH-receptor antibodies (TRAb) were markedly elevated at 220 IU/L (NR <1.0), although other thyroid autoantibodies were in the normal range. Previous thyroid function tests had been normal. Symptoms resolved with levothyroxine replacement. One year later he became mildly thyrotoxic, despite no change in thyroid hormone replacement dose. Nuclear thyroid scan revealed non-suppressed thyroid uptake, despite the exogenous replacement. Levothyroxine therapy was withdrawn, with persistence of subclinical hyperthyroidism.

The patient began experiencing symmetric inflammatory joint pain in early 2009 in the distribution of the proximal interphalangeal and metacarpophalangeal joints of the hands, hips, knees and ankles. Serological tests (Table 1) revealed markedly elevated levels of rheumatoid factor (121 IU/mL rising to 182 IU/mL (NR <20)). An anti-nuclear antibody of titre 1:160 in a speckled pattern (previously negative in 2004) was reported on one occasion, but was not thought to be significant. The only other positive result was the presence of trace levels of polyclonal cryoglobulin (attributed to HCV infection).
A diagnosis of RA was made based on American Rheumatism Association 1987 revised criteria.\(^1\) A strong family history of rheumatologic disease was obtained, with both the patient’s sister and mother dying of complications from systemic lupus erythematous and Sjögren’s syndrome respectively. His younger brother, who is clinically well, was found to have numerous autoantibodies, including a myeloperoxidase positive anti-neutrophil cytoplasmic antibody (MPO-ANCA) and thyroid antibodies. Human leukocyte antigen typing of the index patient demonstrated DRB1*0404, a known autoimmune disease-associated allele.\(^5\) Therapy with hydroxychloroquine led to clinical remission of his RA. Magnetic resonance imaging following therapy revealed no erosive disease and resolution of the synovitis, corresponding with the clinical picture.

**Discussion**

IRIS with antiretroviral therapy was initially documented as exaggerated responses to previously latent microbes, although various autoimmune and inflammatory conditions have now been described. Thyroid disease is the best recognized autoimmune IRIS, with Graves’ disease (GD) most common.\(^1\) Literature review reveals approximately 41 cases of GD following commencement of highly active antiretroviral therapy.\(^4\)–\(^17\) Unlike infection-related IRIS, GD manifests relatively late following antiretroviral therapy commencement. This is thought to be related to biphasic repopulation of CD4+ cells, with memory cells initially increasing, followed by naïve cells – this second wave is postulated to response abnormally to self-antigens and generate autoimmunity.\(^18\) Reflecting the contrasting mechanisms of IRIS components, the term immune restoration disease has been suggested to describe the early exaggerated pathogen-specific immune responses, while immune reconstitution-associated autoimmune disease applies to the late phenomenon.\(^19\)

GD pathogenesis is mediated by stimulating antibodies targeting the TSH receptor, leading to over-production of thyroid hormone. TRAb can exist in multiple forms, with some capable of inhibiting the TSH receptor (‘blocking antibodies’), resulting in hypothyroidism. The phenotype of thyrotoxicosis or hypothyroidism can fluctuate in some people over time, related to the proportion and potency of stimulating or blocking antibodies in serum.\(^20\) This is the likely pathogenesis of the alternating hypothyroidism and hyperthyroidism in our patient. At present no Australian laboratory performs assays to distinguish specifically between blocking and stimulating antibodies. However, the profound hypothyroidism associated with high TRAb titre and the absence of other thyroid autoantibodies strongly argues for this as the causative mechanism for the hypothyroidism. Furthermore, the diffuse non-suppressed thyroid uptake scan in the setting of mild hyperthyroidism while taking levothyroxine can only be achieved by stimulation of the TSH receptor independent of TSH (i.e. by stimulating TRAb).

We are aware of four other reported cases of hypothyroidism following highly active antiretroviral therapy commencement. One patient had evidence of pre-existing thyroid autoimmunity, so the resulting hypothyroidism may have been simple progression of this.\(^21\) IRIS was likely in the other three patients;\(^7\)–\(^22\) blocking TRAb were proven in one.\(^7\)

The inflammatory polyarthritis likewise also occurred in the setting of IRIS. Systemic autoimmune diseases have been reported previously as part of immune reconstitution, with the two most comprehensive reviews of the literature performed by Calabrese et al.\(^23\) and Maganti et al.\(^24\) They found the most commonly reported non-organ specific autoimmune disorders to be sarcoidosis followed by systemic lupus erythematosus, with very rare reports of polymyositis, RA, Kawasaki disease and Behçet’s disease.

Given the overwhelming family history and human leukocyte antigen genotype that strongly predisposed him for rheumatologic disease, an intriguing hypothesis is that the severe longstanding immunodeficiency may have protected our patient from developing disease earlier. Patients with IRIS are susceptible to infection-associated inflammation. In a predisposed individual, the IRIS-induced tissue inflammation may result in an increase in local inflammatory cytokines and recognition of viral and/or self-antigens by the infiltrating T-cells. Peripheral T-cell expansion and loss of peripheral self-tolerance may lead to the development of local and/or systemic autoimmunity.\(^25\) Hence, as in our patient with a strong family history of severe autoimmune disease, the inflammatory environment induced by IRIS and the loss of immune self-tolerance to tissue-associated antigens can result in generation of multiple autoantibodies and tissue damage, which can precipitate clinical disease.

The presence of cryoglobulin potentially complicates assessment of our patient’s clinical features. Cryoglobulin formation in HCV infection is extremely common.\(^26\) Furthermore, both general and organ-specific autoantibodies frequently co-occur with HCV-associated mixed cryoglobulinemia.\(^27\) Our patient was anti-citrullinated cyclic peptide antibody negative, which is common in the setting of arthralgia due to cryoglobulin formation.\(^28\)
However, several features argue against a central pathogenic role for cryoglobulins in our patient, and in any case their presence does not negate the role of immune reconstitution. The cryoglobulin was identified in trace amounts and no other tissue manifestations of cryoglobulinaemia were present, with the patient failing to meet diagnostic criteria for the disorder. While thyroid autoantibody formation is common, previous reports have highlighted anti-thyroglobulin and anti-thyroid peroxidase antibodies not TRAb. These other autoantibodies were serially negative both before and after immune reconstitution. Most importantly, the temporal relationship of symptoms only occurred following immune reconstitution, despite many years of HCV infection.

The role of immune reconstitution in the presentation of the scalp malignancy is unclear. Several reports have claimed malignancies related to this treatment phase, although the association appeared tenuous. Our patient’s malignancy was already present prior to his effective antiretroviral regimen. We hypothesize the SCC invaded the skull during the period of profound CD4+ T-cell depletion. T-cell reconstitution led to significant scalp inflammation in the area of the previously excised SCC with the reforming immune system playing a role in the presentation through a marked inflammatory response.

This case illustrates the rare phenomenon of concomitant autoimmune thyroid disease and RA as part of IRIS. The apparent flare of skin malignancy may also be related. Unlike the more common situation of GD, our patient initially became hypothyroid, but the likely pathogenesis is identical. Clinicians treating patients with HIV should be aware of the possibility of triggering autoimmune conditions as a result of immune reconstitution. This is especially so in the setting of strong family history of autoimmune disorders. There is however, no strong evidence currently for routine screening for autoimmune disorders following immune reconstitution.

References

Massive hiatus hernia presenting as acute chest pain

An 83-year-old man presented to the Emergency Department following the sudden onset of severe chest pain and dyspnoea occurring after breakfast. The pain was sharp, radiating to the back and shoulders and could not be relieved. Past medical history included atrial fibrillation, hypertension, chronic renal failure and gastro-oesophageal reflux disease on a 50-year background history of untreated mild hiatus hernia. On examination, he was afebrile and unable to lie flat. Blood pressure was 80/50, heart rate 40, respiratory rate 22 and oxygen saturation 90%. There were decreased breath sounds bibasally plus epigastric tenderness. There was no radioradial or radiofemoral delay. Troponin was normal.

Computed tomography revealed a massive left hiatus hernia with intrathoracic stomach, proximal small bowel, greater omentum and transverse colon (Fig. 1). An urgent open repair through a transabdominal approach was performed, reducing the intrathoracic abdominal contents. The hiatus was then repaired with prolene sutures followed by gastropexy to prevent recurrent herniation.

Massive type IV hiatal hernias, which are the herniation of intra-abdominal contents such as bowel and omentum in addition to the stomach through the oesophageal hiatus,1 are rare and represent a surgical emergency.2 They pose a significant risk for fatality and serious complications, including volvulus, obstruction, haemorrhage and perforation.1 Thus correct and timely diagnosis is essential.2 However, massive hiatus hernia rarely features on the list of differential diagnoses of acute chest pain,4 which accounts for an estimated 6% of all adult emergency department attendances.5

This case highlights the challenges facing physicians in recognizing non-cardiac causes of acute chest pain and dyspnoea, especially in patients with risk factors for cardiovascular disease.

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Figure 1 Computed tomography reconstruction showing grossly elevated hemidiaphragm with herniated stomach, small bowel, greater omentum and transverse colon. Atelectasis of particularly the left lung and myocardial compression is evident. (a) Coronal. (b) Sagittal.

References
Gallstone ileus

An 84-year-old woman with no notable medical history presented to the Emergency Department with a week’s history of nausea, anorexia and vomiting. On examination she was tachycardic and had a diffusely tender abdomen with no distension. A computed tomographic scan of the abdomen demonstrated gas in the biliary tree (Fig. 1a) and significant distension of the stomach, duodenum and jejunum (Fig. 1b,c). In the distal jejunum there was a round, lamellated, partially calcified body of 2.7 cm size (Fig. 1c, arrow) at the start point of the bowel obstruction. These findings were indicative of gallstone-related bowel obstruction after choledoco-duodenal fistula. An enterotomy was performed and the gallstone retrieved. Postoperatively the patient developed aspiration pneumonia with septic shock and died.

Although a rare cause of bowel obstruction in the general population, gallstone ileus is relatively common in the over-65 age group and accounts for up to 25% of non-strangulated intestinal obstruction.1 Gallstone ileus in many cases can be a difficult clinical diagnosis. The speed of decision-making is crucial and mortality can reach up to 18%.7 Diagnostic imaging is fundamental in diagnosis and should be performed early. Radiological diagnosis is by Rigler’s triad: pneumobilia, small bowel obstruction and an impacted gallstone, usually in the terminal ileum, well demonstrated by the images in this report.

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Figure 1 (a) Arrow demonstrates gas in the biliary tree. (b) The arrowhead demonstrates gas in the common bile duct and the arrow shows the point of exit of the gallstone through a fistula between the collapsed gallbladder and duodenal cap. (c) The arrow demonstrates a round, lamellated, partially calcified body of 2.7 cm size and distended loops of small bowel.
LETTERS TO THE EDITOR

Clinical-scientific notes

Has the disease identity of restless legs syndrome developed or been distorted? Astronauts in zero gravity may know the answer

There has been an unnatural change in the disease identity of restless legs syndrome (RLS). In 1945, Ekbom first applied the term for unpleasant sensations arising in the legs while lying down at night. Ekbom indicated that two-thirds of patients with unpleasant sensations have a sensation of cold in the feet, and he repeatedly advocated the use of vasodilative agents for RLS, with reference to observations of approximately 200 patients. Since the 1990s, neurologists concluded that some forms of central nervous system (CNS) impairment might cause RLS, although the precise pathogenesis was never elucidated. Recently, it has been hypothesized that the unpleasant sensations in the legs might be caused by activation of autonomic nervous system located in blood vessels when vessel wall tension is enhanced by a change in blood flow dynamics. Certain elemental factors of blood vessels, such as elasticity and distensibility, may facilitate the stimulation, especially in patients with disturbance of blood circulation. In a preliminary examination, combined use of vitamins E (daily dose, 300 mg) and B12 (daily dose, 750 μg) appeared to be effective for dermatology patients with enhancement of itching at night in the legs. This hypothesis makes it easy to explain why the sensations occur while lying down at night. The high incidence of RLS seems to be reasonable for a peripheral blood circulation problem that shows a high familial incidence and a predilection for women and elderly persons. Even movement of the legs might be explained as an auto-somatic reflex or compensative behaviour.

The pharmacological mechanisms of the drugs recommended for RLS are still unclear. However, most of them could be explained in terms of action on the peripheral circulation. Dopamine causes vasodilation by stimulating dopaminergic receptors on smooth muscle in vessels. Opioids induce peripheral vasodilation, and also enhance the release of dopamine in the CNS. Benzodiazepines have been shown to induce muscle hypotonia in ileal longitudinal muscle, expecting a vasodilative effect on smooth muscle in vessels. γ-Aminobutyric acid analogues produce oedema in the extremities as a side-effect, suggesting suppression of change in blood flow dynamics in the vessels of the legs. Besides dizziness and drowsiness, the side-effects of CNS drugs can sometimes be serious, such as suicidal ideation. The problems associated with selective serotonin reuptake inhibitors over the last decade should be borne in mind.

Although the RLS hypothesis is difficult to confirm, the effect of zero gravity might provide a clue. So far, more than 500 astronauts have already travelled into space. The prevalence of RLS, affecting 5–10% of the general population, is so high that an appreciable proportion of astronauts with RLS might have already been in space. Therefore, it might be worth asking astronauts about the sensations they experience in their legs while lying down in zero gravity. Because changes in body position would not influence blood flow dynamics in zero gravity, it might be expected that any unpleasant sensations might disappear during the time spent in space, and then become exacerbated after returning to earth.

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References

4 Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J.
Laugh headaches: a rare form of headache associated with type 1 Arnold–Chiari malformation

A 26-year-old white man was referred to our Neurology services due to headaches associated with laughing. They were first noted in childhood and had recently intensified over an 18-month period. The headaches were described as severe, lightning-sharp occipital pains that occurred whenever he had a hearty laugh and disappeared within 5–10 s of cessation of laughter. They were unrelated to coughing or straining.

The past medical history was unremarkable without a history of migraines or head trauma. The patient did not smoke or use recreational drugs and rarely took alcohol. Clinical examination and routine blood tests were entirely normal.

A magnetic resonance imaging scan of the head revealed an enhancing mass lesion measuring 2 × 1 × 1 cm in the inferior half of the fourth ventricle producing mild dilatation of the lateral and fourth ventricles, but without any hydrocephalus (Fig. 1). The cerebellar tonsils were herniating through the foramen magnum to the level of the arch of the first vertebral body which was unexpected for the small tumour and suggested the possibility of an incidental type 1 Arnold–Chiari malformation (ACM).

A provisional diagnosis of a fourth ventricle ependymoma with a type 1 ACM was made, and the patient underwent tumour resection with posterior fossa decompression followed by radiotherapy. The tumour was histologically consistent with an ependymoma. There were no postoperative complications, and he made a good recovery without any subsequent recurrence of tumour or headache after 7 years.

This case is the second in the English literature of laugh headaches associated with type 1 ACM following a Medline search. Type 1 ACM is due to herniation of the cerebellar tonsils and is usually discovered incidentally or diagnosed following investigations for headache symptoms. Typically, the headaches are short-lived and associated with coughing, sneezing or straining, but might also be spontaneous and persistent.

The mechanism behind the short-lived headaches (e.g. cough headache) in type 1 ACM is thought to be due to downward displacement of the cerebellar tonsils, which causes stretching of pain-innervated structures, such as the meninges, nerves roots and blood vessels. These manoeuvres have also been demonstrated to cause sudden increases in intrathecal pressure and obstruct cerebrospinal fluid (CSF) flow in the subarachnoid space, which in these patients have been shown to have abnormal CSF flow patterns. It is likely that a similar mechanism is responsible for the laugh headaches in our patient.
which with tumour growth and progressive obstruction to CSF flow, caused worsening of the headache.

On subsequent consultations, the father of our patient in his late sixties, mentioned experiencing similar headaches associated with laughter since his teenage years, but declined any further investigations.

References

Dangers of ripping in body building

A 35-year-old man felt weak, dizzy, nauseated, had painful muscle cramps and instability while posing during a body building competition.

The ECG showed peaked T waves. Electrolytes and other laboratory tests are shown in Table 1. The serum potassium was 8.0 mmol/L and sodium 119 mmol/L. He was given 4.5 L of normal saline. The serum sodium increased to 130 mmol/L and serum potassium decreased to 4.8 mmol/L, and he self-discharged.

Before discharge he stated that he had prepared for competition by using the diet, shown in Table 2, which contained approximately 713 mmol of potassium daily. He took tri-iodone thyronine (T3) daily and intramuscular testosterone every 2 weeks. Several days before he had undergone a process that he termed ‘ripping’. This consisted of drinking 12 L of water daily for 7 days before the competition and for 2 days before avoiding salt in the diet and taking spironolactone 100 mg daily.

The patient showed hyperkalaemia, water intoxication and rhabdomyolysis.

A Medline search showed 132 results on body building. A search on Google showed over 1000 results on body building. This indicated substantial involvement by industry, highly variable definitions of the jargon used and recommendations.

Based on this and discussion with the patient there were two phases that explained the strategy: the intent of the initial phase, lasting several weeks, was to increase muscle bulk and eliminate fat, referred to as ‘shredding’. A high protein, high potassium, low carbohydrate diet and use of complex carbohydrates to ‘fill the stomach and

<table>
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<th>Table 1</th>
<th>Laboratory results on admission</th>
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<td>Na</td>
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<tr>
<td>K</td>
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<tr>
<td>HCO₃</td>
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<td>urea</td>
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<tr>
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<tr>
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<tr>
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</tr>
<tr>
<td>CK</td>
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<tr>
<td>Albumin</td>
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<table>
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<tr>
<th>Table 2</th>
<th>Diet consumed by the patient each day</th>
<th>Potassium mmol/kg</th>
<th>Total daily potassium (mmol)</th>
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<tr>
<td>1.5 kg red meat</td>
<td>101</td>
<td>151</td>
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<tr>
<td>1.0 kg chicken</td>
<td>84</td>
<td>84</td>
<td></td>
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<tr>
<td>3.0 kg broccoli</td>
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<td>234</td>
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<tr>
<td>2.0 kg sweet potato</td>
<td>62</td>
<td>124</td>
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<tr>
<td>8 bananas</td>
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<td>Total</td>
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<td>3–4 teaspoons salt</td>
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<td>Protein and amino acid supplements</td>
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decrease appetite’ were suggested. Supplements of anabolic steroids and ‘fat burners’, such as T₃, dinitrophenol, products containing ephedrine, aspirin, caffeine and others, were suggested.

The second phase – sometimes referred to as a ‘crap shoot’ was to achieve optimum ‘ripping’ – which is exaggerating the definition of individual muscle groups on the day of the competition. Recommendations to achieve this were to add a large intake of water to the previous diet for 5 days before the competition. One website recommended taking 2–3 gallons of water daily. Two days before the competition salt was eliminated to the extent that there was advice, used by the patient, to cook chicken in distilled water and to take diuretics and potassium supplements to avoid cramp. Spironolactone was suggested to eliminate further sodium but spare potassium loss.

Hyperkalaemia was the most serious abnormality but is rarely due to consumption of potassium alone. Approximately 300 mmol/L of potassium can be consumed in 6 h by unadapted subjects and as much as 800 mmol/L per day in potassium adapted individuals without causing an important rise in serum potassium.¹ Spironolactone and mild renal dysfunction from rhabdomyolysis might have contributed.

In conclusion, water intoxication and hyperkalaemia are hazards of ripping in the days before a body building competition.

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Reference


General correspondence

Erythrocytapheresis treatment in severe malaria

We read Harris et al.’s article with interest.¹ We are clinicians with 20 years’ experience treating malaria in areas of both stable and unstable malaria. This article provides no evidence to support the use of erythrocytapheresis for severe malaria. The patient met the criteria for severe malaria, but was already on quinine and was correctly started on intravenous artesunate and an antibiotic. It would be useful to know if the antibiotic used was one known to be effective against Plasmodium falciparum when used in combination with quinine, for example doxycycline or clindamycin. The decision to add erythrocytapheresis treatment appears to have been made after repeat parasite count 12 h post-presentation had risen to 33% in spite of no reported clinical deterioration. It is well documented that the parasite count may increase during the first 24 h of quinine treatment. The early treatment failure with artesunate reported in Cambodia only occurred with mono Rx and not when artemisinin and mefloquine were used together.² Therefore, was it justified to add a potentially harmful treatment when its contribution to lowering the parasite count was known to be marginal, that is, <1 log compared to 4 log with intravenous artesunate?

Malaria rarely causes cerebrospinal fluid pleocytosis. We feel that the headache and cerebrospinal fluid findings were more likely due to the side-effects of treatment rather than cerebral malaria in a patient with no abnormal neurology.

Pulmonary oedema is a recognized complication of severe malaria but also known to occur with erythrocytapheresis. There is also no evidence to support the use of mannitol in severe malaria.³

In this case of severe malaria where there was no reported clinical deterioration, would it not have been more prudent to use evidence-based combination treatments rather than unproven potentially harmful ones?

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Letters to the Editor

References


Reply

We thank Fegan and Glennon for their interest in our paper. We appreciate their insightful comments and will discuss them seriatim.

The purpose of our report was not to provide evidence to support the use of erythrocytapheresis in severe malaria. This was simply a report on its use and to review the literature. The pros and cons of this are clearly described in the first paragraph of the discussion. It is unlikely that high-level evidence will ever be available.

No parasite active antibiotics were used concomitantly. Parasite loads of 33% are uncommon and carry with them a significant risk of capillary sludging with parasitized red cells. Adjunctive erythrocytapheresis may enhance the removal of these cells in addition to the effective parasite clearing effects of artesininins, thus further reducing circulating parasites available for tissue sequestration. The stimulus for considering erythrocytapheresis was not the rise in parasitaemia observed but the presence of hyperparasitaemia at presentation. A high parasite burden is itself a poor prognostic sign in severe malaria. The United States Centers for Disease Control and Prevention guidelines for the treatment of severe malaria strongly encourage consideration of red cell exchange if the parasitaemia is >10%.2

Procedures such as plasmapheresis, leucocytapheresis or erythrocytapheresis are reasonably standard procedures in units with these facilities and trained staff to use them. We believe it would be undesirable to wait for signs of neurological deterioration before considering this procedure (if available) in the presence of a 33% parasitaemia, especially in a non-immune patient from an area with known artesinin resistance.

We agree that a cerebrospinal fluid (CSF) pleocytosis is rarely seen in cerebral malaria, and its presence should prompt consideration of other causes. Fegan and Glennon state that the CSF pleocytosis and raised intracranial pressure were likely due to treatment but do not provide a reference for this. Although concerns over artemisinin neurotoxicity have been expressed as a result of animal studies, this has not been clearly demonstrated in humans. We are unaware of any association between artesunate therapy or apheresis and CSF pleocytosis.

Pulmonary oedema is a very uncommon complication of any pheretic procedure largely because it is highly controlled. This is in contrast to a manual exchange transfusion which certainly can cause pulmonary oedema.

Mannitol was not used for malaria but as an attempt to reduce the high intracranial pressure. The lack of evidence for its use in cerebral malaria is referenced in the text, and we would not advocate its use in this context.

Malaria is an increasingly common problem being seen in Australian hospitals. This is particularly so in North Queensland which has a high incidence of travellers from Papua New Guinea. The vast majority of cases of falciparum malaria is treated with evidence-based measures as suggested by Fegan and Glennon. This single report serves to remind clinicians that hyperparasitaemia is a serious complication and that erythrocytapheresis, if available, may be an option. It is, in our opinion, better than waiting for significant neurological deficit before considering its use.

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References


Scurvy: old and new

Dr Holley and his colleagues remind us that scurvy still remains part of the differential diagnosis of an at-risk patient with ecchymoses, purpura and with wounds that will not heal.1

Thirty-six years ago, I presented a case of scurvy in a man whose diet consisted of alcohol and a daily pie. Despite very low levels of plasma and leucocyte ascorbic acid, most attendees at that teaching hospital ‘grand round’ regarded me as diagnostically deficient. A dermatologist stepped forward, pulled out his magnifying loop and examined the hairs on the patient’s arm. ‘Corkscrew hairs!’ he exclaimed. All diagnostic doubt vanished.

Vitamin C deficiency and scurvy can be found in unusual circumstances. The first case I ever saw was in a famous London teaching hospital. It was in a fellow resident medical officer who I would now recognize as having Asperger’s disorder. He was overly conscientious and had not eaten a single meal outside of the hospital in 11 months.

In western New South Wales in the early 1970s, Aboriginal babies breastfed by vitamin C-deficient mothers and then weaned onto vitamin C-deficient tinned spaghetti, also developed infantile scurvy.2 And several children whose families were members of a strict evangelical Christian sect also had bleeding gums and very low levels of plasma ascorbic acid.3 They did not pinch fruit from the citrus orchards.

17th century scurvy bones

I recently visited the Svalbard Museum in Longyearbyen and was shown the excavated bones of a Dutch whaler who died from scurvy at Ytre Norsköya in north-west Svalbard. There were seven whalers left to guard the whaling station during the winter of 1634. All died. Their logbook describes their pitiable condition:

They could not move, were not able to masticate and had increasingly more pain in their legs, arms and body. In the end everybody was bedridden and unable to move and by the end of February all had died.4

The haem stained longitudinal fractures show why this whaler had pain in his arms and legs and could not move (Fig. 1). Neither I, nor any of my orthopaedic colleagues, have ever seen such longitudinal fractures (Fig. 2).

Figure 1 Intraosseous bleeding due to scurvy in 1634.

Figure 2 Longitudinal fractures from scurvy in 1634.

The pathognomonic features of scurvy occur because vitamin C is essential for the synthesis of the proteins, collagen and elastin. Without them, blood vessels, connective tissue and bone fall apart and hair curls and then falls out. Old, healed wounds re-open and fractures disunite. That is what happened to Captain Lawrence Oates on the ill-fated Scott expedition to be first to the South Pole. Oates’ Boer War wounds of 1901 re-opened in 1912.5

Vitamin C is also required for the synthesis of the neurotransmitter, norepinephrine. A lack of it affects a person’s mood. In the Italian language, an irritable, quarrelsome person is described as a ‘scorbutico’. This is another symptom of scurvy that has contributed to the demise of sailors and explorers marooned together in the polar winter.
Acknowledgement

I thank Mr Sander Solnes, conservator in Svalbard Museum, for access to the scurvy bones and permission to photograph them.

References

1 Holley AD, Osland E, Barnes J, Krishnan A, Fraser JF. Scurvy: historically a plague of the sailor that remains a consideration in the modern intensive care unit. Intern Med J 2011; 41: 283–5.
NEBILET® Nebivolol Hydrochloride.

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**Contraindications:** Hypersensitivity to the active or any of the excipients. Liver insufficiency (in liver function impairment). Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring IVotropic therapy. Sickle cell syndrome, including sickle cell block. Second and third degree heart block (without a pacemaker). History of bronchospasm, including that in chronic obstructive pulmonary disease) and/or asthma. Untreated phaeochromocytoma. Metabolic acidosis.

**Pharmacodynamic interactions:** Combinations not recommended: verapamil, diltiazem, quinidine, flecainide, disopyramide, lignocaine, mexiletine clonidine, moxonidine, methyldopa and other beta-blockers including eye drops.

**Children and adolescents. Elderly and renal insufficiency – see Dosage and Administration. Limited data in hepatic insufficiency or impaired liver function – see Contraindications. Driving vehicles or operating machines. Interactions:**

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**To have a passion in life is great, but to be able to enjoy that passion day after day means so much more to patients.**

Introducing Nebilet - the only β-blocker with proven efficacy in typical heart failure patients [770 years and wide range of LVEF].

Nebilet + standard therapy significantly reduced all-cause mortality or CV hospitalisation vs placebo + standard therapy (p=0.039) in heart failure patients.

To review Product Information before prescribing. Product Information is available from CSL Biotherapies.

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**References.**

1,2  *β*-adrenergic receptor antagonists: reducing mortality and morbidity in chronic heart failure: a meta-analysis of randomised placebo-controlled trials. Br Heart J 2002;87:46–53. 3 Nebilet + standard therapy significantly reduced all-cause mortality or CV hospitalisation vs placebo + standard therapy (p=0.039) in heart failure patients. 4 In patients >75 years, caution must be exercised and these patients monitored closely.

**Contraindications:** Hypersensitivity to the active or any of the allergens and severity of anaphylactic reactions. Regular monitoring during initiation of nebivolol in CHF. Galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption. Pregnancy – Category C. Lactation.

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