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Domestic violence: it is time for the medical profession to play its part

Ignored for a long time, domestic violence is now recognised as one of the major public health issues in Australia. The financial cost of the problem to the community, estimated at $14.7 billion in 2013, is similar to that of obesity and far in excess of diabetes. However, beyond the monetary cost the personal and social damage associated with domestic violence is regarded by many as sufficient to constitute a national emergency.

Intensifying public interest in the problem is reflected in the appointment as the 2015 Australian of the Year of Rosie Batty, a courageous victim of a tragic case of domestic violence, together with the establishment of a special Domestic Violence Task Force in Queensland and a Royal Commission in Victoria. While these initiatives are most welcome, they will not on their own provide a solution. What is needed is a national strategy that brings together diverse groups and individuals from the community around a multidisciplinary programme that includes information, support, education and research. Such a programme will require support and resources from government as well as active participation from the medical profession.

Despite their potential influence and importance, medical professionals, with rare exceptions, have been strangely silent in this area. The Australian Medical Association has had an admirable policy on its books for 10 years and the Royal Australian College of General Practitioners has developed guidelines for family doctors. However, many other Colleges – including the Royal Australasian College of Physicians – appear not even to have developed policies on the subject, let alone effective action strategies. It is time that the wider medical profession contributed actively to addressing this scourge on Australian society.

Any coordinated strategy on domestic violence will need to be informed by accurate and reliable data. Unfortunately, such data are, at the present time relatively limited. It is known that domestic violence extends to a vast array of abusive settings, covering physical, sexual, emotional and financial abuse among intimate partners, same sex couples, elders and children. It crosses all socioeconomic, cultural, ethnic and religious boundaries. The vast majority of victims are women, with 17% of all Australian women aged more than 18 years having experienced violence from a partner at some time, compared with 5.3% for men, and that domestic violence is especially marked in pregnancy, during which up to 36% of all violence occurs, and when up to 20% of women experience it for the first time.

More than 65 000 cases of domestic incidents are reported to police in Victoria each year, and nearly 35 000 intervention orders related to family violence are issued, both of these numbers are rapidly increasing. Sadly, even death is a not infrequent outcome, with 185 domestic homicides having been reported across Australia in the 3 years to 2010.

It is known that, despite its frequent occurrence, domestic violence is recognised only rarely by medical practitioners. Indeed, the Bettering the Evaluation and Care of Health (BEACH) study, which monitors patterns of consultations in general practice, reported that in more than 95 000 consultations examined in 2013–2014, domestic violence was never cited as a reason for encounters by patients or a problem managed by general practitioners (GP). Similarly, an Irish study of women attending general practices showed that while 39% had experienced violent behaviour from their partner, only 12% were questioned about it by their doctors.

There is much, however, that remains to be explained. In particular, it is not clear why doctors are doing so badly. Contributing factors no doubt include a reluctance of many patients themselves to volunteer that they have been abused. However, a lack of awareness by practitioners is also important. Sufferers of violence frequently make contact with GPs, emergency medicine physicians, obstetricians, psychiatrists, specialist physicians or in other clinical settings. Indeed, full time GP may see up to five women per week who have experienced partner violence, of which two are severe. Patients may present with unexplained physical injury, bruising, chronic fatigue, anxiety, depression, insomnia or undifferentiated somatic symptoms. Although each of these should raise the possibility of domestic violence, very frequently the warning signs are missed.

Nor is it well understood why victims are so reluctant to report abuse and seek help. Power differences within relationships, especially those between men and women, and an associated sense of shame among the victims are likely to be relevant here, perhaps leading women to believe that the attacks on them were provoked by their
own failures as mothers and wives. Victims may also feel that help is hard to obtain, based on the common perception, that police officers are reluctant to become involved in domestic violence, seeing the problem as one of interpersonal conflict outside their legitimate responsibilities. The courts have contributed to this sense of a lack of support by the application until recently of the so-called ‘doctrine of provocation’ as a formal basis for excusing violence against women. Doctors, frequently lacking training, skills, confidence and practical resources to enable them to respond effectively, are all too often caught up in this sad labyrinth of unconscious collusion. The final result of all these factors is that doctors mostly don’t ask and women mostly don’t tell.

It is not known what social and psychological forces drive some people to commit acts of violence against the people who are closest to them and who trust them most. And most importantly of all, evidence is lacking about what interventions are effective for responding to domestic violence and for preventing its occurrence in the first place.17

Up until now, attempts by the medical profession to respond to the problem have largely focused on guidelines to assist in the detection, management and referral of patients experiencing domestic violence.1,18 It is apparent that more than broad guidelines are needed. Also required are society-wide approaches that mobilise individuals and groups within the community and draw on a wide range of resources. The response must incorporate support for victims to become empowered to speak out and accept help, and understanding and management of the underlying problems of those committing the violence. Here, a move away from the traditional approach based on shame, recrimination and blame to a recognition that domestic violence is usually a symptom of deep underlying social and psychological pathologies is more likely than existing strategies to bear fruit.

It is clear from this formulation that there are many ways in which doctors can help. They can provide safe trusted spaces in which both the victims and their assailants can express their pain and explore options for change. They can play a key part in detection, intervention and provision of specialised treatment of the physical, mental and emotional damage caused by domestic violence. They can provide support and, where appropriate, active treatment for the direct victims of the violence as well as for all those harmed by being drawn into its fatal web; this includes the child witnesses of the violence, who often carry the damaging effects into their own subsequent relationships. However, they cannot do all this without a well coordinated, locally driven multidisciplinary team-based approach.

Doctors can participate in much-needed research into the emotional and social roots of domestic violence, and development and testing of intervention programmes for both offenders and victims. The methodologies required for such research are often complex, but the experience gained from the study of other major public health problems, such as obesity, will provide a fecund resource.

Above all, they can help – along with many others – in action to prevent the violence occurring in the first place. This will involve work to change prevailing assumptions that narrowly stereotype women and impose unrealistic demands on all the parties in a relationship. Preventive work must start early, involve both boys and girls, and continue throughout school years. The media could play a positive and ongoing role in promoting awareness of the nature of the problem.

The contribution of domestic violence to both physical and mental health problems should be included in under- and postgraduate educational programmes, including continuing professional development, to enhance the possibility of effective responses.

Doctors can play an important role in developing and implementing major changes in the social response to the problem of domestic violence. It is time this was recognised and it is time they started doing so.

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References


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Physical activity and sedentary behaviour: applying lessons to chronic obstructive pulmonary disease
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Key words
physical activity, sedentary behaviour, chronic obstructive pulmonary disease.

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Abstract
In health and disease, the benefits of regular participation in moderate to vigorous intensity physical activity are well documented. However, individuals with chronic conditions, such as those with chronic obstructive pulmonary disease (COPD), typically do very little activity at a moderate or vigorous intensity. Much of their day is instead spent in sedentary behaviour, such as sitting or reclining, which requires very little energy expenditure. This high level of time spent in sedentary behaviour can have serious health consequences, including increased risk of diabetes, cardiovascular disease and premature mortality. There is emerging evidence to suggest that participation in light intensity physical activities (e.g. standing or slow walking) may have benefits for cardio-metabolic health. Given the low aerobic capacity of individuals with moderate to severe COPD, increasing light intensity activity (through reducing sedentary time) may be a feasible additional strategy to improve health in this population, alongside traditional recommendations to increase the time spent in moderate to vigorous intensity physical activity. This review provides an overview of physical activity and sedentary behaviour, with a particular emphasis on these behaviours for people with COPD. It provides suggestions for the measurement of these behaviours within the clinical setting, as well as for interventions that may be effective at increasing physical activity and reducing sedentary behaviour in this population.

Introduction
The widespread benefits of regular participation in moderate to vigorous intensity physical activity are well established.1 However, consistent with international data, the majority of Australian adults fail to meet the recommended levels of physical activity to produce health benefits.2 This high level of inactivity contributes significantly to healthcare costs.3 Recently, there has been a focus on sedentary behaviour, or too much sitting. Specifically, there is growing evidence that excessive sedentary time, in particular time accumulated in uninterrupted bouts of sedentary behaviour, is associated with adverse health outcomes.4,5 Individuals with chronic obstructive pulmonary disease (COPD) typically engage in very little physical activity due to exertional dyspnoea and fatigue. Although pulmonary rehabilitation, which has a focus on exercise training, has strong evidence for reducing symptoms, improving exercise tolerance and quality of life, and reducing healthcare utilisation in this patient population, there is limited evidence that pulmonary rehabilitation increases daily levels of physical activity and reduces sedentary time.

This review provides an overview of the health benefits of physical activity across the spectrum, from light intensity through to moderate and vigorous intensity, as well as the health consequences of sedentary behaviour.
as the adverse health effects of too much time spent in sedentary behaviour. It includes a summary of the methods used to measure physical activity and sedentary behaviour in research and clinical settings. Estimates of time spent in physical activity and sedentary behaviour by people with COPD are described as well as some direct and ‘stealth’ interventions that aim to increase physical activity and reduce sedentary behaviour.

**Physical activity: definition and measurement**

Physical activity is defined as any bodily movement generated by skeletal muscle that results in energy expenditure.\(^1\) It is often classified as light, moderate or vigorous intensity, according to the level of energy expenditure required (Fig. 1).\(^9\) Multiple different behaviours fall under these intensity classifications. For example, light intensity physical activity would include activities, such as showering and ironing.\(^10\) In contrast, vigorous intensity physical activity would include activities, such as running and walking up hills.\(^10\) Physical activity may also be classified as activities undertaken as part of daily living, such as domestic and occupational tasks, or as exercise, which is a form of physical activity that is planned, structured and undertaken regularly with the goal of improving or maintaining fitness (Table 1).\(^4\)

Obtaining accurate and detailed measures of physical activity are useful when designing and evaluating interventions to optimise activity levels. Measures of physical activity can broadly be grouped into subjective (i.e. self-report) and objective. Subjective measures rely on an individual’s recall of their activity levels. Although data obtained through subjective measures, such as questionnaires, may lack precision,\(^11\) detailed questioning over recent time periods has been shown to improve the reliability of the data obtained.\(^12\) Subjective measures also offer the opportunity to obtain detailed information regarding the type of activities undertaken during daily life, which allows clinicians to establish targets and goals regarding participation in physical activity, based on individual preferences. The low cost associated with self-report measures of physical activity has resulted in their widespread use in clinical practice and epidemiological research.

Objective measures involve using a device, commonly a motion sensor, to capture physical activity. Devices range in complexity and price. The most basic option is a pedometer, which records the number of steps taken. More sophisticated devices may use accelerometry to measure movement and/or non-invasive physiological sensors to estimate energy expenditure. The measurement properties of these devices and their output vary

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**Table 1** Definition of key terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Physical activity</td>
<td>Any bodily movement produced by skeletal muscles that results in energy expenditure above resting levels. Physical activity broadly encompasses exercise, sports and physical activities done as part of daily living, occupation, leisure and active transportation.</td>
</tr>
<tr>
<td>Light physical activity</td>
<td>Activity with a relative intensity of 20% to &lt;40% of VO(<em>2)(</em>\text{max}). For the general population, it has been defined as activities that have an energy expenditure of &gt;1.5 to 3 MET. It includes activities, such as showering and ironing.</td>
</tr>
<tr>
<td>Moderate to vigorous physical activity</td>
<td>Activity with a relative intensity of 40% to &lt;60% (moderate) or ≥60% (vigorous) of VO(<em>2)(</em>\text{max}). For the general population, it has been defined as activities that have an energy expenditure ≥3 MET. It includes activities, such as brisk walk, cycling, walking uphill, rowing and running.</td>
</tr>
<tr>
<td>MET</td>
<td>An index of energy expenditure. One MET is equal to an oxygen uptake of 3.5 mL/kg/min, which is the rate of energy expenditure while sitting at rest.</td>
</tr>
</tbody>
</table>

\(^1\) MET, metabolic equivalent of tasks; VO\(_2\)\(_\text{max}\), maximum rate of oxygen uptake.
considerably. Most devices require technical expertise to collect, download and interpret the data. Nevertheless, technology in this area is advancing quickly, and it is likely that the collection of robust physical activity data through objective methods will be feasible for clinicians in the near future. Further information on the measurement of physical activity is available elsewhere.13,14

Health effects of moderate to vigorous physical activity

In adults, the benefits of regular participation in moderate to vigorous intensity physical activity have been well established and include a reduction in the risk of cardiovascular disease as well as all-cause mortality.1 These effects are likely to be mediated by several mechanisms, including production, expression and release of myokines by the skeletal muscle, improvement in endothelial function, cardiovascular fitness and insulin sensitivity, maintenance of a healthy body weight, preservation of fat-free mass and a reduction in circulating systemic inflammatory biomarkers.1,15 Evidence of health benefits has resulted in a range of public health messages designed to promote participation in daily physical activity, with current guidelines from the United States recommending that adults perform a minimum of 150 min of moderate intensity physical activity or 75 min of vigorous intensity physical activity each week.1 However, despite the obvious health benefits of an active lifestyle, 31% of adults worldwide do not meet these guidelines and are considered physically inactive.16 This high level of inactivity has serious public health and economic consequences, with low levels of physical activity increasing the risk of developing conditions, such as obesity and type II diabetes.1 Further, there is evidence to suggest that low levels of physical activity also play a part in the development of some cancers, dementia and mood disturbances, such as depression.1 Overall, low levels of physical activity have been estimated to account for 9% of premature mortality, or more than 5.3 million deaths worldwide each year.17

What about time spent in activity other than moderate to vigorous physical activity?

To date, much of the public health research and resources have been targeted towards increasing population levels of moderate to vigorous intensity activity. However, on average, adults spend more than 90% of their waking day in activities other than those classified as moderate or vigorous intensity.1 Even if an individual was to undertake the minimum of 30 min/day of moderate to vigorous intensity activity specified in public health guidelines,7 time in this activity intensity would still constitute less than 5% of a typical 16-h waking day. Accordingly, a more comprehensive view of inactivity has increasingly penetrated research, policy and practice. This approach considers activities across a spectrum from sedentary, to light intensity activity to moderate and vigorous, with a focus on understanding the distribution and health effects across this range of physical activity (Fig. 1).

Sedentary behaviour: definition and measurement

On average, the majority (46–59%) of adults spend their waking hours at the low end of the spectrum, that is, in sedentary behaviour.7 Sedentary behaviours are defined both by low energy expenditure (<1.5 metabolic equivalent of tasks) and a sitting or reclining posture.18 They occur throughout the waking day (i.e. sleep is not considered a sedentary behaviour), and across work, leisure, domestic and transport domains. Common behaviours that occur while sedentary include television viewing, reading, driving, using a computer and playing cards. Importantly, an individual can be both physically active (i.e. meet the physical activity guidelines)1 and highly sedentary; a concept coined ‘the active couch potato’.19 As outlined later, time spent in both physical activity and sedentary behaviour contributes to health outcomes.

As is the case for physical activity, both subjective and objective measures can be used to measure sedentary time. In addition to measuring the total time spent in sedentary behaviours, measures can also be used to assess behaviours within individuals and groups, in the context of the domains in which they occur. To date, self-report measures of time spent in sedentary behaviour have typically been used, with generally good reliability, but poor-to-modest validity.20 More recently, methods, such as past day recall show improved validity over previous recall periods, and may be useful for large-scale implementation.21 However, even a simple question, such as ‘in the last week, how much time per day would you typically spend sitting down?’ could be useful in a clinical setting to provide tailored advice and monitor changes over time.

Objective measures, such as those derived from accelerometers and inclinometers, have also been used to measure sedentary time. Importantly, these devices provide date and time stamped data, which enable analysis of not only the total amount of time spent in sedentary behaviours, but also how and when the sedentary time was accumulated. Ideally, such measures derive sedentary time not only from low energy expenditure,
but also posture in order to distinguish time spent sedentary (low energy, sitting or reclining posture) from time spent standing (low energy, upright posture). Postural-based measures, such as the activPAL monitor (PAL Technologies, Glasgow, UK), have been shown to be highly accurate compared to direct observation, and their use is becoming more widespread within both intervention and observation research. However, these objective measures do not capture domain or behaviour-specific information; contextual information that is useful for the development of intervention targets aimed at individuals and public health messages on how to reduce sedentary time. Therefore, it is recommended that a combination of both self-report and objective measures is used.

**Health impacts of too much sitting**

The last decade has seen rapid advances in our understanding of the relationship between time spent in sedentary behaviours and health outcomes. A recent review reported that those categorised in the most sedentary group, regardless of how it was measured, had on average, twice the risk of developing type II diabetes or cardiovascular disease, or of dying from cardiovascular disease, and 1.5 times the risk of dying prematurely compared to those in the group who were the least sedentary. Detrimental associations with excessive sedentary time have also been observed with weight gain, depressive symptoms, biomarkers of chronic disease risk (including triglycerides, HDL cholesterol and insulin), musculoskeletal symptoms, poor quality of life and chronic kidney disease. Notably, although those who are both inactive and have high sedentary time are at the highest risk, even in those who met physical activity guidelines (i.e. are ‘active’), detrimental associations with sedentary time have been observed. This highlights the need to measure both sedentary time and physical activity within lifestyle assessments. Mechanisms proposed for the associations observed include the minimal muscular contractions in the large postural muscles occurring during sitting, together with the lower energy expenditure compared to non-sedentary behaviours.

Importantly, it is not just total sedentary time that appears to be relevant for health, but also the manner in which it is accumulated. Regularly interrupting sedentary time, with either light or moderate intensity activity, has been beneficially associated with biomarkers of chronic disease. Conversely, long, unbroken periods of sitting have been associated with increased insulin resistance and poor glycaemic control. This evidence has informed the development of national and international recommendations to minimise the amount of time spent in prolonged sitting and to break up sitting as often as possible. Although sufficient robust evidence regarding ‘how often should we get up?’ is not yet available, a practical message may be to ‘sit less throughout the day, and stand up at least every 30 minutes’.

**If not sedentary, then what?**

The strong negative correlations observed between sedentary time and light intensity physical activity suggests that if we are not sedentary, we are typically undertaking light intensity activities. This highly heterogeneous group of behaviours includes standing, incidental movement and slow walking; activities that are difficult to quantify through self-report measurement tools. Correspondingly, despite being high volume (on average, 37% to 46% of adults’ waking hours), little is known about the health effects of behaviours that fall within the light intensity physical activity spectrum. Nevertheless, associations observed with light intensity physical activity tend to be opposite to those demonstrated with sedentary time. Of note, there is preliminary evidence to suggest that there are cardio-metabolic benefits for those who have a positive light-sedentary balance (i.e. more time is spent in light intensity physical activity than sedentary), even if recommended levels of moderate to vigorous intensity physical activity are not achieved. Though it is ideal if adults have both low sedentary time, and high moderate to vigorous intensity physical activity time, these findings collectively suggest that there may also be benefit from shifting sedentary time to light intensity activities; a potentially more feasible and acceptable target for change especially for those with chronic conditions, such as COPD.

**How are physical activity and sedentary time affected in people with COPD?**

Dyspnoea and fatigue during daily activities are frequently reported by people with COPD and appear to contribute to the low levels of physical activity undertaken in this population. Specifically, there are now robust data showing that people with COPD participate in less physical activity when compared with healthy people of a similar age. One of the first studies reporting this difference using an objective measure of physical activity showed that people with COPD spent less time standing and walking when compared with healthy adults of a similar age and gender proportion (Fig. 2). A review of 11 studies that measured physical activity levels in people with COPD and healthy controls revealed that the proportion of time people with COPD spent participating in...
physical activity, relative to the healthy controls, was 57%. The level of physical activity of people with COPD decreases with increased disease severity and in response to an acute exacerbation. Besides engaging in lower levels of physical activity, people with COPD spend a large proportion of their waking hours sitting and lying down. That is, compared to healthy controls, during waking hours, people with COPD spend nearly 25% more time sitting and 200% more time lying down (Fig. 2). In contrast to data on physical activity, sedentary time does not seem to differ across severities of COPD. Of note, it appears that sitting time in this population is associated with lower exercise capacity, lower motivation to exercise and higher number of exacerbations in the past year.

Health benefits of physical activity and consequences of low levels of physical activity in people with COPD

The benefits of participating in regular physical activity are not limited to the general population. Specifically, in people with COPD, regular participation in physical activity has been shown to reduce the risk of hospitalisation and lower all-cause mortality. Higher levels of physical activity in those with COPD also appear to minimise extrapulmonary manifestations of the disease, such as systemic inflammation and cardiac dysfunction. The benefits of physical activity appear to be present prior to the development of COPD as current smokers who participate in regular physical activity have a reduced rate of decline in lung function. Participation in low levels of physical activity by individuals with a chronic health condition is likely to have additional health consequences to those described in the general population. That is, in addition to the impairments imposed by the disease process itself, deconditioning of both the cardiovascular system and muscles of locomotion resulting from participation in low levels of physical activity often contributes to their decline in functional status. This has led to an interest in the role of rehabilitative strategies that aim to optimise participation in physical activity in people with a chronic health condition.

How can we change physical activity and sedentary behaviour in people with COPD?

There are broadly two approaches to increasing physical activity: direct and ‘stealth’ interventions. Direct interventions use strategies to influence directly physical activity, while ‘stealth’ interventions may target other values and beliefs that extend beyond health to increase physical activity. Data pertaining to interventions that may improve sedentary behaviour in people with COPD are scarce. Regarding physical activity, one direct intervention that has received attention in people with COPD is the use of exercise training, within the framework of pulmonary rehabilitation. Despite achieving strong evidence for reducing symptoms of dyspnoea and fatigue, increasing exercise capacity, improving quality of life and reducing hospitalisations related to acute exacerbations of COPD, the effects of exercise training on physical activity appear to be limited. A systematic review and...
meta-analysis of seven studies (two randomised trials and five single-group interventional studies) examining the effect of exercise training on physical activity in a total of 472 people (419 males) with COPD demonstrated minimal change, with an overall effect size of 0.12 ($P = 0.01$), which was equivalent to an increase of approximately 5 min per day. This small change may be because pulmonary rehabilitation programmes lack an effective behavioural component that targets changes in physical activity outside of what people complete as part of their structured exercise.

Examining the effects of embedding psychosocial interventions in pulmonary rehabilitation programs is a promising area for future research and may have real potential for changing physical activity and sedentary time in people with compromised lung function. A recent study in overweight and obese adults showed that combining a behavioural intervention with prescribed exercise increased physical activity more so than exercise prescription alone. This would suggest the utility of this approach in people with chronic conditions. The recent Lancet series on physical activity contained a comprehensive review of approaches for increasing physical activity within different population groups, and found strong evidence for behavioural and social approaches. Interventions within the primary care setting are successful at increasing the self-reported physical activity levels of inactive individuals at 12 months, with recent reviews of physical activity interventions in adults and older adults reporting that interventions containing behavioural strategies, such as goal setting, self-monitoring and feedback were most effective. Nevertheless, in people with COPD who are commencing a pulmonary rehabilitation programme, the timing of such interventions may be critical given that for many people, it may be too much to commence a regular exercise programme and at the same time undertake more physical activity in their daily lives.

An example of an evidence-based behavioural approach used in the primary care setting is the 5As approach. This has been used widely in smoking cessation and was adopted in the 2013 National Health and Medical Research Council clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia as a useful framework for general practitioners to help obese patients manage their weight and is based on: Assess level of behaviour; Advise based on personal health risks; Agree on a realistic set of goals; Assist to anticipate barriers and develop a specific action plan; and, Arrange follow-up support. Figure 3 contains an example of how this approach may be used in clinical practice to influence sedentary behaviour.

Rather than direct interventions to increase physical activity, it is possible that ‘stealth’ interventions, such as reducing time spent in sedentary behaviours (e.g. television viewing) in order to increase physical activity, may offer greater success in people with COPD. This fits nicely with the premise that sedentary behaviour is a new health behaviour change target in its own right. While most sedentary behaviour interventions have been conducted with children and adolescents, emerging evidence suggests the utility of this stealth approach in adults. Three studies (all in non-COPD populations) are worth noting here. TVview evaluated a 3-week programme using an electronic television lock-out system with 36 overweight and obese participants aged 22–61 years. Stand Up For Your Health took a whole-of-day approach to reduce and interrupt prolonged sedentary time, targeting television time as well as other sedentary behaviours, such as sitting and reading, or engaging in computer use. This single-group feasibility study conducted over 2 weeks with 59 older adults (aged 60–92 years) used a face-to-face goal-setting consultation and one tailored mailing. The final single group feasibility study was conducted with 24 older adults (aged mean ± SD, 68 ± 6 years) and also used a face-to-face consultation and feedback on sedentary time as part of the intervention. All three interventions achieved around a 30 min per day reduction in sedentary time (24 to 37 min per day), of which approximately one third (7 to 13 min/day) of this time was reallocated to moderate to vigorous intensity physical activity.

The findings from these studies suggest that changes in sedentary time are achievable and that increases in physical activity are likely. Environmental changes, such as devices to limit the amount of TV a person watches, may be difficult to implement; however, behavioural approaches produced similar changes in sedentary time.

Figure 3 Example of using a ‘stealth’ behaviour to increase physical activity by reducing sedentary time.
The consultation sessions in the two feasibility studies\textsuperscript{49,50} used concepts from the 5As approach in that they: assessed participants’ level of sedentary time (using devices); advised participants of the pros and cons of reducing sedentary time; agreed on a set of goals (in conjunction with the participants); and assisted with overcoming barriers. No arrangements were made for follow-up support. These interventions took an average of 45 min\textsuperscript{50} and 30 min\textsuperscript{11} to deliver. The appeal of these approaches is that they are simple, achievable and unlikely to do any harm. However, randomised trials of longer term interventions are needed to evaluate intervention efficacy in a range of populations. While these studies were conducted in non-COPD populations, they were in overweight and obese and older adult populations with a range of chronic conditions.

Earlier work has suggested that people with COPD utilise 58\% of their aerobic capacity to complete usual activities of daily living.\textsuperscript{52} This is considerably more than individuals with normal aerobic capacity, who have been estimated to utilise 40\% of their aerobic capacity during usual activities of daily living.\textsuperscript{31} Given the limited aerobic capacity of individuals with COPD, an intervention focused on increasing light intensity physical activity and breaking up time spent in sedentary behaviour may be more appropriate in this population than one focussed primarily on increasing time spent in moderate to vigorous intensity physical activity. The development of such interventions – a key area for future research in individuals with COPD – should consider the approaches described above (i.e. the 5As; stealth interventions) in conjunction with evidence-based intervention strategies (e.g. motivational interviewing; self-monitoring) for behaviour change.

**Conclusion**

This paper has reviewed the benefits of physical activity and the adverse effects of sedentary behaviour. Exertional dyspnoea and fatigue pose additional challenges for people with COPD when attempting to undertake physical activity. Strategies are needed to assist both healthy individuals and those with chronic conditions, such as COPD to: (i) increase the time spent in physical activity (which includes activity across the intensity spectrum); (ii) reduce total time spent sitting; and (iii) break up any periods of prolonged sitting across the day.

**References**


Activity and sitting: lessons for COPD


CLINICAL PERSPECTIVES

Familial colorectal cancer

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Abstract

Identifying individuals with a genetic predisposition to developing familial colorectal cancer (CRC) is crucial to the management of the affected individual and their family. In order to do so, the physician requires an understanding of the different gene mutations and clinical manifestations of familial CRC. This review summarises the genetics, clinical manifestations and management of the known familial CRC syndromes, specifically Lynch syndrome, familial adenomatous polyposis, MUTYH-associated neoplasia, juvenile polyposis syndrome and Peutz–Jeghers syndrome. An individual suspected of having a familial CRC with an underlying genetic predisposition should be referred to a familial cancer centre to enable pre-test counselling and appropriate follow up.

Introduction

Australia and New Zealand have the highest incidence rate of colorectal cancer (CRC) in the world, with an age-adjusted rate of 46 per 100 000 men and 32 per 100 000 women in 2008.1 The risk of developing CRC by age 85 is 1 in 10 for men and 1 in 15 for women.2 Approximately 30% of the risk of sporadic CRC is thought to be due to inherited genetic factors.3 Conversely, hereditary CRC syndromes with a known high-risk genetic aetiology make up approximately 5% of CRC. Such disorders include Lynch syndrome (LS), familial adenomatous polyposis (FAP), MUTYH-associated neoplasia and the hamartoma syndromes (Table 1).

Identification of individuals and families with these syndromes allows the implementation of effective surveillance strategies which result in a reduction in cancer incidence and death in many cases.

Here we discuss the genetics, clinical manifestations and management of the known familial CRC syndromes,
and offer guidelines on whom to refer to a familial cancer clinic for risk assessment and potential genetic testing.

**Lynch syndrome**

LS (hereditary non-polyposis CRC, HNPCC) is the most common inherited CRC syndrome, accounting for approximately 3% of all CRC diagnoses.4

**Genetics**

LS is an autosomal dominant syndrome caused by a mutation in one of four mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) or the EPCAM gene, which is situated upstream of MSH2. Interestingly, EPCAM is not involved in MMR, but deletions in this gene indirectly cause abrogation of MSH2 function.5,6 Germline MLH1 and MSH2 mutations account for >80% of LS cases,7 MSH6 for up to 10%,7 PMS2 for 2–3% and EPCAM for 1–3%.8 It is likely that PMS2 mutations make a significant contribution to LS but the exact extent of this contribution is currently unclear because of difficulties in distinguishing genuine mutations in this gene from those present in numerous pseudogenes.9

The types of inactivating mutations in the MMR genes include frameshift, nonsense, splice site, missense/in-frame deletions or genomic rearrangements which can occur throughout each gene.10,11 Amino acid altering missense mutations are more common in MLH1 than MSH2.12 Large deletions of the 3' end of the EPCAM gene result in transcriptional read-through and epigenetic silencing of MSH2.13 Founder mutations have also been described such as an A→T transversion in the donor splice site of intron 5 of MSH2, which occurs in Newfoundland,15 but also occurs as a recurrent mutation worldwide and may account for up to 10% of LS cases.14

LS tumours arise when the wild type copy of the gene is lost in the tumour, resulting in inactivation of the MMR pathway in the tumour. This causes an accumulation of errors in long repetitive stretches of DNA called microsatellites, resulting in alleles of differing lengths or 'microsatellite instability' (MSI).15,16

Genes with microsatellites in their coding region often undergo frameshift mutations in MSI tumours and include genes involved in cell proliferation, apoptosis and DNA repair such as TCF4, ILGFR-2, TGFB2, AXIN2, BAX, PTEN, CHK1, MLH3, MSH3 and MSH6.17

**Clinical features and genotype-phenotype correlations**

Individuals with LS are at risk of developing CRC at an earlier age (median age 45) than the general population (median age 71). They have a varying risk to age 70 years of developing CRC which depends upon the gene that is mutated (Table 2). The majority (~70%) of CRC develop proximal to the splenic flexure.18 CRC in LS tends to be poorly differentiated, have mucinous or signet ring histology and have a marked lymphocytic infiltrate.4

Female carriers of a LS mutation carry a 12–54% lifetime risk of endometrial cancer depending on the gene that is mutated (Table 2). The majority (~70%) of CRC develop proximal to the splenic flexure.18 CRC in LS tends to be poorly differentiated, have mucinous or signet ring histology and have a marked lymphocytic infiltrate.4

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**Table 1: Summary of main familial colorectal cancer syndromes with associated genes and phenotypes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated genes(s)</th>
<th>Colonic phenotype</th>
<th>Major extra-colonic associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>CRC often R-sided; tends to be poorly-differentiated; mucinous/signet ring histology; lymphocytic infiltrate</td>
<td>Endometrial, ovarian, gastric, small bowel, urinary tract, brain, biliary cancers; sebaceous gland tumours; keratoacanthomas</td>
</tr>
<tr>
<td>Classical FAP</td>
<td>APC</td>
<td>Multiple adenomatous polyps</td>
<td>Gastric fundic polyps; duodenal adenomas; papillary thyroid cancer; medulloblastomas; desmoids; osteomas</td>
</tr>
<tr>
<td>MUTYH-associated neoplasia syndrome</td>
<td>MUTYH</td>
<td>Adenomatous polyps or CRC without adenomatous polyps</td>
<td>Juvenile polyps throughout gastrointestinal tract; increased risk of small bowel, stomach and pancreas cancers</td>
</tr>
<tr>
<td>Juvenile polyposis syndrome</td>
<td>SMAD4, BMPR1A</td>
<td>Juvenile polyps</td>
<td>Hereditary haemorrhagic telangiectasia</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome</td>
<td>STK11</td>
<td>Hamartomas</td>
<td>Mucocutaneous pigmentation</td>
</tr>
</tbody>
</table>

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In LS, cancers may harbour somatic mutations in KRAS and adenomatous polyposis coli (APC) but rarely BRAF.18

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keratoacanthomas (previously known as Muir–Torre variant).4 The risk of these cancers varies with the specific gene mutated.

**Diagnosis of LS**

The revised Bethesda guidelines22 were developed to help clinicians decide on which CRC to test for MSI. These guidelines are highly sensitive but have poor specificity.23 The Amsterdam criteria 24 have been used since prior to the discovery of MMR gene mutations to identify LS families.24 They remain highly specific for LS mutations (60–70%) but do not have the sensitivity to be used for population screening.

Molecular testing of CRC using MSI or immuno-histochemistry (IHC) for the four MMR proteins is used, where possible, to aid in choosing patients for Lynch syndrome genetic testing. The sensitivity of both methods is high and comparable.25 These tests are also useful in screening for LS in endometrial cancer.26

Certain caveats apply to IHC testing however. False negatives may occur if the protein is present but not functional, which can occur in the presence of germline pathogenic missense mutations.27 Also, 15% of sporadic CRC harbour somatic hypermethylation of the MLH1 promoter causing an MSI phenotype in the cancers with loss of MLH1 IHC and may therefore be mistaken for LS.28 These patients do not have LS and 40% of these CRC may harbour a V600E BRAF mutation that is very rare in LS.29

If a mutation is found in a MMR gene, predictive genetic testing can be offered to unaffected family members before the age at which screening should commence.

**Surveillance and management**

CRC surveillance in LS reduces CRC-related mortality.30,31 is estimated to increase life expectancy by 7 years32 and is cost-effective.33

There is non-randomised, controlled trial evidence that three yearly colonoscopies reduce incidence and mortality from CRC in LS33; however, level IIIC evidence favours 1–2-year intervals between colonoscopies due to the rapid adenoma to carcinoma development in LS and this is the standard practice in Australia.5,34–36

LS mutation carriers should start surveillance colonoscopy at the ages of 25 or 5 years prior to the earliest diagnosis of CRC in the family, whichever is younger.36 There is no recommended age at which surveillance colonoscopies should be stopped.

Guidelines based on expert consensus regarding the management of LS34 suggest that screening for extra-colonic cancers should ideally be done as part of a clinical trial as no direct evidence for reduction in mortality from screening is available. Prophylactic hysterectomy and bilateral salpingo-oophorectomy is recommended for female mutation carriers when they have completed their families and reached the age of 40 years34 as no effective surveillance exists for ovarian or endometrial cancer.37,38 For patients with a family history of gastric cancer or those from a high-risk background (Chinese, Korean, Japanese, Chilean), second yearly gastroscopy may be considered.

**Surgical management of CRC in LS**

When a LS mutation carrier develops CRC, several factors need to be considered when deciding between a partial colectomy and a subtotal colectomy. The risk of interval cancers on surveillance colonoscopies post partial colectomy is between 6% and 35%.37 However, no difference in 10-year survival was seen in a retrospective cohort study of 382 patients who underwent either extended colectomy or a segmental resection for their first CRC, despite a metachronous CRC rate of 0% in those who had an extended colectomy versus 22% for those who had a segmental resection.39 In a separate study, quality of life did not differ significantly between 23 patients who had a segmental operation compared with 27 patients who had extended surgery.40 Both the European Society of Medical Oncology 2013 familial CRC guidelines46 and the LS management guidelines by the Mallorca group47 recommend discussing the option of an extended colectomy with a
LS patient with CRC. Factors including patient wishes, family planning and likely adherence to close follow-up colonoscopic surveillance should be considered.

Chemoprevention

The Colorectal Adenoma/Carcinoma Prevention Program 2 trial randomised over 1000 individuals with known or suspected LS to 600 mg per day of aspirin for 2 years versus placebo. The study’s primary end-point was development of colorectal adenoma or carcinoma. There was no difference in the incidence of colorectal adenomas or carcinomas between the two groups at a mean follow-up time of 27 months. At a mean follow up of 55.7 months, the hazard ratio (HR) for developing CRC in the aspirin group was 0.63 (95% confidence interval (CI) 0.35–1.13, P = 0.12) on an intention-to-treat analysis. In the subgroup of patients who completed 2 years of 600 mg aspirin, the HR was 0.41 (95% CI 0.19–0.86, P = 0.02) compared with the placebo group. There was also a trend to a decrease in non-CRC LS cancers, with the group of patients who completed 2 years of aspirin having a HR of 0.47 (95% CI 0.21–1.06, P = 0.07). Adverse events did not differ while on treatment; however, data were not collected on post-intervention adverse effects. The ongoing Colorectal Adenoma/Carcinoma Prevention Program 3 trial is determining the optimal dose of aspirin.

Constitutive MMR deficiency

Constitutive mismatch repair deficiency, a rare autosomal recessive condition, has been described primarily in the paediatric population. The inheritance of biallelic MMR gene mutations results in lack of competent MMR in all tissues. Individuals develop haematological malignancies and rare brain tumours such as gliomas in childhood as well as LS-associated tumours and café au-lait spots. It can also present with colonic polyposis suggestive of attenuated FAP or MUTYH-associated neoplasia. This condition is diagnosed on IHC for MMR proteins, and demonstrates absent MMR staining in both tumour and surrounding normal tissue.

Familial adenomatous polyposis

Classical FAP results in the development of hundreds to thousands of polyps in the colon and/or rectum by the time of adolescence. Untreated, FAP results in CRC in –100% of cases by the fourth decade. Seventy to eighty per cent of these CRC are left sided. FAP occurs in 1 in 8000–10 000 individuals and accounts for <1% of cases of CRC.

Genetics

FAP is caused by germline mutations in the APC gene on chromosome 5q. Ninety-five per cent of APC mutations are protein truncating. While FAP is an autosomal dominant syndrome, it has been estimated that 25% of germline APC mutations occur de novo. APC is a tumour suppressor gene. It is thought of as a ‘gatekeeper’ gene as it inhibits cell growth by regulating signalling through the Wnt pathway. It also plays a role in other processes including cellular adhesion, cytoskeleton stabilisation and possibly cell cycle and apoptosis.

The position of a germline mutation within the APC gene is associated with particular clinical features producing a phenotype/genotype correlation. Mutations between codons 1250 and 1464 are associated with a more severe form of the disease (>5000 polyps). Mutations in codon 1309 result in an earlier onset of CRC at a mean age of 35 years. Mutations at or beyond codon 1444 confer an 11-fold increase in risk of developing desmoids. Mutations between exons 9 and 15 (codons 311 to 1444) are associated with congenital hypertrophy of the retinal pigment epithelium (CHRPE), which is the commonest extra-intestinal manifestation of FAP. Once a pathogenic mutation in the APC gene is found, presymptomatic genetic screening can be offered to blood relatives.

An attenuated form of FAP is associated with mutations in the 5’ end, exon 9 and 3’ ends of the APC gene. This group of patients generally has a delayed appearance of colonic adenomas and CRC by around 10–20 years. In clinically determined attenuated FAP with 30–100 polyps, an APC mutation is found in 30% of cases.

Extra-intestinal manifestations of FAP

FAP is associated with gastric fundic gland polyps and duodenal adenomas, duodenal cancer, papillary thyroid cancer (rare), hepatoblastoma in childhood (rare) and central nervous system tumours (predominantly medulloblastoma). Non-malignant associations include desmoid tumours, CHRPE, epidermoid skin cysts and osteomas (Gardner syndrome), lipomas and adrenal tumours (very rarely malignant). CHRPE associated with FAP tends to manifest as multiple bilateral lesions with a depigmented halo.

The main causes of death in FAP patients following colectomy are duodenal cancer and desmoid tumours. Desmoid tumours are locally aggressive connective tissue tumours that do not have metastatic potential. They usually occur in the abdominal wall or mesentery or in an abdominal surgical scar, and may cause morbidity and mortality due to small bowel obstruction, ischaemia or...
perforation, intra-abdominal abscesses and fistulas, or ureteric obstruction.\textsuperscript{35}

**Surveillance and management**

Since the advent of molecular diagnosis and prophylactic surveillance and surgery, the mortality from CRC in FAP has decreased significantly.\textsuperscript{35} For known APC mutation carriers and at risk relatives from families where a clinical diagnosis has been made but in which mutation testing is not possible, two yearly flexible sigmoidoscopy should start at the age of 12–14 years of age.\textsuperscript{34} Yearly colonoscopy should be done when polyps are seen and continued until colectomy.\textsuperscript{36} Colectomy is usually performed in late adolescence or early adulthood. Surgical options are proctocolectomy with ileal pouch-anal anastomosis in individuals with a high rectal polyp burden or total colectomy with ileorectal anastomosis. Those with a retained rectum require annual endoscopy post-colectomy.

For attenuated FAP cases, two yearly colonoscopy is recommended rather than sigmoidoscopy, starting at the age of 18–20 years,\textsuperscript{36} as adenomas are found throughout the colon.

Screening for extra-intestinal manifestations of FAP should begin at diagnosis or at the age of 25–30 years, whichever is earlier.\textsuperscript{34} Upper gastrointestinal endoscopy using both front- and side-viewing endoscopy is performed every 5 years until the detection of adenomas.

The frequency of upper endoscopies once adenomas are detected depends on the Spigelman stage of the polyps,\textsuperscript{60} which takes into account polyp number, size, histology and dysplasia.

Symptomatic desmoid tumours may be treated with medical therapy including non-steroidal anti-inflammatory drugs with tamoxifen or raloxifene\textsuperscript{64} and with chemotherapy.\textsuperscript{65} Surgical manipulation may result in disease progression and should only be undertaken by specialist surgeons after multidisciplinary consultation.\textsuperscript{64}

**Chemoprevention**

Small trials have suggested that ascorbate,\textsuperscript{63} sulindac\textsuperscript{64} and the COX-2 inhibitors\textsuperscript{65} may result in a reduction in adenoma burden of 10–40% while on treatment.\textsuperscript{64} Some patients had regression of their adenomas; however, the adenomas recurred when treatment was stopped. The Concerted Action Polyp Prevention 1 trial did not find any effect on polyp number with the use of aspirin or resistant starch. Aspirin is not currently used for chemoprevention of FAP.

**MUTYH-associated neoplasia**

MUTYH-associated polyposis (MAP) is an autosomal recessive syndrome that results in the development of several to hundreds of colorectal polyps and/or CRC\textsuperscript{47} and can present in a similar manner to FAP. MUTYH is an important differential diagnosis in individuals with presumed de novo FAP, and genetic testing is the only means to differentiate between these two conditions, which have significantly different clinical implications to relatives of the affected individual. While the association of MUTYH gene mutations with hereditary CRC was first defined in patients with colorectal polyposis,\textsuperscript{67,68} subsequent population-based CRC studies have found that up to one third of patients with biallelic MUTYH mutations develop CRC without additional polyps being identified at the time of diagnosis.\textsuperscript{69,70} Hence MUTYH-associated CRC is not invariably associated with colorectal polyposis and is a diagnosis that should be considered in young onset CRC irrespective of polyp status. Patients with biallelic mutations in MUTYH have a 93-fold increased risk of CRC although this figure is subject to ascertainment bias.\textsuperscript{71} MAP is associated with duodenal polyposis (<20%) and gastric fundic polyps (11%).\textsuperscript{72} Other extra-intestinal manifestations have been observed in case reports, including ovarian cancer and sebaceous gland tumours but not desmoids.\textsuperscript{73}

**Genetics**

The MUTYH gene is critical in the base excision repair pathway. It is an adenine-specific DNA glycosylase responsible for removing mispaired adenines. Biallelic MUTYH mutations result in persistence of mispairing between an oxidatively modified form of deoxyguanine and adenine, leading to G:C→T:A transversion mutations.\textsuperscript{69} This is frequently seen in the APC and KRAS genes in tumours from MAP patients.\textsuperscript{74}

There are two founder mutations in MUTYH in the Caucasian European population: p.Tyr179Cys and p.Gly396Asp, which account for approximately 73% of MUTYH mutations in these populations.\textsuperscript{73} Homozygosity for the p.Tyr179Cys mutation is associated with a more severe phenotype, with a significantly increased risk of CRC (56-fold vs 19-fold) and an earlier mean age of diagnosis (49.5 years vs 57.9 years) compared with homozygosity for p.Gly396Asp.\textsuperscript{74} The mean age of onset of the p.Gly396Asp/p.Tyr179Cys compound heterozygote is in between the two homozygous groups at 52.5 years.\textsuperscript{76}

Other pathogenic MUTYH mutations have been identified in different ethnic groups. For example, the p.Val466Leu mutation was found to be homozygous in four apparently unrelated affected Indian patients.\textsuperscript{77}
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suggesting that this may be an important pathogenic variant in the Indian population.

Under 1% of CRC is due to inherited biallelic mutations of the MUTYH gene.\textsuperscript{71,74}

**MUTYH heterozygotes**

Multiple studies have attempted to ascertain if carriers of one MUTYH gene mutation have an increased risk of CRC.\textsuperscript{69,71,74,79} A large meta-analysis found a small increase in CRC in monoallelic mutation carriers (odds ratio (OR) 1.15 (95% CI = 0.98–1.36)).\textsuperscript{80} Several smaller well-designed studies suggest a modestly increased risk.\textsuperscript{71,78,79}

In this context, it is reasonable to offer individuals with one MUTYH mutation population screening advice, or five yearly colonoscopy from the age of 50 if they have a family member affected with CRC before the age of 55 years.\textsuperscript{81}

**Surveillance and management for MAP**

There are no controlled clinical trials of surveillance in biallelic MUTYH mutation carriers to inform practice. The European Society for Medical Oncology guidelines\textsuperscript{86} suggest following the surveillance and management recommendations for attenuated FAP. Upper gastrointestinal endoscopy is reasonable but the optimal frequency is unknown.

**Hamartoma syndromes**

Hamartomas are benign tumours consisting of cells from the tissue of origin growing in a disorganised way. The hamartomatous polyposis syndromes juvenile polyposis syndrome (JPS) and Peutz–Jeghers syndrome (PJS) are associated with an increased risk of various malignancies.

JPS is an autosomal dominant condition. The word ‘juvenile’ in juvenile polyposis refers to the polyp histology, not the patient age. The diagnosis of juvenile polyposis requires at least three juvenile polyps, a family history of juvenile polyposis or juvenile polyps throughout the entire digestive tract. The incidence of JPS is 1:15 000–1:50 000. Children with juvenile polyposis may present with rectal bleeding, anaemia, obstruction or abdominal pain between the ages of 4 and 14 years of age. Individuals with JPS have an increased risk of CRC (39–68%) and small bowel, stomach and pancreas cancers (21%).\textsuperscript{52,81} SMAD or BMPRIA gene mutations are seen in approximately 40–60% of JPS cases.\textsuperscript{84–86} Around 20% of SMAD4 mutation carriers have associated hereditary haemorrhagic telangiectasia (HHT),\textsuperscript{86} which manifests as recurrent epistaxis, mucocutaneous telangiectasia or pulmonary, cerebral or hepatic arteriovenous malformations. A suggested approach to surveillance in JPS is colonoscopy every 2 years from the age of 15 years and upper gastrointestinal endoscopy every 2 years from the age of 25 years.\textsuperscript{27} Upper and lower gastrointestinal scopes should occur yearly once polyps are seen.\textsuperscript{27} Consideration of HHT is required for all individuals carrying a SMAD4 mutation, and appropriate surveillance and management is required.\textsuperscript{87}

PJS may present with typical mucocutaneous pigmentation in childhood and/or bowel intussusception, obstruction or bleeding. Hamartomatous polyps are found throughout the gastrointestinal tract, particularly in the jejunum. They can also be found in extra-intestinal sites such as the bladder and respiratory tract. The incidence of PJS is 1:50 000–1:200 000. There is an increased risk of CRC (39%), breast cancer (45%), pancreatic cancer (11%), stomach cancer (29%), gynaecological cancer (18%) and Sertoli cell tumours of the testis.\textsuperscript{71,78} Mutations in the STK11 gene are found in up to 70% of cases.\textsuperscript{71} It is inherited in an autosomal dominant fashion, although up to 40% may occur de novo.\textsuperscript{87}

Surveillance for cancer in asymptomatic individuals with PJS should begin at age 30 years, and include gastroduodenoscopy, colonoscopy and video capsule endoscopy or barium follow through or magnetic resonance endoscopy at least three yearly.\textsuperscript{90} Recommendations for women with PJS include annual breast MRI and bilateral mammography ± ultrasound from the age of 30–50 years and annual mammography and clinical breast examination from the age of 50 years.\textsuperscript{90} Bilateral risk reducing mastectomy may be considered. Individuals with a family history of breast cancer under the age of 35 years may require modified screening plans. A pelvic examination, endoscopy and pap smear by a gynaecologist every 2 years from the age of 18 years is also recommended.\textsuperscript{90}

**Conclusion**

Cancer is, in essence, a genetic disease.\textsuperscript{71} There is an increasing focus on categorising cancers according to their molecular aetiology, rather than their clinical manifestation, or phenotype, as has been done in the past. Neither is sufficient on its own. We now know that the same clinical picture can come about as a result of inherited mutations in different genes.\textsuperscript{89} Conversely, a mutation in the same gene can give rise to different phenotypes, for example biallelic mutations in MUTYH can present with polyposis or CRC without polyposis.\textsuperscript{71} Classifying a cancer by its phenotype alone may put cancers with very different patterns of inheritance and natural histories in the same group.
This has implications for inherited CRC as the diagnostic algorithms are now more complex. Germline DNA tests should ideally be carried out at a familial cancer centre to enable appropriate pre-test counselling and follow up. The Cancer Council of New South Wales has published referral guidelines for clinicians to refer patients who may be at risk of familial CRC. These guidelines are available on the website www.eviq.org.au and are summarised in Table 3.

Genetic counselling should be offered before a diagnostic genetic test is carried out. Genetic testing should begin with an affected family member as this will allow more focused genetic tests to be performed subsequently on other family members. In the event that a germline mutation is not identified, surveillance is still recommended and tailored to the individual and family.

There has been significant progress in the understanding of the genetic mechanisms underlying familial CRC since the discovery of the APC gene in 1987. However, there remains a group of affected families for which a causative genetic mutation has yet to be identified. Further research is required to delineate the hereditary factors that may account for the increased risk of CRC in these families. Identification of the hereditary factors responsible for this increased risk will lead to more streamlined counselling and management of these affected families.

### Table 3 CRC and polyposis referral guidelines based on eviQ Cancer Treatment Online

<table>
<thead>
<tr>
<th>Individual characteristics</th>
<th>Blood relative of a known mutation carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 20 cumulative adenomatous polyps at any age</td>
<td>Greater than 20 cumulative adenomatous polyps at any age</td>
</tr>
<tr>
<td>Greater than 3 cumulative adenomatous polyps by 30 years of age</td>
<td>Greater than 30 polyps of any type at any age</td>
</tr>
<tr>
<td>Multiple Lynch or Peutz–Jeghers syndrome-related cancers in the same individual</td>
<td>Isolated CRC before 50 years of age</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history characteristics</th>
<th>Tumour pathology characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three Lynch syndrome-related cancer cases (CRC, small bowel, endometrial, ovarian, gastric, brain, urothelial transitional cell carcinoma) in 1st or 2nd-degree relatives of any age</td>
<td>Greater than 2 hamartomatous polyps at any age</td>
</tr>
<tr>
<td>Two CRC cases in 1st or 2nd-degree relatives before the age of 50 years</td>
<td>Greater than 2 juvenile polyps at any age</td>
</tr>
<tr>
<td>Gastrointestinal polyposis at any age</td>
<td>Gastrointestinal polyposis at any age</td>
</tr>
<tr>
<td>MSI or abnormal MMR IHC on CRC before the age of 60 years</td>
<td>MSI or abnormal MMR IHC on CRC before the age of 60 years</td>
</tr>
</tbody>
</table>

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Familial colorectal cancer


Lung et al.


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polyposis due to inherited mutations of $\text{MYH}$.


Clinical triage for colonoscopy is useful in young women

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Key words
colonoscopy, endoscopy, diagnosis, human, female.

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Abstract

Background: Colonoscopy is an invasive procedure and a limited resource. It is therefore desirable to restrict its use to those in whom it yields an important diagnosis, without missing pathology in others.

Aim: The aim of this study was to determine whether standard clinical criteria can be used to reliably distinguish when colonoscopy is advisable in women 30 years and younger.

Methods: A retrospective audit was performed at a single centre of 100 consecutive colonoscopies performed in women 30 years old and younger. The indications for the colonoscopy were recorded, and divided into clear and relative indications. The primary outcome of whether an endoscopic diagnosis was made was compared between the two groups. Clear indications for colonoscopy included overt rectal bleeding, elevated inflammatory markers, anaemia, iron deficiency and strong family history of colorectal cancer. Relative indications included abdominal pain or discomfort, bloating and altered bowel habit/motions.

Results: The average age was 23 years. Sixty women had both relative and clear indications. Eleven had only clear indications and 28 only relative indications. Altogether, 58 colonoscopies were normal, and 17 showed inflammatory bowel disease. No subject with only relative indications had an abnormal finding (0/28). The diagnostic yield was significantly different between those with only relative indications (0%) versus those with at least one clear indication (59%; \( P < 0.0001 \)).

Conclusions: Standard clinical criteria can be used to restrict safely the use of colonoscopy in young women. This will avoid performing procedures in people without clear indications, saving costs, resources and complications.

Introduction

The indications for colonoscopy are clearly defined by various organisations. However, what is not clear is whether we can use standard clinical criteria in low-risk populations to restrict reliably the use of colonoscopy. Colonoscopy is an invasive procedure with a documented rate of serious complications, such as bleeding and perforation, varying from 0.2–0.3%. Despite the risks of the procedure staying relatively stable with age, the pick-up rate of a serious finding is far lower in younger as compared with older subjects – even without considering symptoms. For example, the chance of a 30-year-old patient presenting with colorectal cancer within the next 5 years is 1 in 7000, as compared with 1 in 100 for a 60 year old. In addition, resources for colonoscopy are limited, and there are significant costs associated with it, both direct and indirect. Common reasons given for requesting a colonoscopy, especially in the young, are symptoms pertaining to irritable bowel syndrome (IBS) or other functional abdominal symptoms, with up to a quarter of colonoscopies being performed in those with IBS-related symptoms.
This is despite recommendations that a positive diagnosis of IBS should be made on clinical grounds, with colonoscopy specifically not indicated in those less than 50 years with typical IBS symptoms and no alarm features. Therefore, it is important, based on a large number of personal and population-based factors, to restrict the use of colonoscopy to those for whom it is genuinely medically indicated. This has not been studied in a young population. Despite this, we know anecdotally that many individual clinicians find it hard to resist actively performing a procedure as they worry about the implications of a missed diagnosis. Therefore, we set out to determine the ability of standard clinical criteria to predict reliably a clinical finding in young patients undergoing diagnostic colonoscopy. Given that functional disorders, particularly IBS, are more prevalent in females, we focussed on females 30 years old and younger.

Methods

A retrospective audit was carried out of the last 100 consecutive colonoscopies in women aged 30 years old or younger. The audit was carried out at the Royal Adelaide Hospital, a large metropolitan teaching hospital in South Australia. The endoscopy unit has an annual load of approximately 1800 colonoscopies, with roughly 350 colonoscopies on the waiting list for a 6-month period.

Reports were obtained from the electronic recording system, ‘Endoscribe’. Inclusion criteria were colonoscopy reports of patients who were female and aged 30 years old or less at the time of colonoscopy. There were no exclusion criteria. The clinical indications documented on the colonoscopy report, the request form or the case notes were recorded as were any available blood test results pre-procedure which were obtained from electronic sources and case notes. The clinical diagnosis, as well as progress and complications immediately post-colonoscopy, was obtained from the same sources.

Indications for colonoscopy were classified as either ‘clear’ or ‘relative’ as generally accepted medically (Table 1). Clear indications included overt rectal bleeding, elevated inflammatory markers, anaemia, iron deficiency or a strong family history affording at least moderately elevated risk of colorectal cancer (according to Australia’s National Health and Medical Record Council (NHMRC) guidelines). Relative indications included abdominal pain or discomfort, bloating and altered bowel habit.

The results were analysed to assess the diagnostic yield of colonoscopies stratified according to indication (relative vs clear). STATA version 10.0 (Statcorp, Texas, USA) was used for statistical analysis. Binary variables were arranged into two by two contingency tables, from which positive predictive value, negative predictive value, sensitivity and specificity were derived. Comparisons were made using Pearson’s Chi-squared statistics for categorical variables. The study was approved by the Royal Adelaide Hospital Human Research Ethics Committee as a clinical audit.

Results

One hundred sequential colonoscopy records were reviewed. The average age of patients was 23 years (range 16–30). Of the 100 patients, 11 patients had clear indications, 28 patients had only relative indications, and 60 patients had clear as well relative indications. In one case, insufficient data were available to determine the indications fully. In the analysis, this case was assumed to have a clear indication as it could not be safely judged that she did not. Thus, in total, 72 patients had at least one clear indication.

The most commonly noted relative indications were: abdominal pain (n = 64), chronic diarrhoea (n = 33), acute diarrhoea (n = 17), constipation (n = 14) and alternating stool form/frequency (n = 17). Of the clear indications, the most common was overt rectal bleeding (n = 48), followed by iron deficiency (n = 15), 11 of whom were also anaemic (Table 2).

In the 100 colonoscopy reports audited, 58 procedures were reported as normal. The most common single abnormal finding was inflammatory bowel disease (IBD) (n = 17). Other diagnoses included polyps, haemorrhoids, anal fissure, rectal prolapse and one rectal carcinoma (Table 3). In this cohort, no subject had more than one diagnosis.

Of those with only relative indications (n = 28) none had a positive finding at colonoscopy (0%, 95% confidence interval (CI) 0–12.1%). Of those with any clear indication (n = 72), a positive finding was noted in

Table 1 Clear and relative indications†

<table>
<thead>
<tr>
<th>Clear indications</th>
<th>Relative indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt rectal bleeding</td>
<td>Abdominal pain or discomfort</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Bloating</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Altered bowel habit/motions</td>
</tr>
<tr>
<td>Elevated inflammatory markers</td>
<td>(temperature, ESR, CRP, WBC or platelets)</td>
</tr>
<tr>
<td>Strong family history of colorectal cancer</td>
<td></td>
</tr>
</tbody>
</table>

†As per NHMRC guidelines. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells.
42/72 (58%, 95% CI 47–69%). This difference in yield between those with only relative versus any clear indication was statistically significant (P < 0.0001). The positive predictive value of an abnormal colonoscopy with any clear indication was 58.5%, and the negative predictive value in the absence of any clear indication(s) was 100%. Even if findings of a non-serious nature were excluded (n = 10: haemorrhoids, anal fissure or prolapse – all of which could have been diagnosed with proctoscopy or sigmoidoscopy), the difference in yield remained highly clinically relevant and statistically significant – 0% versus 44% (P < 0.0001).

It is important to note that in those without any ‘clear’ indication for colonoscopy, no pathology would have been missed if the colonoscopy had been avoided. The single patient with rectal carcinoma presented with overt rectal bleeding. It was also noted that a higher number of clear indications denoted a higher chance of an abnormal finding at colonoscopy (Table 3). Specifically, of the 17 patients with a finding of IBD, all had at least two clear indications, and 11 of the 17 had three or more clear indications.

Two patients in the study had significant morbidity associated with the procedure, predominantly pain post-procedure. Both patients had presented with only relative indications and had normal colonoscopies. One patient required imaging, opiate analgesia and hospital admission. As expected in such a small cohort, there were no reported perforations or clinically significant haemorrhage.

**Discussion**

In this audit, it was found that, of consecutive women under 30 who had undergone colonoscopy in our unit, 42% overall had a positive finding. This is a very high yield compared with what one might expect. This is likely to be so, due to the fact that many patients were referred for clinically accepted, clear indication(s). Therefore, our data indicate that even in a young woman, any clear indication (such as anaemia, bleeding or raised inflammatory markers) should justify a prompt referral.

However, perhaps the more interesting finding is that the simple application of well-accepted triage criteria would allow further limitation of colonoscopy in this demographic, without any loss of safety or accuracy. This would potentially free up some colonoscopy resources to be used in those who would benefit most, and would save unnecessary risk or morbidity in those who have no medical need for the procedure. However, it needs to be noted that only 28% of our colonoscopy cohort fell into this group. Thus, utilising the criteria, only 28% of colonoscopies could be avoided.

The diagnostic yield of colonoscopy varies greatly depending on indication. One study of 736 colonoscopies (average age 43.6 years), examined diagnostic yield of colonoscopy according to American Society of Gastrointestinal Endoscopy (ASGE) indications.7 The yield ranged from 38% for indications considered ‘generally indicated’, 20% for indications ‘generally not indicated’ and 13% for indications ‘not listed’. Generally indicated indications included such things as haematochezia, unexplained iron deficiency anaemia and acceptable colonic cancer screening or surveillance, whereas ‘generally not indicated’ included ‘chronic, stable, irritable bowel syndrome or chronic abdominal pain’. If we examine the diagnostic yield of the patients in our study, we have figures of 58% for those with a clear (or appropriate) indication, and 0% for those with only relative indications. In a demographic where the prevalence of IBS is relatively high, this audit suggests a conservative approach be taken in the investigation of young women with only relative symptoms, rather than referring directly to colonoscopy given the absent diagnostic yield. The fact that there were complications in two of the 28

### Table 2 Distribution of indications

<table>
<thead>
<tr>
<th>Indications for colonoscopy</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative indications</td>
<td>n</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>64</td>
</tr>
<tr>
<td>Chronic diarrhoea</td>
<td>33</td>
</tr>
<tr>
<td>Acute diarrhoea</td>
<td>17</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
</tr>
<tr>
<td>Alternating bowel motions</td>
<td>17</td>
</tr>
<tr>
<td>Clear indications</td>
<td>48</td>
</tr>
<tr>
<td>Overt rectal bleeding</td>
<td>15</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>11</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
</tr>
<tr>
<td>Family history CRC</td>
<td>0</td>
</tr>
</tbody>
</table>

Note that n > 100, as some patients had more than one indication. CRC, colorectal cancer.

### Table 3 Findings at colonoscopy

<table>
<thead>
<tr>
<th>Outcome colonoscopy</th>
<th>Number of clear indications</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Polyp</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Haemorrhoids</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Anal fissure</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Prolapse</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Histological inflam</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Cancer†</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>39</td>
</tr>
</tbody>
</table>

†Presentation for this patient was overt rectal bleeding.
(7%) patients coming to colonoscopy with only relative indications is concerning enough in our audit to recommend holding off endoscopic evaluation in this low-risk population.

A Scandinavian retrospective study analysed diagnostic yield at colonoscopy according to indication/symptom. They had a similar finding to us, with a high diagnostic yield for clear indications, such as bleeding (67%) and weight loss (33%), and a low diagnostic yield for patients with non-specific gastrointestinal (GI) symptoms, including abdominal pain, change in bowel habit, constipation, flatulence and weight loss (13.2%). We feel that weight loss is a more clear indication for colonoscopy, rather than a non-specific symptom, and the yield in this setting was higher. They did find a significant yield for nonbloody diarrhoea – 31.2% of 176 patients. However, they failed to mention whether there were abnormalities in inflammatory markers, haemoglobin or weight loss, which we feel may well have contributed to increase the pre-test probability. Additionally, the mean age of their patients was 54 years old, with half being male, two factors which may arguably increase diagnostic yield. We are not saying that diarrhoea is not an appropriate indication for colonoscopy, but rather that diarrhoea alone may have a low diagnostic yield in this younger female demographic, as supported by our findings, and that supportive features for organic pathology should be sought before considering endoscopic investigation.

There is one caveat to mention regarding the above, and that is to identify the minor subset of patients who present with diarrhoea who may have a form of microscopic colitis (collagenous or lymphocytic). This is a diagnosis made in predominantly middle-aged to older women (average age at diagnosis 53–69 years), and invariably patients have very watery and frequent stools, with a frequency above four times per day, and often the presence of nocturnal diarrhoea. These specific features of high frequency and nocturnal diarrhoea are unusual in IBS. This small subset of patients would be best served with a flexible sigmoidoscopy (rather than colonoscopy) with colonic biopsies to look for this diagnosis, as recent literature suggests that left-sided colonic biopsies are just as sensitive as full colonic series biopsies in making a diagnosis of microscopic colitis.

The ASGE guidelines give recommendations for indications and contraindications for colonoscopy, as well as settings in which colonoscopy is ‘generally not recommended’. As mentioned above, falling under this latter heading is ‘chronic, stable, irritable bowel syndrome or chronic abdominal pain’. Twenty-eight patients in our audit had only relative indications, and based on our data it might be concluded that colonoscopy may have been reasonably avoided in these patients without missing pathology. On the other hand, our study did not assess the impact of the colonoscopy for the management of these patients. We cannot exclude that the potential ‘therapeutic effects’ due to the reassurance of a normal colonoscopy actually has a relevant influence on the outcome or healthcare utilisation that would justify the procedure.

If a colonoscopy is normal in a patient with symptoms, it is possible that the very fact of doing the procedure may make it more difficult to help the patient come to terms with a functional diagnosis. The flip side of this is that a negative colonoscopy in a young female may provide reassurance, although this is unproven. Pertinently, this issue has been addressed in two previous studies with conflicting results. A prospective study of 59 patients aged less than 50 years old undergoing colonoscopy found a mean reduction in anxiety scores as well as symptom scores, despite a minimal diagnostic yield. However, a second retrospective study of 458 patients under 50 years old with IBS found the opposite, with no association between a negative colonoscopy and reassurance or health-related quality of life. Hence, the justification of doing a colonoscopy in a young female with only relative indications for the sake of reassurance might not be necessarily justifiable. We additionally note that procedure-related pain may be higher in those with functional GI disorders, such as IBS – in one study, 7% needed admission for pain post procedure – which further justifies restriction of use of colonoscopy in this demographic unless there are real concerns for a positive finding.

Another observation made in this study is that the finding of IBD at colonoscopy in this young female population was related to the number of clear indications they possessed. All patients with IBD had at least two clear indications, with 64% of them having three clear indications. This indicates that one should have a higher suspicion of IBD in the patient with multiple clear indications prior to colonoscopy in this demographic. While colonoscopy in this group is necessary to confirm the diagnosis, the diagnosis itself should be anticipated.

The limitations of the study were the retrospective nature, and the small sample size. It was therefore not powered to look at complications, nor cost-effectiveness, but rather yield. One should therefore note, that although none of 28 patients with only relative indications had a significant finding, the 95% CI was 0% to 12%. Hence, based on our sample size, up to 12% of patients may still have had a significant finding. The use of faecal calprotectin to enhance diagnostic accuracy may be of benefit here, by minimising the risk in not performing colonoscopy where only ‘relative’ indications exist.
Conclusion

In women, under 30 years of age, after simple clinical and laboratory parameters are found to be normal, colonoscopy can be safely avoided. These data should encourage gastroenterologists to be confident in making a positive diagnosis of functional GI disease on clinical grounds in the absence of alarm symptoms (or ‘clear indications’), and reserve colonoscopy for subjects in whom the medical need for the procedure is greater.

Acknowledgements

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References

Comparison of the management and in-hospital outcomes of acute coronary syndrome patients in Australia and New Zealand: results from the binational SNAPSHOT acute coronary syndrome 2012 audit


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Key words
cardiology, audit, acute coronary syndrome.

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Abstract

Background/Aims: We aimed to assess differences in patient management, and outcomes, of Australian and New Zealand patients admitted with a suspected or confirmed acute coronary syndrome (ACS).

Methods: We used comprehensive data from the binational Australia and New Zealand ACS ‘SNAPSHOT’ audit, acquired on individual patients admitted between 00.00 h on 14 May 2012 to 24.00 h on 27 May 2012.

Results: There were 4387 patient admissions, 3381 (77%) in Australia and 1006 (23%) in New Zealand; Australian patients were slightly younger (67 vs 69 years, \( P = 0.0044 \)). Of the 2356 patients with confirmed ACS, Australian patients were at a lower cardiovascular risk with a lower median Global Registry Acute Coronary Events score (147 vs 154 \( P = 0.0008 \)), but as likely to receive an invasive coronary angiogram (58% vs 54%, \( P = 0.082 \)), or revascularisation with percutaneous coronary intervention (32% vs 31%, \( P = 0.92 \)) or coronary artery bypass graft surgery (7.0% vs 5.6%, \( P = 0.32 \)). Of the 1937 non-segment elevation myocardial infarction/unstable angina pectoris (NSTEMI/UAP) patients, Australian patients had a shorter time to angiography (46 h vs 67 h, \( P < 0.0001 \)). However, at discharge, Australian NSTEMI/UAP survivors were less likely to receive aspirin (84% vs 89%, \( P = 0.0079 \), a second anti-platelet agent (57% vs 63%, \( P = 0.050 \)) or a beta blocker (67% vs 77%, \( P = 0.0002 \)). In-hospital death rates were not different (2.7% vs 3.2%, \( P = 0.55 \)) between Australia and New Zealand.

Conclusions: Overall more similarities were seen, than differences, in the management of suspected or confirmed ACS patients between Australia and New Zealand. However, in several management areas, both countries could improve the service delivery to this high-risk patient group.
Introduction

The medical knowledge which directs the optimal management of patients with an acute coronary syndrome (ACS) is the result of numerous clinical trials and is summarised in local1–3 and international4–7 guidelines. A key step in the management of ACS patients is for them to access cardiac angiography in a timely manner.1–7 From this investigation revascularisation with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery can be undertaken, where appropriate. Another key area of management is in the provision of proven secondary prevention medication and participation in a cardiac rehabilitation/secondary prevention programme.1–7

The principal challenge for the management of ACS patients is the translation of this robust evidence into clinical practice.8–10 Better delivery of proven care has more immediate potential to improve outcomes than treatment innovations.11

To facilitate better service provision, there is a growing recognition of the need for comparative effectiveness research. The American Institute of Medicine identified healthcare delivery systems and cardiovascular care as among the highest priorities for comparative effectiveness research.12 However, there are few studies that simultaneously examine care and outcomes between countries,13 although international comparisons of healthcare systems have the potential to yield important insights and guide policies.14

Australia and New Zealand have many historical, cultural, economic and medical similarities. However, there are also differences in the delivery of healthcare and other variables between the two countries. For example Australia has a major private healthcare contribution to supplement public hospital care of ACS patients, with significant inter-state differences,15 whereas much less privately funded ACS care is seen in New Zealand.16

The ‘SNAPSHOT’ ACS study was a prospective audit of the care provided to consecutive patients admitted with suspected ACS during a 2-week period in Australia and New Zealand in May 2012.15,16 The purpose of the study was to identify current management and available treatments, with the aim of better understanding the ACS environment, in order subsequently to improve ACS patient care. It provided a unique opportunity to examine the delivery of care between the two countries.

Methods

Study group

The binational SNAPSHOT ACS study was a prospective audit of the care provided to consecutive patients

Australia and New Zealand SNAPSHOT ACS 2012 Steering Committee

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Australia and New Zealand SNAPSHOT ACS 2012 Support

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admitted to an Australian or New Zealand hospital with suspected ACS over a 2-week period: 00.00 h on Monday 14 May to 24.00 h on Sunday 27 May 2012. The study methods are outlined in the initial publications.\textsuperscript{15,16}

In summary, the study was designed and run by academic clinicians and researchers from both countries, with widespread support from the Cardiac Society of Australia and New Zealand, and from many associated state and national groups, including cardiac clinical networks.\textsuperscript{15,16} The binational steering committee, project and data management teams consisted of 31 representatives (see Acknowledgements).

A 2-week audit period was accepted as a compromise between the need to collect sufficient patient numbers to obtain an accurate representative cohort versus the ability of unfunded clinicians and nurses to collect consecutive patient data.

**Data collection**

Written study protocols were supplied to all participating sites, along with definitions of the various data being collected.

The data collection form recorded patient demographics, initial and discharge diagnosis, medication use in hospital and at discharge, as well as investigations undertaken, invasive treatments received and major adverse cardiovascular events (MACE) experienced by patients. Clinical variables enabled the calculation of the Global Registry Acute Coronary Events (GRACE) risk score.\textsuperscript{17} Ethnicity was self-reported at hospital admission.

**Patient eligibility and diagnosis**

The inclusion criterion for the audit was ‘a patient admitted overnight with a suspected or confirmed ACS’. Patients were tracked for the duration of the acute care episode including all transfers between hospitals.

Following admission and investigations, a ‘discharge diagnosis’ was subsequently determined by the local clinical team who confirmed the diagnosis of an ACS as an ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) or unstable angina pectoris (UAP) or determined a ‘non-ACS’ presentation resultant on investigations undertaken in hospital and the patient’s clinical course.

‘STEMI/LBBB’ required ST elevation or new onset left bundle branch block (LBBB) on an electrocardiogram (ECG) at any time during the admission, with elevation of cardiac biomarkers except where patients had died prior to biomarkers being taken. ‘NSTEMI’ required evidence of biomarker elevation with or without ECG changes consistent with ischaemia. ‘UAP’ and ‘chest-pain unlikely ischaemic’ reflected local clinical determination. Where the diagnosis remained uncertain in the absence of definitive ECG changes and/or biomarker elevation, but where the patient received in-hospital coronary revascularisation (either PCI or CABG), the classification of ‘chest-pain likely ischaemic’ was applied. Where a clear alternative primary diagnosis emerged, or when evidence of myonecrosis was considered secondary to another disease process (e.g. pulmonary embolus, sepsis), patients were grouped as ‘other diagnosis including secondary myonecrosis’.

**Patient events and outcome**

In-hospital MACE, previously defined,\textsuperscript{15,16} included the occurrence of any one of the following events: death, new or recurrent myocardial infarction (MI), MI following PCI or CABG, major bleeding, stroke, cardiac arrest or worsening heart failure. Clinical event reporting relied on local documentation using a standardised completion note. Formal adjudication of events was not possible.

**Ethical approval**

Ethical approval (with opt-out consent) was obtained for Australian sites, except for two hospitals in one state where informed consent applied. In New Zealand’s case, following review by the national multicentre ethics committee, the study was deemed to be an audit of clinical management, and a consent waiver was given for all participating sites.\textsuperscript{15,16}

**Statistical analysis**

Data are presented as mean (standard deviation) or median (interquartile range) as indicated. Comparisons between groups for categorical variables were made using Fisher’s exact test, or the Chi-squared test as appropriate. Between groups comparison of non-normally distributed data was made using Wilcoxon/Kruskall–Wallis test. Confidence intervals for rates were calculated using a mid-P method\textsuperscript{18} (www.openepi.com, cited 2014 Sept 10).

All tests were two tailed, $P < 0.05$ was considered significant and since all comparisons had been pre-specified no adjustment to the overall significance level was made. All analyses were performed using SAS (v9.4, SAS Institute Inc., Cary, NC, USA). A deliberate response to some late data clarification from smaller sites led to minor changes to the baseline data; hence, some data have slightly changed from earlier publications.\textsuperscript{15,16,19}
Results

Patient demographics

Over the 2-week period of 14 to 27 May 2012, 4387 patients were admitted with a suspected or confirmed ACS to an Australian (3381 (77%)) or a New Zealand (1006 (23%)) hospital (Fig. 1). Australian patients were 2 years younger; there were mild differences in ethnicity ($P < 0.0001$) and minor clinical differences (Table 1).

Of the 2356 patients with a final diagnosis of a locally confirmed ACS, Australian patients were again younger at 69 vs 72 years ($P = 0.0004$), and again had mild ethnic differences ($P < 0.0001$) and modest clinical differences (Table 2). Australian patients were at a lower cardiovascular risk, as assessed by the GRACE hospital admission score, with a lower median GRACE score (147 vs 154, $P = 0.0008$).

Investigations, revascularisations and adverse events

For the entire cohort ($n = 4387$), Australian patients were less likely to report the receipt of a chest X-ray (80% vs 91%, $P < 0.0001$), or a standard exercise treadmill test (8.8% vs 23%, $P < 0.0001$), but slightly more likely to receive a stress echocardiogram (2.7% vs 1.4%, $P = 0.014$), stress nuclear study (4.4% vs 0.1%, $P < 0.0001$) or an invasive cardiac angiogram (38% vs 33%, $P = 0.0012$) (Table 3). Australian patients had a longer hospital length of stay (2.6 vs 2.2 days, $P = 0.019$).

For patients subsequently determined to have a confirmed ACS ($n = 2356$), Australian patients were still less likely to report the receipt of a chest x-ray (83% vs 92%, $P < 0.0001$) or a standard exercise treadmill test (4.4% vs 17%, $P < 0.0001$) (Table 4). However, there was no difference in the number receiving an invasive cardiac angiogram (58% vs 54%, $P = 0.082$), or revascularisation with PCI (32% vs 31%, $P = 0.92$) or CABG surgery (7.0% vs 5.6%, $P = 0.32$). Further, the hospital length of stay did not differ between the two countries.

STEMI/LBBB patients

There were 419 STEMI/LBBB patients admitted over 2 weeks (Table 5). There was no statistically significant difference between Australia and New Zealand with regards to standard patient demographics; however, Australian patients had fewer exercise treadmill tests (0.6% vs 4.1%, $P = 0.029$) (Table 5).

Reperfusion management and time to treatment of STEMI/LBBB patients

Primary PCI in 39% of STEMI/LBBB patients (Australian 37% vs New Zealand 43%, $P = 0.34$) was the most common form of reperfusion therapy (Table 6). There was no difference in the door to device time (DTDT) with an overall median DTDT of 82 (53, 138) min. Further, 59% patients had a DTDT of ≤90 min (Australia 57% vs New Zealand 67%, $P = 0.28$), the current target time.1–7 Some 29% of patients had a DTDT of >120 min (Australia 32% vs New Zealand 21%, $P = 0.24$).

Fibrinolytic therapy was received by 25% of STEMI/LBBB patients (Australian 23% vs New Zealand 32%, $P = 0.42$). There was no difference in the overall median door to needle time (DTNT) of 42 (interquartile range 25, 70) min. Further, 34% patients had a DTNT of ≤60 min (Australia 36% vs New Zealand 31%, $P = 0.81$) (Table 6), the current target time.1–7

Australian patients were more likely to receive neither fibrinolysis nor primary PCI as a reperfusion strategy (40% vs 27%, $P = 0.017$). In addition, although the use of glycoprotein 2b/3a inhibitor medication, bivalirudin and unfractionated heparin were similar, Australian patients were less likely to receive a low molecular weight heparin (42% vs 56%, $P = 0.020$, Table 5).

In both countries, in-hospital death was seen in 7% of patients, with 29% of patients experiencing a MACE (death, new or recurrent MI, major bleeding, stroke, cardiac arrest or worsening heart failure).

NSTEMI/UAP patients

Of the total 1937 NSTEMI/UAP patients, Australian patients were younger (70 vs 73 years, $P = 0.0006$) and more likely to be male (64% vs 59%, $P = 0.048$); there
were minor clinical differences (Table 7). Australian patients had a lower GRACE score (143 vs 151, *P* = 0.0014).

**Anticoagulation management, GRACE scores and time to treatment of NSTEMI/UAP patients**

Overall, of the 1937 NSTEMI/UAP patients, 982 (51%) received an invasive coronary angiogram (Table 8). Australian patients had higher rates of coronary angiography than New Zealand patients (52% vs 46%, *P* = 0.0011), and Australian patients had a shorter time to angiography (46 h vs 67 h, *P* < 0.0001).

More high-risk Australian NSTEMI/UAP patients with a GRACE score ≥140 received an angiogram (51% vs 42%, *P* = 0.013) than equivalent New Zealand patients. These high-risk Australian patients were also more likely to receive their angiogram within 24 h (24% vs
17%, P < 0.0001) or within 72 h (74% vs 57%, P = 0.0053) than similar New Zealand patients (Fig. 2). Australian patients were less likely to receive low molecular weight heparin treatment (50% vs 68%, P < 0.0001) (Table 7).

Overall 12% of patients experienced a MACE, with a hospital death rate of 1.8%. There was no statistical difference in these outcomes between the two countries (Table 8).

### Discharge medications

Of the 2356 confirmed ACS patients, 49 (2.6%) of 1825 Australian patients and 17 (3.2%) of 531 New Zealand patients died in hospital, with 2290 patients subsequently being discharged. Of the 388 surviving patients following a STEMI/LBBB presentation, the use of aspirin, statins, beta-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACE-I/ARB) and other

### Table 2: Baseline demographic data of patients admitted with confirmed ACS (n = 2356)

<table>
<thead>
<tr>
<th>Country</th>
<th>Australia (n = 1825)</th>
<th>New Zealand (n = 531)</th>
<th>Total (n = 2356)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ACS admissions/All</td>
<td>54%</td>
<td>53%</td>
<td>54%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Age median (range) (years)</td>
<td>69 (20,99)</td>
<td>72 (21,97)</td>
<td>70 (20,99)</td>
<td>0.12</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1194 (65%)</td>
<td>328 (62%)</td>
<td>1522 (65%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Family history</td>
<td>656 (36%)</td>
<td>137 (26%)</td>
<td>793 (34%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Australia (n = 1825)</th>
<th>New Zealand (n = 531)</th>
<th>Total (n = 2356)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>1593 (87%)</td>
<td>430 (81%)</td>
<td>2024 (86%)</td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>5 (0.3%)</td>
<td>43 (7.9%)</td>
<td>48 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Aboriginal</td>
<td>47 (2.6%)</td>
<td>0</td>
<td>47 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Torres Strait Islander</td>
<td>2 (0.1%)</td>
<td>0</td>
<td>2 (0.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asian</td>
<td>21 (1.2%)</td>
<td>10 (1.9%)</td>
<td>31 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>23 (1.2%)</td>
<td>18 (3.6%)</td>
<td>41 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>128 (7.0%)</td>
<td>9 (1.7%)</td>
<td>137 (5.8%)</td>
<td></td>
</tr>
</tbody>
</table>

### Tobacco smoking

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Australia (n = 1825)</th>
<th>New Zealand (n = 531)</th>
<th>Total (n = 2356)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>354 (19%)</td>
<td>85 (16%)</td>
<td>439 (19%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Past</td>
<td>708 (39%)</td>
<td>232 (44%)</td>
<td>940 (40%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Never</td>
<td>763 (42%)</td>
<td>214 (41%)</td>
<td>977 (42%)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

### Clinical factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Australia (n = 1825)</th>
<th>New Zealand (n = 531)</th>
<th>Total (n = 2356)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1240 (68%)</td>
<td>357 (67%)</td>
<td>1597 (68%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>540 (30%)</td>
<td>144 (27%)</td>
<td>684 (29%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1062 (59%)</td>
<td>309 (58%)</td>
<td>1391 (59%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>234 (13%)</td>
<td>92 (17%)</td>
<td>326 (14%)</td>
<td>0.0054</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>208 (11%)</td>
<td>108 (20%)</td>
<td>316 (13%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On dialysis</td>
<td>17 (5.3%)</td>
<td>5 (5.5%)</td>
<td>22 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>Morbid obesity</td>
<td>155 (8.5%)</td>
<td>29 (5.5%)</td>
<td>184 (7.8%)</td>
<td>0.022</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>33 (1.8%)</td>
<td>5 (0.9%)</td>
<td>38 (1.6%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>38 (2.1%)</td>
<td>2 (0.4%)</td>
<td>40 (1.7%)</td>
<td>0.0040</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>254 (14%)</td>
<td>68 (13%)</td>
<td>322 (14%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Active cancer limiting life</td>
<td>48 (2.6%)</td>
<td>8 (1.5%)</td>
<td>56 (2.4%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dementia/cognitive impairment</td>
<td>56 (3.1%)</td>
<td>23 (4.3%)</td>
<td>79 (3.4%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Significant impairment mobility/dependent for ADL</td>
<td>95 (5.2%)</td>
<td>34 (6.4%)</td>
<td>129 (5.5%)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

### Prior vascular disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Australia (n = 1825)</th>
<th>New Zealand (n = 531)</th>
<th>Total (n = 2356)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior myocardial infarction</td>
<td>573 (31%)</td>
<td>179 (34%)</td>
<td>752 (32%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>420 (23%)</td>
<td>118 (22%)</td>
<td>538 (23%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>222 (12%)</td>
<td>67 (13%)</td>
<td>289 (12%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Prior TIA/Stroke</td>
<td>194 (11%)</td>
<td>80 (15%)</td>
<td>274 (12%)</td>
<td>0.0070</td>
</tr>
<tr>
<td>Prior PAD</td>
<td>126 (6.9%)</td>
<td>54 (10%)</td>
<td>180 (7.6%)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

### Grace risk score (Granger)

<table>
<thead>
<tr>
<th>Grace score</th>
<th>Australia (n = 1825)</th>
<th>New Zealand (n = 531)</th>
<th>Total (n = 2356)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRACE score, median [IQR]</td>
<td>147 (125, 173)</td>
<td>154 (132, 181)</td>
<td>149 (126, 175)</td>
<td>0.0008</td>
</tr>
<tr>
<td>% GRACE score ≥ 140</td>
<td>1035 (58%)</td>
<td>346 (66%)</td>
<td>1381 (60%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Killip class (I or II or III/IV)</td>
<td>86% (11/3 of 0.0053)</td>
<td>81% (16/3.5%</td>
<td>85% (12/3.2%</td>
<td>0.053</td>
</tr>
</tbody>
</table>

ADL, activities of daily living; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; GRACE, Global Registry Acute Coronary Events; IQR, interquartile range; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.
### Table 3: Investigations, revascularisations and events. (All patients, \( n = 4387 \))

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Australia ( n = 3381 )</th>
<th>New Zealand ( n = 1006 )</th>
<th>Total ( n = 4387 )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>2725 (80%)</td>
<td>910 (91%)</td>
<td>3635 (83%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>1006 (30%)</td>
<td>287 (29%)</td>
<td>1293 (29%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Stress echocardiogram</td>
<td>92 (2.7%)</td>
<td>14 (1.4%)</td>
<td>106 (2.4%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Exercise test</td>
<td>299 (8.8%)</td>
<td>229 (23%)</td>
<td>528 (12%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stress nuclear study</td>
<td>148 (4.4%)</td>
<td>1 (0.1%)</td>
<td>149 (3.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CT coronary angiogram</td>
<td>125 (3.7%)</td>
<td>39 (3.9%)</td>
<td>164 (3.7%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Conventional angiogram</td>
<td>1299 (38%)</td>
<td>330 (33%)</td>
<td>1629 (37%)</td>
<td>0.0012</td>
</tr>
<tr>
<td>PCI</td>
<td>582 (17%)</td>
<td>169 (17%)</td>
<td>751 (17%)</td>
<td>0.78</td>
</tr>
<tr>
<td>CABG</td>
<td>128 (3.7%)</td>
<td>34 (3.4%)</td>
<td>162 (3.7%)</td>
<td>0.63</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>706 (21%)</td>
<td>202 (20%)</td>
<td>908 (21%)</td>
<td>0.60</td>
</tr>
<tr>
<td>In-hospital events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleed</td>
<td>34 (1.0%)</td>
<td>6 (0.6%)</td>
<td>40 (0.9%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>65 (1.9%)</td>
<td>18 (1.8%)</td>
<td>83 (1.9%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>236 (7.0%)</td>
<td>60 (6.0%)</td>
<td>296 (6.7%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Stroke</td>
<td>16 (0.5%)</td>
<td>5 (0.5%)</td>
<td>21 (0.5%)</td>
<td>0.99</td>
</tr>
<tr>
<td>MI post-admission</td>
<td>63 (1.9%)</td>
<td>22 (2.2%)</td>
<td>85 (1.9%)</td>
<td>0.52</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>63 (1.9%)</td>
<td>20 (2.0%)</td>
<td>83 (1.9%)</td>
<td>0.79</td>
</tr>
<tr>
<td>MACE†</td>
<td>354 (103)</td>
<td>98 (9.7%)</td>
<td>453 (103)</td>
<td>0.72</td>
</tr>
<tr>
<td>Length of stay, median (IQR) (days)</td>
<td>2.6 (1.2, 4.8)</td>
<td>2.2 (1.0, 4.6)</td>
<td>2.5 (1.1, 4.8)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

†MACE includes all cause death, new or recurrent MI, major bleeding, stroke, cardiac arrest, worsening heart failure. CABG, coronary artery bypass graft; CT, computed tomography; IQR, interquartile range; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

### Table 4: Investigations and revascularisations in patients with confirmed ACS (\( n = 2356 \))  STEMI/LBBB (\( n = 419 \)), NSTEMI (\( n = 1012 \)) or UAP (\( n = 925 \))

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Australia ( n = 1825 )</th>
<th>New Zealand ( n = 531 )</th>
<th>Total ( n = 2356 )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>1515 (83%)</td>
<td>488 (92%)</td>
<td>2003 (85%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>662 (36%)</td>
<td>210 (40%)</td>
<td>872 (37%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Stress echo</td>
<td>35 (1.9%)</td>
<td>4 (0.8%)</td>
<td>39 (1.7%)</td>
<td>0.080</td>
</tr>
<tr>
<td>Exercise test</td>
<td>81 (4.4%)</td>
<td>89 (17%)</td>
<td>170 (7.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stress nuclear study</td>
<td>64 (3.5%)</td>
<td>1 (0.2%)</td>
<td>65 (2.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CT coronary angiogram</td>
<td>67 (3.7%)</td>
<td>23 (4.3%)</td>
<td>90 (3.8%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Conventional angiogram</td>
<td>1054 (581)</td>
<td>284 (54%)</td>
<td>1338 (57%)</td>
<td>0.082</td>
</tr>
<tr>
<td>PCI</td>
<td>577 (323)</td>
<td>166 (31%)</td>
<td>743 (323)</td>
<td>0.92</td>
</tr>
<tr>
<td>CABG</td>
<td>127 (7.03)</td>
<td>30 (5.6%)</td>
<td>157 (6.7%)</td>
<td>0.32</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>700 (380)</td>
<td>195 (37%)</td>
<td>895 (380)</td>
<td>0.51</td>
</tr>
<tr>
<td>In-hospital events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleed</td>
<td>28 (1.5%)</td>
<td>5 (0.9%)</td>
<td>33 (1.4%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>50 (2.7%)</td>
<td>14 (2.6%)</td>
<td>64 (2.7%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>189 (103)</td>
<td>47 (8.9%)</td>
<td>236 (103)</td>
<td>0.33</td>
</tr>
<tr>
<td>Stroke</td>
<td>12 (0.6%)</td>
<td>4 (0.8%)</td>
<td>16 (0.7%)</td>
<td>0.77</td>
</tr>
<tr>
<td>MI post-admission</td>
<td>58 (3.2%)</td>
<td>20 (3.8%)</td>
<td>78 (3.3%)</td>
<td>0.49</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>49 (2.7%)</td>
<td>17 (3.2%)</td>
<td>66 (2.8%)</td>
<td>0.55</td>
</tr>
<tr>
<td>MACE†</td>
<td>272 (15%)</td>
<td>80 (15%)</td>
<td>352 (15%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Length of stay, median (IQR) (days)</td>
<td>3.6 (2.0, 5.8)</td>
<td>3.5 (1.9, 6.0)</td>
<td>3.6 (2.0, 5.8)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

†MACE includes all cause death, new or recurrent MI, major bleeding, stroke, cardiac arrest, worsening heart failure. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CT, computed tomography; NSTEMI, non-segment elevation myocardial infarction; MACE, major adverse cardiovascular events; STEMI/LBBB, segment elevation myocardial infarction/ left bundle branch block; PCI, percutaneous coronary intervention; UAP, unstable angina pectoris.

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lipid medication was not statistically different, but fewer Australian patients received dual anti-platelet therapy at discharge (83% vs 98%, \( P < 0.0001 \)) (Table 9). Of the 1902 surviving patients after a NSTEMI/UAP presentation, Australian patients were less likely to receive aspirin (84% vs 89%, \( P = 0.0079 \)) or a beta-blocker (67% vs 77%, \( P = 0.0002 \)), but more likely to receive an ACE-I/ARB medicine (65% vs 58%, \( P = 0.0060 \)) or ‘other’ lipid lowering agent (8.2% vs 5.47%, \( P = 0.024 \)). Statin use was similar in Australia (80%) and New Zealand (83%) (\( P = 0.21 \)) (Table 9).

### Discussion

The SNAPSHOT ACS study has enabled a comparison of 4387 Australian and New Zealand patients admitted to hospital with a suspected or confirmed ACS. Overall, the patient demographic differences between the two countries were quite small, although the ethnic mix gives an interesting insight into some minor population differences. Nonetheless, the similar ACS population does allow a reasonably valid comparison of ACS management across the two countries.

Patients admitted with a suspected ACS require investigations to help to make an accurate medical diagnosis. However, we found that less than half of patients received an anatomical assessment of left ventricular function with an echocardiogram, or of the coronary arteries with a computed tomography coronary angiogram or an invasive angiogram.

### Rehabilitation/scheduled outpatient investigations

Referrals for cardiac rehabilitation were low, with less than half of discharged confirmed ACS patients having a recorded referral for any of the six indicators assessed (Table 10). Australian patients were less likely to be referred as an in-patient in four of the five services, whereas they were more likely to be referred to an outpatient service (Table 10). Few patients were scheduled for outpatient investigations after hospital discharge, and there was no statistical difference in these numbers of patients between the two countries.

### Table 5 Demographics, investigations and management of 'STEMI/LBBB' patients

<table>
<thead>
<tr>
<th></th>
<th>STEMI/LBBB</th>
<th>STEMI/LBBB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Australia n = 321 (77%)</td>
<td>New Zealand n = 98 (23%)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>63 (30, 99)</td>
<td>68 (33, 97)</td>
<td>0.092</td>
</tr>
<tr>
<td>Sex (male %)</td>
<td>228 (71%)</td>
<td>73 (75%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Family history</td>
<td>102 (32%)</td>
<td>22 (22%)</td>
<td>0.079</td>
</tr>
<tr>
<td>Prior MI</td>
<td>59 (18%)</td>
<td>15 (15%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>36 (11%)</td>
<td>11 (11%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>18 (5.6%)</td>
<td>3 (3.1%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Prior TIA/Stroke</td>
<td>16 (5.0%)</td>
<td>7 (7.1%)</td>
<td>0.45</td>
</tr>
<tr>
<td>GRACE dcore median (IQR)</td>
<td>170 (145, 199)</td>
<td>171 (149, 193)</td>
<td>0.79</td>
</tr>
<tr>
<td>% GRACE score ≥ 140</td>
<td>250 (80%)</td>
<td>83 (86%)</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>Investigations/Management</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>268 (82%)</td>
<td>87 (89%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>194 (60%)</td>
<td>70 (71%)</td>
<td>0.056</td>
</tr>
<tr>
<td>Stress echo</td>
<td>2 (0.6%)</td>
<td>3 (3.1%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Exercise test</td>
<td>2 (0.6%)</td>
<td>3 (3.1%)</td>
<td>0.77</td>
</tr>
<tr>
<td>CT angiogram</td>
<td>12 (3.7%)</td>
<td>3 (3.1%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Conventional angiogram</td>
<td>270 (84%)</td>
<td>46 (88%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Total PCI</td>
<td>208 (65%)</td>
<td>66 (67%)</td>
<td>0.72</td>
</tr>
<tr>
<td>CABG</td>
<td>28 (8.7%)</td>
<td>6 (6.1%)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Anti-coagulation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor</td>
<td>90 (28%)</td>
<td>28 (29%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>7 (2.2%)</td>
<td>3 (3.1%)</td>
<td>0.70</td>
</tr>
<tr>
<td>UF heparin</td>
<td>219 (68%)</td>
<td>73 (75%)</td>
<td>0.26</td>
</tr>
<tr>
<td>LMW heparin</td>
<td>136 (43%)</td>
<td>55 (56%)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; CT, computed tomography; GRACE, Global Registry Acute Coronary Events; IQR, interquartile range; LMW, low molecular weight; MACE, major adverse cardiovascular events; MI, myocardial infarction; STEMI/LBBB, segment elevation myocardial infarction/left bundle branch block; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; UAP, unstable angina pectoris; UF, unfractionated.
cardiac angiogram. Further, less than one fifth received a functional cardiac assessment with a standard treadmill test, stress echocardiogram or a stress nuclear study. The ‘optimal’ level for these tests is unclear, but the numbers do suggest a limited availability or underutilisation of diagnostic investigations. This was seen across Australia and New Zealand.

For patients with a confirmed ACS, optimal management is already defined in guidelines.1–7 Overall, a low level of cardiac investigations was available to patients admitted with an ACS. Many ACS patients are not assessed with an echocardiogram or an invasive cardiac angiogram. Even if some patients are particularly frail, and it would be inappropriate for them to undergo an invasive cardiac angiogram, just under half of the patients who did not receive this test would not fit into this category. Further, few patients would be so frail that a non-invasive echocardiogram would not help to guide good management, but it was performed in only one third of the confirmed ACS patients. There was again a similarly low level of investigations seen in both countries.

It might have been thought that increased spending on health would result in increased access to these investigations. The 2011 Organisation for Economic Co-operation and Development reported that Australia has about twice the gross domestic product of New Zealand (US$ 68 099.60 vs US$ 38 587.90 per capita, respectively) and spends about 8.6% of gross domestic product (GDP) on health compared with 10% of GDP spent on health in New Zealand.20 Total health expenditure per capita (USD purchasing power parity) was reported to be $3800 in Australia and $3182 in New Zealand. However, despite

Table 6  Reperfusion management and time to treatment of 'STEMI/LBBB' patients

<table>
<thead>
<tr>
<th></th>
<th>STEMI/LBBB</th>
<th>STEMI/LBBB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Australia</td>
<td>New Zealand</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 321 (77%)</td>
<td>n = 98 (23%)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Reperfusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinolysis†</td>
<td>74 (23%)</td>
<td>31 (32%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>120 (37%)</td>
<td>42 (43%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Neither fibrinolysis nor Primary PCI</td>
<td>129 (40%)</td>
<td>26 (27%)</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Reperfusion time frames</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number with pre-hospital fibrinolysis (n)</td>
<td>10 (3.1)</td>
<td>3 (3.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Number with in-hospital fibrinolysis (n)</td>
<td>64 (203)</td>
<td>28 (29%)</td>
<td>0.096</td>
</tr>
<tr>
<td>Median DTNT [IQR] (min)‡</td>
<td>42 (25, 68)</td>
<td>48 (28, 84)</td>
<td>0.32</td>
</tr>
<tr>
<td>% DTNT ≤ 30 min</td>
<td>22 (64%)</td>
<td>9 (31%)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Primary PCI time frames</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number with primary PCI (PCI)</td>
<td>120 (37%)</td>
<td>42 (43%)</td>
<td>0.42</td>
</tr>
<tr>
<td>DTDT (All in-hospital PCI) median [IQR] (min)</td>
<td>82 (52, 143)</td>
<td>82 (56, 93)</td>
<td>0.81</td>
</tr>
<tr>
<td>DTDT ≤ 90 min</td>
<td>68/120 (57%)</td>
<td>28/42 (67%)</td>
<td>0.28</td>
</tr>
<tr>
<td>DTDT ≤ 120 min</td>
<td>82/120 (68%)</td>
<td>33/42 (79%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Start of angiogram to DT median [IQR] (min)</td>
<td>20 (14, 29)</td>
<td>22 (13, 27)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Angiogram time frames</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Points with routine angiogram (excluding PCI/Rescue PCI)</td>
<td>65 (203)</td>
<td>18 (18%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Time to routine angiogram (h)</td>
<td>23 (14, 52)</td>
<td>36 (21, 67)</td>
<td>0.098</td>
</tr>
<tr>
<td>Time to routine angiogram ≤ 24 h</td>
<td>34 (52%)</td>
<td>5 (28%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>In-hospital events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleed</td>
<td>9 (2.8%)</td>
<td>1 (1%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>25 (7.7%)</td>
<td>9 (9%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>61 (19%)</td>
<td>10 (16%)</td>
<td>0.66</td>
</tr>
<tr>
<td>CVA</td>
<td>7 (2.3%)</td>
<td>1 (1%)</td>
<td>0.69</td>
</tr>
<tr>
<td>MI post-admission</td>
<td>17 (5.3%)</td>
<td>5 (5%)</td>
<td>0.99</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>24 (7.5%)</td>
<td>7 (7%)</td>
<td>0.99</td>
</tr>
<tr>
<td>MACE§</td>
<td>93 (29%)</td>
<td>29 (30%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Length of stay [median IQR]</td>
<td>4.4 (3.0, 6.6)</td>
<td>3.7 (2.9, 6.1)</td>
<td>0.081</td>
</tr>
</tbody>
</table>

†Includes one NZ patient and two Australian treated with pharmaco-invasive intervention (fibrinolysis + PCI). ‡Excludes pre-hospital fibrinolysis. §MACE includes all cause death, new or recurrent MI, major bleeding, stroke, cardiac arrest, worsening heart failure, CVA, cerebrovascular accident; DTNT, door to needle time; DTDT, door to device time; DT, device time; IQR, interquartile range; MACE, major adverse cardiovascular events; NZ, New Zealand; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention. STEMI/LBBB, segment elevation myocardial infarction/left bundle branch block.
### Table 7  Demographics, investigations and management of ‘NSTEMI/UAP’ patients

<table>
<thead>
<tr>
<th></th>
<th>NSTEMI/UAP</th>
<th>NSTEMI/UAP</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Australia</td>
<td>New Zealand</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 1504 (78%)</td>
<td>n = 433 (22%)</td>
<td>n = 1937</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR) (years)</td>
<td>70 (60, 79)</td>
<td>73 (62, 82)</td>
<td>0.0006</td>
<td>71 (61, 80)</td>
</tr>
<tr>
<td>Sex (male %)</td>
<td>966 (64%)</td>
<td>255 (59%)</td>
<td>0.048</td>
<td>1221 (63%)</td>
</tr>
<tr>
<td>Family history</td>
<td>554 (37%)</td>
<td>115 (27%)</td>
<td>&lt;0.0001</td>
<td>669 (35%)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>514 (34%)</td>
<td>164 (38%)</td>
<td>0.17</td>
<td>678 (35%)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>384 (26%)</td>
<td>107 (25%)</td>
<td>0.75</td>
<td>491 (25%)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>204 (14%)</td>
<td>64 (15%)</td>
<td>0.53</td>
<td>268 (14%)</td>
</tr>
<tr>
<td>Prior TIA/Stroke</td>
<td>178 (12%)</td>
<td>73 (17%)</td>
<td>0.0073</td>
<td>251 (13%)</td>
</tr>
<tr>
<td>GRACE score (median IQR)</td>
<td>143 (122, 166)</td>
<td>151 (127, 175)</td>
<td>0.0014</td>
<td>145 (123, 168)</td>
</tr>
<tr>
<td>% GRACE score ≥ 140</td>
<td>785 (53%)</td>
<td>263 (61%)</td>
<td>0.0024</td>
<td>1482 (78%)</td>
</tr>
<tr>
<td><strong>Investigations/Management</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>1247 (83%)</td>
<td>401 (93%)</td>
<td>&lt;0.0001</td>
<td>1648 (85%)</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>468 (31%)</td>
<td>140 (32%)</td>
<td>0.64</td>
<td>608 (31%)</td>
</tr>
<tr>
<td>Stress echo</td>
<td>33 (2.2%)</td>
<td>3 (0.7%)</td>
<td>0.043</td>
<td>36 (1.9%)</td>
</tr>
<tr>
<td>Stress nuclear study</td>
<td>62 (4.0%)</td>
<td>1 (0.2%)</td>
<td>&lt;0.0001</td>
<td>63 (3.8%)</td>
</tr>
<tr>
<td>Exercise test</td>
<td>79 (5.3%)</td>
<td>85 (20%)</td>
<td>&lt;0.0001</td>
<td>164 (8.5%)</td>
</tr>
<tr>
<td>CT angiogram</td>
<td>55 (3.7%)</td>
<td>19 (4.4%)</td>
<td>0.46</td>
<td>74 (3.8%)</td>
</tr>
<tr>
<td>Conventional angiogram</td>
<td>784 (52%)</td>
<td>198 (46%)</td>
<td>0.019</td>
<td>982 (51%)</td>
</tr>
<tr>
<td>Total PCI</td>
<td>349 (25%)</td>
<td>100 (23%)</td>
<td>0.57</td>
<td>449 (24%)</td>
</tr>
<tr>
<td>CABG</td>
<td>99 (6.5%)</td>
<td>24 (5.5%)</td>
<td>0.50</td>
<td>123 (6.4%)</td>
</tr>
<tr>
<td><strong>Anti-Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>2 (0.1%)</td>
<td>0</td>
<td>0.99</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>UF heparin</td>
<td>452 (30%)</td>
<td>131 (30%)</td>
<td>0.95</td>
<td>583 (30%)</td>
</tr>
<tr>
<td>LMW heparin</td>
<td>750 (50%)</td>
<td>293 (68%)</td>
<td>&lt;0.0001</td>
<td>1043 (54%)</td>
</tr>
<tr>
<td>GPIIb/IIIa inhibitor</td>
<td>62 (4.1%)</td>
<td>11 (2.5%)</td>
<td>0.15</td>
<td>73 (3.8%)</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>20 (1.3%)</td>
<td>3 (0.7%)</td>
<td>0.45</td>
<td>23 (1.2%)</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; CT, computed tomography; GP, glycoprotein; GRACE, Global Registry Acute Coronary Events; IQR, interquartile range; MI, myocardial infarction; NSTEMI/UAP, segment elevation myocardial infarction/unstable angina pectoris; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; UF, unfractionated.

### Table 8  Anticoagulation management, GRACE scores and time to treatment of ‘NSTEMI/UAP’ patients

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>New Zealand</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1504 (78%)</td>
<td>n = 433 (22%)</td>
<td>n = 1937</td>
<td></td>
</tr>
<tr>
<td><strong>Angiogram time frames</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of conventional angiograms</td>
<td>784 (52%)</td>
<td>198 (46%)</td>
<td>0.0011</td>
<td>982 (51%)</td>
</tr>
<tr>
<td>Time to angiography (median IQR) (h)</td>
<td>46 (23, 77)</td>
<td>67 (32, 94)</td>
<td>&lt;0.0001</td>
<td>49 (24, 85)</td>
</tr>
<tr>
<td>GRACE score ≥ 140</td>
<td>785 (53%)</td>
<td>263 (61%)</td>
<td>0.0024</td>
<td>1048 (53%)</td>
</tr>
<tr>
<td>GRACE score ≥ 140 + angiogram</td>
<td>398 (51%)</td>
<td>110 (42%)</td>
<td>0.013</td>
<td>508 (48%)</td>
</tr>
<tr>
<td>GRACE score ≥ 140 + angiogram ≤ 24 h</td>
<td>96 (24%)</td>
<td>19 (7%)</td>
<td>&lt;0.0001</td>
<td>115 (23%)</td>
</tr>
<tr>
<td>GRACE score &lt; 140 (h)</td>
<td>677 (47%)</td>
<td>166 (39%)</td>
<td>0.0024</td>
<td>863 (45%)</td>
</tr>
<tr>
<td>GRACE score &lt; 140 + angiogram</td>
<td>375 (54%)</td>
<td>87 (52%)</td>
<td>0.75</td>
<td>462 (54%)</td>
</tr>
<tr>
<td>GRACE score &lt; 140 + angiogram ≤ 72 h</td>
<td>278 (74%)</td>
<td>50 (57%)</td>
<td>0.0053</td>
<td>328 (71%)</td>
</tr>
<tr>
<td><strong>In-hospital events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleed</td>
<td>19 (1.3%)</td>
<td>4 (0.9%)</td>
<td>0.80</td>
<td>23 (1.2%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>25 (1.7%)</td>
<td>5 (1.2%)</td>
<td>0.66</td>
<td>30 (1.5%)</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>128 (8.5%)</td>
<td>31 (7.2%)</td>
<td>0.43</td>
<td>159 (8.2%)</td>
</tr>
<tr>
<td>CVA</td>
<td>5 (0.3%)</td>
<td>3 (0.7%)</td>
<td>0.39</td>
<td>8 (0.4%)</td>
</tr>
<tr>
<td>MI post-admission</td>
<td>41 (2.7%)</td>
<td>15 (3.5%)</td>
<td>0.42</td>
<td>56 (2.9%)</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>25 (1.6%)</td>
<td>10 (2.3%)</td>
<td>0.41</td>
<td>35 (1.8%)</td>
</tr>
<tr>
<td>MACE§</td>
<td>179 (12%)</td>
<td>51 (12%)</td>
<td>0.99</td>
<td>230 (12%)</td>
</tr>
<tr>
<td>Length of stay (median IQR) (days)</td>
<td>3.2 (1.8, 5.5)</td>
<td>3.5 (1.8, 6.0)</td>
<td>0.34</td>
<td>3.3 (1.8, 5.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>New Zealand</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1504 (78%)</td>
<td>n = 433 (22%)</td>
<td>n = 1937</td>
<td></td>
</tr>
<tr>
<td>Data from two angiograms are excluded because times unavailable.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1GRACE score could not be calculated for 28 patients.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2MACE includes all cause death, new or recurrent MI, major bleeding, stroke, cardiac arrest, worsening heart failure. CVA, cerebrovascular accident; GRACE, Global Registry Acute Coronary Events; IQR, interquartile range; MACE, major adverse cardiovascular events; MI, myocardial infarction.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
this difference in healthcare spending, the investigations received by suspected or confirmed ACS patients were remarkably similar. We found that for NSTEMI/UAP patients, there was a slightly higher rate and more rapid access to cardiac angiography in Australia. This might be a reflection of higher healthcare spending in Australia, although the differences between the two countries were not great. Further, there are so many unknown variables, such as the relative costs of angiography, the availability and cost of medical and non-medical staff, the relative costs of maintaining the healthcare facilities, the relative geography, local and regional hospital provision, etc., which prevent any firm conclusion being drawn. However, overall the data are remarkable for the similarities seen between the two countries rather than the differences.

We also found some other areas of ACS management where there seemed to be suboptimal delivery of proven treatments. Approximately one third of STEMI patients did not receive reperfusion therapy. This figure is consistent with overseas experience. In a recent study describing

Figure 2: Proportion of ‘high risk’ NSTEMI/UAP patients (GRACE score ≥ 140) with time to angiogram less than 24 or 72 h. □, New Zealand; ■, Australia.

Table 9 Discharge medications of confirmed ACS patients (NZ n = 514; – 17 in hospital deaths, Australia n = 1776; – 49 in hospital deaths)

<table>
<thead>
<tr>
<th></th>
<th>STEMI/LBBB</th>
<th></th>
<th>NSTEMI/UAP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Australia</td>
<td>New Zealand</td>
<td>Total</td>
<td>Australia</td>
</tr>
<tr>
<td>Aspirin (1)</td>
<td>n = 297</td>
<td>n = 91</td>
<td>p-value</td>
<td>n = 1429</td>
</tr>
<tr>
<td>Other antiplatelet (2)</td>
<td>245 (83%)</td>
<td>89 (98%)</td>
<td>&lt;0.0001</td>
<td>334 (86%)</td>
</tr>
<tr>
<td>Dual antiplatelet (1&amp;2)</td>
<td>242 (82%)</td>
<td>90 (98%)</td>
<td>&lt;0.0001</td>
<td>331 (85%)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>242 (82%)</td>
<td>75 (82%)</td>
<td>0.99</td>
<td>317 (82%)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>221 (74%)</td>
<td>74 (81%)</td>
<td>0.21</td>
<td>295 (76%)</td>
</tr>
<tr>
<td>Statin</td>
<td>270 (91%)</td>
<td>86 (95%)</td>
<td>0.38</td>
<td>356 (93%)</td>
</tr>
<tr>
<td>Other lipid lowering</td>
<td>14 (5%)</td>
<td>1 (1%)</td>
<td>0.13</td>
<td>15 (5.8%)</td>
</tr>
</tbody>
</table>

ACE-I/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blocker; ACS, acute coronary syndrome; NSTEMI/UAP, non-segment elevation myocardial infarction/unstable angina pectoris; STEMI/LBBB, segment elevation myocardial infarction/left bundle branch block.

Table 10 In-hospital cardiac rehabilitation/scheduled outpatient investigations in those discharged alive

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>New Zealand</th>
<th>p-value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital rehabilitation/screening</td>
<td>n = 1776</td>
<td>n = 514</td>
<td>&lt;0.0001</td>
<td>n = 2290</td>
</tr>
<tr>
<td>In-hospital cardiac rehabilitation</td>
<td>703 (40%)</td>
<td>258 (50%)</td>
<td></td>
<td>961 (42%)</td>
</tr>
<tr>
<td>Smoking cessation advice/intervention</td>
<td>355 (20%)</td>
<td>143 (28%)</td>
<td></td>
<td>499 (22%)</td>
</tr>
<tr>
<td>Screening for depression</td>
<td>163 (9.2%)</td>
<td>65 (13%)</td>
<td>0.024</td>
<td>228 (10%)</td>
</tr>
<tr>
<td>Dietary modification advice</td>
<td>668 (37%)</td>
<td>161 (31%)</td>
<td>0.0092</td>
<td>829 (36%)</td>
</tr>
<tr>
<td>Physical activity advice</td>
<td>775 (44%)</td>
<td>212 (41%)</td>
<td>0.34</td>
<td>987 (43%)</td>
</tr>
<tr>
<td>Referral to OP cardiac rehabilitation</td>
<td>853 (48%)</td>
<td>210 (41%)</td>
<td>0.0042</td>
<td>1063 (46%)</td>
</tr>
<tr>
<td>Scheduled outpatient investigations</td>
<td>101 (5.7%)</td>
<td>18 (3.5%)</td>
<td>0.055</td>
<td>119 (5.2%)</td>
</tr>
<tr>
<td>Coronary angiogram</td>
<td>53 (3.0%)</td>
<td>9 (1.8%)</td>
<td>0.16</td>
<td>62 (2.7%)</td>
</tr>
<tr>
<td>CAGB</td>
<td>42 (2.4%)</td>
<td>11 (2.1%)</td>
<td>0.53</td>
<td>53 (2.3%)</td>
</tr>
<tr>
<td>Function test</td>
<td>199 (11%)</td>
<td>49 (9.5%)</td>
<td>0.30</td>
<td>248 (11%)</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>145 (8.2%)</td>
<td>43 (8.4%)</td>
<td>0.86</td>
<td>188 (8.2%)</td>
</tr>
</tbody>
</table>

CAGB, coronary artery bypass graft; OP, outpatient; PCI, percutaneous coronary intervention.

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the current situation in 30 European countries, no reperfusion therapy was given to 7% to 63% of patients.23 Why this occurs is unknown, and further assessment as to how an increase in reperfusion in Australia and New Zealand can be achieved is certainly required. Improvements in ACS patient care have been reported with attention to detail in several clinical areas resulting in improved patient outcomes.24

We also found that many areas of secondary prevention management seemed to be suboptimal. Up to half of ACS events occur in individuals who have had a prior hospital admission for coronary heart disease,25 emphasising the need for widespread use of secondary prevention medication as well as comprehensive cardiac rehabilitation/secondary prevention programmes. There are certainly some patients who are unsuitable candidates for individual medications, but the numbers of patients not being discharged on proven secondary medication is of concern. Once more, although there was a minor difference in uptake of these services between Australia and New Zealand, the major issue is clearly one of a missed opportunity to better deliver these proven strategies to many patients in each country26).

The SNAPSHOT ACS Study has been an extensive programme designed to understand current ACS patient management in Australia and New Zealand. Further in depth assessment of the structure of the clinical services, which are central to the delivery of healthcare to individual patients, is certainly warranted to try to find solutions to the limitations seen across the two countries. These challenges of service delivery are common to all contemporary ACS management services, and warrant the ongoing development of therapeutic advances, clinical trials, practice guidelines and performance and outcome measures, termed the ‘cycle of quality’.25 The advent of local clinical networks is likely to facilitate greatly improvements in ACS care in many areas.27

There are several limitations to our study, including the fact that although the majority of ACS patients were identified, we could not guarantee consecutive recruitment over the 2-week period. The scope of this paper was to report binational comparison data of acute in-hospital management and outcomes, thus we have not included follow-up data nor have we reported differences in ACS management between city and more geographically isolated, rural populations. Neither has the scope of this paper included a review of comparative cost structures across Australia and New Zealand, although all of these areas may importantly advance knowledge.

Conclusion

Overall the management of suspected or confirmed ACS patients showed more similarities than differences between Australia and New Zealand. However, some limitation to important investigations and treatments was seen in both countries. It is likely that most patient benefit will come from a coordinated, ongoing assessment of the available clinical services within each country, with timely feedback to focus improvements in the management of ACS patients in both countries.

References


Appendix I Participating hospitals.

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Assessing the use of initial oxygen therapy in chronic obstructive pulmonary disease patients: a retrospective audit of pre-hospital and hospital emergency management

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Key words
oxygen, emergency, chronic obstructive pulmonary disease, ambulance, hospital.

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Abstract

Background: Carbon dioxide retention in chronic obstructive pulmonary disease (COPD) exacerbations can be a complication of oxygen therapy. Current recommendations suggest an inspired oxygen level (FiO₂) < 0.28, aiming for saturation (SpO₂) of 88–92% until arterial blood gas analysis is available.

Aims: This study aims to assess the use of O₂ therapy and FiO₂ in the emergency management of patients with a known diagnosis of COPD.

Methods: Retrospective audit of 150 COPD patients admitted over 18 months, data being extracted from the hospital records.

Results: Of the records reviewed, 57% were male, mean age 75 years. COPD was recognised in 53%. SpO₂ recorded in 124 patients, with SpO₂ < 88% seen in 40 patients. Oxygen was administered in 123 patients in ambulances; high flow in 111 patients, and only 12 patients received O₂ therapy in line with the recommended FiO₂ < 0.28. In the emergency department (ED), 112 patients received O₂ supplementation; high flow given in 68 patients. Hypercapnia was seen in 71 patients; FiO₂ > 0.28 given in 54 patients in ambulances and in 35 patients in ED. Non-invasive ventilation was required in 53 patients; FiO₂ > 0.28 given in 29 patients in the ED. Seven patients were admitted to intensive care unit, and 10 patients died.

Conclusion: High-flow oxygen is used for the initial treatment of COPD exacerbations, but only 53% are recognised as having COPD. A FiO₂ > 0.28 is often initiated before admission and continued in the ED. A larger study would be required to assess any possible harm of this approach, but education of those involved in the care of COPD patients may reduce the risk of complications of hypercapnia.

Introduction

The administration of oxygen (O₂) is a common intervention during acute medical care in emergency situations. It is often initially administered in high concentrations. Hypoxaemia should be treated without delay, but the development of carbon dioxide (CO₂) retention following O₂ therapy is a complication seen in some patients with lung diseases including chronic obstructive pulmonary disease (COPD). Hypercapnia in COPD patients following O₂ therapy is a well-established risk that has been described in many papers dating back more than 50 years.¹⁻⁴

The current recommendation by the British Thoracic Society (BTS) and the Australian COPDX Plan is that the fractional inspired O₂ (FiO₂) should be no more than 0.28 when administered to patients with an exacerbation of COPD, until the result of an arterial blood gas analysis (ABG) is available, and for nebulised bronchodilators to be given with compressed air rather than oxygen as the driving gas.⁵⁻⁶ The importance of controlled O₂ therapy may be a lower priority in pre-hospital and emergency settings as failure to correct inadequate oxygenation is often perceived to be more dangerous than excessive administration.⁷⁻⁹ Hypercapnic respiratory failure and respiratory acidosis associated with a FiO₂ > 0.28 are
observed in patients admitted under the care of respiratory services.  

We conducted this study with the aims of assessing the use of O2 therapy and FiO2 in the emergency management of COPD patients who were admitted to this hospital, and to assess any associated outcomes with regards to this practice.

**Aims**

This study assessed retrospectively the use of O2 therapy and FiO2 in the emergency management of COPD patients who were admitted to hospital, and to document the outcomes. We hypothesised that a higher FiO2 administration may be used than recommended and might be associated with higher rates of morbidity and mortality.

**Methods**

A retrospective audit was performed randomly on 150 medical records of patients who were admitted to Prince of Wales Hospital Respiratory Department with an acute exacerbation of COPD between 1 January 2011 and 30 June 2013. Patients included in the audit had to present initially through the emergency department (ED), and they also had to be brought into the hospital by ambulance. The audit included assessment of the ambulance records in the paper hospital records, as well as the electronic medical records. Only patients who had a known pre-existing COPD diagnosis were included in this study. The diagnosis of COPD was obtained via the disease-related group coding provided by the medical records department and a record of a diagnosis of COPD by a respiratory physician on an outpatient clinic letter together with previous appropriate spirometry results and a history of current or previous smoking. The severity was assessed by the spirometry results based on the COPDX criteria. In cases where the clinic letter did not specify the severity of COPD, this was recorded as unknown.

The patients’ demographics, oxygen saturations (SpO2), oxygen delivery and types of oxygen supplementation, blood gas results, mortality and associated morbidity such as hypercapnia, non-invasive ventilation (NIV) usage, intensive care unit (ICU) admission and requirement for intubation were collated. Hypercapnia was defined as a partial pressure of arterial carbon dioxide (PaCO2) > 45 mmHg. Oxygen therapy was classified as high flow or low flow, with high flow being defined as O2 delivery by Hudson Mask (HM), non-re-breather mask (NRB) or via nasal cannula with flow rate >2 L/min. Oxygen delivery by nasal cannula is highly variable, but 1–2 L/min of O2 delivers a FiO2 between 0.24–0.38, depending on whether the patient mouth breathes during the administration.

**Results**

In this audit of 150 medical records, 86 patients were male and 64 were female. The mean age of the patient cohort was 75 years old (SD = 8.7). Outside the hospital, the initial recognition of COPD was noted in 80 patients (53%), and the majority of the patients had severe COPD (Table 1).

Thirty-six patients were on long-term home O2 supplementation and of these, 29 received O2 supplementation at a flow rate higher than their usual rates. Twenty-one of these patients had received the FiO2 > 0.28 via either HM or NRB (HM = 15, NRB = 6). Out of the 29 patients, 11 patients had O2 saturations defined as low by standard convention (i.e. SpO2 < 94%). The median SpO2 in these 20 patients was 89% (range 60–95%).

**Oxygen saturations**

The O2 saturation was recorded in 124 patients (83%) prior to hospital. The mean O2 saturation in patients audited was 88% (SD 7.73, CI 95% = 86.76–89.24%). An oxygen saturation of <88% was observed in 40 patients, SpO2 of 88–92% seen in 42 patients and SpO2 >92% in 42 patients.

**Initial oxygen therapy**

Oxygen supplementation was administered at some stage during the ambulance transfers in 123 patients (82%), with 111 patients (75%) receiving a FiO2 > 0.28. The most common device to deliver O2 therapy was via HM (Fig. 1). Nebulised bronchodilators were given in 25 patients, but in 18 these were administered with 8 L/min O2 rather than air.

A FiO2 of >0.28 was administered in 33 patients with SpO2 < 88%, 27 patients with SpO2 88–92% and in 32 patients with SpO2 > 92% (Fig. 2). Of those with SpO2 > 92%, 22 patients received O2 supplementation via HM, five patients via NRB, five patients via naso cannula at.

<table>
<thead>
<tr>
<th>Severe</th>
<th>102 patients</th>
<th>68%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>28 patients</td>
<td>18%</td>
</tr>
<tr>
<td>Mild</td>
<td>10 patients</td>
<td>7%</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 patients</td>
<td>7%</td>
</tr>
</tbody>
</table>
>2 L/min and only one patient received O₂ supplementation via nasal cannula at ≤2 L/min (Fig. 2).

Of the 80 patients recognised as having a pre-existing diagnosis of COPD, 51 of them received high flow O₂ therapy. Overall, only 12 patients received O₂ therapy in line with the BTS and COPDX recommendation with FiO₂ < 0.28.

Oxygen supplementation was administered in the ED in 112 patients (75%), and high flow O₂ was administered in 68 patients (45%). The most common type of O₂ delivery device in the ED was also a HM (34 patients,
Long-standing hypercapnia was previously known to be present in 39 patients, and O2 supplementation with a FiO2 > 0.28 was administered in 24 of these patients.

Blood gas measurements

Blood gas analysis was performed in 93% of patients arriving in the ED with an exacerbation of COPD. Venous blood gas (VBG) was the most common type of blood gas measurement, being performed in 88 patients (59%), although recognised not to reflect accurately an arterial blood gas (ABG).13 Of the 88 patients who had VBG measurement, 41 patients had a venous CO₂ level above the range for a normal arterial value. ABG was performed subsequently in 13 out of the 41 patients who were deemed to have an elevated partial pressure of carbon dioxide (PCO₂) level on a VBG. These ABG measurements did confirm the presence of hypercapnia in all of the patients shown to have an elevated PCO₂ level on a VBG. An initial ABG was performed in 52 patients (35%) in the ED.

Morbidity

Hypercapnia was seen in 71 patients, and in these patients a FiO₂ > 0.28 was given in 54 patients outside the hospital and continued in 35 patients in ED (Table 2). NIV was required in 53 patients, of whom 29 were given a FiO₂ > 0.28, 19 patients were given a FiO₂ < 0.28, and five patients were given an unknown FiO₂ in ED. Intubation was required in only one patient, and a FiO₂ > 0.28 was administered in this patient in the ambulance as well as in ED. The majority of patients were managed in the ward, with only seven patients requiring admission to the ICU or high dependency unit (HDU). The median length of stay (LOS) for those receiving low flow O₂ was 6.5 days (range 2–27 days), and those receiving high flow O₂ was 5 days (range 1–32 days).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Morbidity based on FiO₂ given in the ambulance and in emergency department (ED)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In ambulance</td>
</tr>
<tr>
<td></td>
<td>FiO₂ &lt; 0.28</td>
</tr>
<tr>
<td>Acute hypercapnia (71 patients)</td>
<td>8 (36%)</td>
</tr>
<tr>
<td>NIV (53 patients)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>ICU/HDU (7 patients)</td>
<td>1 (53)</td>
</tr>
</tbody>
</table>

FiO₂, fraction of inspired oxygen; ICU, intensive care unit; NIV, non-invasive.
Mortality

There was a total of 10 deaths, of which nine patients had known severe COPD. In those who died, a FiO₂ > 0.28 was given in six patients in ambulances and in eight patients in the ED.

Discussion

This audit confirms that oxygen administration is a common medical intervention for emergency treatment of COPD exacerbations, and that high flow oxygen is often administered. Based on current guidelines, the majority of the patients had not required the initial oxygen supplementation given that their mean oxygen saturation was ≥88% or could have been managed on a lower FiO₂.

This audit shows that a diagnosis of COPD was not necessarily appreciated as being a relative contraindication for high-flow supplemental oxygen. Interestingly, a previous audit performed in the United Kingdom had also shown a similar problem indicating that a lack of recognition of COPD is widespread. Initial assessments outside hospital often recorded asthma, cardiac failure or simply ‘shortness of breath’ as an alternative pre-existing diagnosis. This lack of recognition of a pre-existing diagnosis of COPD could account for the high number of uncontrolled oxygen administration episodes; however, more than half of those patients recognised as having pre-existing diagnosis of COPD still had received a FiO₂ > 0.28.

It is understandable that, when presented with an acutely ill patient who cannot breathe or communicate, oxygen supplementation takes priority, and this is appropriate. A long-term history of carbon dioxide retention would not be obtained in such circumstances. This audit also shows that while high-flow oxygen therapy is often initiated in the ambulances, in more than half of cases this was continued in the ED and probably a down-titration of this treatment was required.

Administration of high-flow oxygen in general leads to an increase in minute ventilation, which leads to a lower end-tidal carbon dioxide concentration. In patients with COPD, however, hyperoxia leads to a decreased minute ventilation and increase in transcutaneous carbon dioxide. These changes have been postulated to be a result of either depression of ventilation or due to worsening ventilation perfusion inequality relating to recruitment of poorly ventilated lung units by reversal of local hypoxic pulmonary vasoconstriction with subsequent release of sequestered carbon dioxide. The clinical effects of supplemental oxygen-induced hypercapnia have been known for a long time, and these include depression of neurological and cardiorespiratory function.

In a study of blood gas data of patients with COPD, a negative correlation was shown between pH and partial pressure of arterial oxygen (PaO₂) after O₂ therapy with increased oxygenation associated with a lower pH, especially in those with hypercapnia. Several other studies have also reported a greater incidence of adverse outcomes associated with higher flow oxygen in COPD patients.

While a higher proportion of those who were given high-flow oxygen therapy developed hypercapnia and required NIV in this study, logistic regression analysis showed that the higher FiO₂ administered was not necessarily a significant variable associated with the development of these morbidities (Tables 3, 4). This result could however be related to missing data with an unknown FiO₂ and a lack of statistical power. This study showed that the severity of COPD (OR 4.64, 95% CI 1.63–13.22) and older age group (OR 6.09, 95% CI 1.18–31.36) were significant variables associated with the development of hypercapnia. In an unadjusted OR analysis, pre-existing home oxygen usage was also significantly associated with development of hypercapnia, likely to be a reflection of the underlying severity of the COPD.

There was an overall mortality rate of 6.7%, which is similar to the 6–10% rates quoted in other studies. The length of stay in our study is longer than the quoted average in the National Health Performance Authority (NHPA) of 5 days in COPD admission.

Table 3 Variables associated with hypercapnia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe COPD</td>
<td>4.76</td>
<td>—</td>
<td>2.04–11.11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>—</td>
<td>4.64</td>
<td>1.63–13.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>—</td>
<td>6.09</td>
<td>1.18–31.36</td>
<td>0.03</td>
</tr>
<tr>
<td>FiO₂ &gt; 0.28 in ambulance</td>
<td>—</td>
<td>2.05</td>
<td>0.70–6.01</td>
<td>0.19</td>
</tr>
<tr>
<td>FiO₂ &gt; 0.28 in ED</td>
<td>—</td>
<td>1.37</td>
<td>0.59–3.15</td>
<td>0.46</td>
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</tbody>
</table>

Table 4 Variables associated with usage of NIV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe COPD</td>
<td>1.93</td>
<td>0.56–6.64</td>
<td>0.30</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>0.32</td>
<td>0.07–1.41</td>
<td>0.13</td>
</tr>
<tr>
<td>FiO₂ &gt; 0.28 in ambulance</td>
<td>1.05</td>
<td>0.32–3.45</td>
<td>0.94</td>
</tr>
<tr>
<td>FiO₂ &gt; 0.28 in ED</td>
<td>5.10</td>
<td>1.79–14.50</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
are unable to estimate the PaO$_2$ and PaCO$_2$ and further spread practice. While the study by Joosten had a significant proportion of patients who did not have ABG performed as part of their COPD management, further highlighting this wide variability in the PCO$_2$ level matches that of the ABG in the 13 patients who had ABG repeated following VBG sampling, a recent meta-analysis by Byrne et al. showed that while VBG analysis compares well to ABG for pH estimations, VBG results show an unacceptably large variability in the PCO$_2$ and partial pressure of oxygen (PO$_2$). At present the accepted view is that VBGs are unable to estimate the PaO$_2$ and PaCO$_2$ and furthermore, VBGs are not commonly used outside Australasia.

A similar study performed by Joosten et al. in a Melbourne university teaching hospital found comparable results to ours, with similar demographic characteristics and findings that high flow O$_2$ administration is a common practice that is initiated in the ambulance and then carried on in the ED. Also similar to our study, Joosten pointed out the significant proportion of patients who did not have ABG performed as part of their COPD management, further highlighting this widespread practice. While the study by Joosten had a smaller number of audit samples, they managed to show significant relationship between higher PaO$_2$ measured (>74.5 mmHg) and morbidity variables such as increased LOS, NIV usage and HDU admission. These findings’ differences with ours likely reflect the different measurement of relationships with the variables rather than a contradiction of findings. We did not use PaO$_2$ as a measurement variable given the high proportion of VBG performed which limited our ability to document PO$_2$ confidentially.

Overall, this study has confirmed that un-titrated administration of oxygen in COPD patients is a common practice. An audit that was recently performed in Waikato hospital in New Zealand further highlights that the practice of un-titrated oxygen administration is common and is not only limited to the respiratory specialty. We acknowledge that given that this is an audit study with multiple variables, it is not possible to conclude that there is a causal relationship between a higher FiO$_2$ administration and adverse outcomes such as hypercapnia or need for NIV. Indeed, other variables such as COPD severity or age also play a significant part in the development of morbidity and mortality in this cohort and could have been detailed along with type of exacerbation and medication. We acknowledge the limitations of this study being that of a retrospective study with a relatively small sample size and a proportion of missing data, all of which limit the analysis of this study. To date, there has only been one randomised controlled trial that studied the relationship between high flow oxygen therapy and mortality in patients with COPD which indicated a reduced risk of death in patients with titrated oxygen therapy. Larger, prospective studies would be required to confirm the possible harm of un-titrated oxygen approach in COPD patients.

The implementation of current oxygen guidelines for use in the pre-hospital setting and education of those who are involved in treating COPD patients in emergency care and other situations may reduce the risk of complications in COPD patients. Oxygen is not commonly titrated in the pre-hospital setting and administered using high-flow delivery devices on the perception that failure to correct oxygenation is more dangerous than excessive administration. Perhaps consideration of developing oxygen administration guidelines depending on the initial SpO$_2$ would be useful as this could potentially prevent administration of high-flow oxygen as first line treatment. Beasley et al. recommended no oxygen supplementation for those with a SpO$_2$ > 92%, 2–3 L O$_2$ via nasal cannula in those with SpO$_2$ 85–92% and usage of simple masks at higher flows for those with SpO$_2$ < 85%, titrated to aim for a SpO$_2$ > 92%. Other potential useful interventions which can be considered include education of patients regarding their diagnosis of COPD, the importance of alerting ambulance and medical personnel to the diagnosis and the provision of a medical alert bracelet or oxygen alert card, especially in those with known hypercapnia. The utilisation of a dedicated oxygen prescription chart, which has been used in some hospitals, may also be of some benefit.

Conclusion

Our study highlights that high flow oxygen is commonly used for the initial treatment of COPD exacerbations but that the diagnosis of COPD is often not recognised. The administration of oxygen supplementation with a FiO$_2$ >0.28 is often initiated during ambulance transfers and subsequently continued in the ED. A larger prospective study would be required to confirm any possible harm of
this approach, but education of those involved in the care of COPD patients may reduce the risk of complications of hypercapnia.

Acknowledgements

We thank Eilish Portelli, Annie Blenkinsopp and the Medical Records Department at Prince of Wales Hospital for their invaluable help in obtaining the disease-related group coding and medical records. We also thank Professor Jenny Peat for her invaluable statistical advice.

References

Obvious emphysema on computed tomography during an acute exacerbation of chronic obstructive pulmonary disease predicts a poor prognosis

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1Department of Respiratory Medicine, Ruijin Hospital, North, 2Department of Respiratory Medicine, Ruijin Hospital and 3Department of Biostatistics, Shanghai Jiaotong University School of Medicine, Shanghai, China

Abstract

Background: Emphysematous change on computed tomography (CT) during the stable phase of chronic obstructive pulmonary disease (COPD) is reported to correlate with COPD prognosis. Acute exacerbation of COPD (AECOPD) is associated with a high risk of mortality and a poor prognosis.

Aims: This study aims to study the relationship between prognosis and emphysematous changes on CT during an AECOPD.

Methods: Histories were recorded, and CT acquired for 106 patients who visited the emergency department for an AECOPD. Emphysematous change was quantified by measuring the percentage of low-attenuation areas (LAA%) in the entire lung on CT images with a threshold of –950 Hounsfield units. Other factors that could influence AECOPD prognosis were also recorded on admission and analysed. At follow ups conducted in 1 year, patient survival, the modified Medical Research Council (mMRC) Dyspnoea Scale, and performance status (PS) were evaluated, and a COPD Assessment Test (CAT) was completed.

Results: The 1-year follow up was completed by 103 of 106 patients. The median LAA% was significantly higher in non-survivors (11%, n = 16) than in survivors (5.69%, n = 87) (P = 0.006) at the 1-year follow up. LAA% was significantly correlated with mMRC grade (r = 0.285, P = 0.008), PS (r = 0.397, P < 0.001) and CAT score (r = 0.27, P = 0.017) at the 3-month follow up, and with mMRC grade (r = 0.405, P < 0.001) and PS (r = 0.377, P < 0.001) at the 1-year follow up. LAA% > 7.5% was a significant predictor of 1-year mortality, higher mMRC and PS at the 3-month and 1-year follow ups, after adjustment for other prognostic predictors.

Conclusion: Obvious emphysematous changes on CT (LAA% > 7.5%) during an AECOPD predicts a poor prognosis independent of other known indicators.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation and is a leading cause of morbidity and mortality worldwide.1 An acute exacerbation of COPD (AECOPD) is an acute event characterised by worsening of the patient’s respiratory symptoms beyond normal day-to-day variations, and leads to changes in medication. It contributes to overall disease severity in individual patients.1 The mean frequency of exacerbations is 0.9 times per year, according to the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) cohort.2 The prognosis of an AECOPD is poor. In the United States, the in-hospital mortality was 4.3% in 2006.3 In Chang’s study, the 30-day mortality was 8.5% (21/248), and the 1-year mortality was 18.5% (42/227) among inpatients in New Zealand.4

Screening high-risk patients helps in selecting more aggressive treatments for certain patients while avoiding unnecessary treatment in others. However, knowledge about the determinants of prognosis is limited.

Key words
chronic obstructive, pulmonary disease, acute exacerbation of chronic obstructive pulmonary disease (AECOPD), X-ray computed, tomography, emphysema, prognosis.

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In stable COPD, the severity of emphysema as measured by low-attenuation areas (LAA%) has been established to be a stronger predictor of mortality than lung function, age or body mass index (BMI). The LAA% is positively correlated with dyspnoea severity (the modified Medical Research Council (mMRC) Dyspnoea Scale) and negatively correlated with forced expiratory volume in 1 s (FEV1) % predicted, the 6-min walk test distance (6MWT) and BMI. However, to the best of our knowledge, the prognostic value of LAA% in an AECOPD has not yet been studied.

Many studies have shown that after an exacerbation, most patients gradually return to their baseline level, and almost no patient will attain better lung function than in the stable phase of their disease. During the exacerbation, the aggravation of airflow limitations is mainly caused by greater mucus production, airway wall oedema and bronchoconstriction. These changes are reversed during recovery. In contrast, emphysema is defined as the abnormal, permanent enlargement of air spaces distal to the terminal bronchioles, and accompanied by the destruction of their walls. Therefore, we hypothesised that the severity of emphysema may reflect the irreversibility and prognosis of an AECOPD.

The present study was designed to assess prospectively the ability of LAA% measurements during COPD exacerbations to predict the mortality and severity of COPD after the exacerbation.

**Methods**

**Patients**

Consecutive patients with a primary AECOPD diagnosis who visited the emergency department from December 2011 to May 2012 were recruited. An AECOPD was diagnosed by the admitting physician and defined as two out of three of: an increase in dyspnoea, sputum volume or sputum purulence from COPD beyond normal day-to-day variations that required emergency treatment. COPD was diagnosed on the basis of history and spirometry (Fig. 1) and confirmed by spirometry when the patients were stable whenever possible. Exclusion criteria were a history of other respiratory illnesses, such as lung cancer, pneumothorax, hydrothorax, severe bronchiectasis, thoracic malformation, destroyed lung, illness too severe to undergo routine examinations (for example, haemodynamic instability) and those who visited the emergency department for reasons other than an AECOPD. Only the first visit was included in the analysis, even if the patient visited the emergency department more than once during the study period. Patients were treated according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. The Ethics Committee of Ruijin Hospital approved the study protocol (2009-23), and informed consent was obtained from all participants.
Clinical data collection

Medical history and physiological variables were recorded during the first visit (Fig. S1). CRB-65 score was calculated and one point given for each of the following features present: confusion; respiratory rate ≥ 30/min; diastolic blood pressure ≤ 60 mmHg or systolic blood pressure < 90 mmHg; and age ≥ 65 years.12 Follow ups were performed at 1 month, 3 months and 1 year after the first visit. If the patient had died, survival time and cause of death were registered. At the 3-month and 1-year follow ups, if the patient was alive, mMRC grade,13 performance status (PS),13 COPD Assessment Test (CAT) score14 and severity of cough and sputum were evaluated (Fig. S2).

Computed tomography emphysema evaluation

Chest computed tomography (CT) without contrast media was performed during the first visit. Imaging was performed during breath holding at full inflation with the patient in supine positioning using the same scanner (Light Speed 16; GE Medical Systems, Milwaukee, WI, USA) and protocol (tube voltage, 120 kV; tube current, 220 mA; tube rotation time, 0.8 s; and collimation, 1.25 mm). Images were reconstructed with the ‘standard algorithm’ at a 1.25-mm section thickness, 1.25-mm interval and a 512 × 512 matrix, as in previous studies.15 Sixteen patients underwent follow-up CT with the same parameters at the 3-month follow-up visit. The LAA% was calculated automatically using commercial software (Myrian, Intrasense; Montpellier, France) using a threshold of -950 Hounsfield units to determine emphysema-tous extent, as in previous studies.16

Statistical analysis

All statistical analyses were conducted with SPSS 17.0 (SPSS, Chicago, IL, USA). The LAA% of patients who died within 1 month, between 1 month and 1 year, and those who were alive at the 1-year follow-up were rank transformed and compared using a one-way analysis of variance and the least significant difference method. Spearman’s correlation was used to establish the relationship between LAA% and mMRC grade, performance status and CAT score at the follow up. A Cox regression was used to examine risk factors for mortality. An ordinal logistic regression was performed to examine factors influencing mMRC grade and performance status at the follow ups.

Results

Population characteristics

One hundred and six patients were enrolled (Table 1). Two patients were lost to follow up within 1 month, and
the same parameter. A good correlation \( r = 0.840, P < 0.001 \) and no significant difference \( (13.38\% \pm 9.04\% \text{ vs } 11.43\% \pm 7.1\%), P = 0.135 \) was observed between the LAA% measured during the exacerbation and during the stable phase (the LAA% of these patients followed a normal distribution) (Fig. S3). The median CRB-65 score was 1 (interquartile range: 1–4, \( n = 83 \)). The CRB-65 score could not be calculated for 23 patients because of missing data. There was no significant difference between patients with or without a CRB-65 score with respect to LAA% or prognosis (Table S1). Twenty-nine patients underwent standard pulmonary function tests (mean FEV1 = 44.77 ± 18.54% predicted), and 13 underwent bronchodilation tests (mean post-bronchodilator FEV1 = 48.65 ± 13.8% predicted) at follow up (Tables S2, S3). Most AECOPD patients (86/105) have lung infiltration to a greater or lesser extent on CT; however, the clinical significance is limited. The presence of asthma or pneumonia was not significantly associated with any other factor, including LAA%, CRB-65 score, smoking history or prognosis (Table S4).

**The risk of death and LAA%**

The LAA% of patients who died within 1 year was significantly higher than that of survivors (median (interquartile range): 11% (7.14–24.5%) vs 5.69% (2.35–11.0%), \( P = 0.006 \)). The LAA% during an AECOPD was significantly higher in patients who died between 1 month and 1 year than in 1-year survivors (23.2% (2.64–29.9%) vs 5.69% (2.35–11.0%), \( P = 0.03 \)). (B) A Kaplan-Meier survival curve for patients with an AECOPD stratified according to LAA%. Survival was worse in patients with LAA% > 7.5% (\( P = 0.009 \), Cox regression). LAA%, the percentage of low-attenuation areas (emphysema) on computed tomography (CT) imaging during an AECOPD using a threshold of –950 Hounsfield units; \( y \), year; mo, month; f/u, follow up.
Emphysema during AECOPD and prognosis

Table 2 An univariate Cox regression analysis of risk factors for 1-year mortality in patients who came to the emergency department for an AECOPD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (increment by 1 year)</td>
<td>1.063</td>
<td>0.047</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.913</td>
<td>0.209</td>
</tr>
<tr>
<td>Male</td>
<td>1.55</td>
<td>0.562</td>
</tr>
</tbody>
</table>

Clinical presentation

- Increase in cough
- Increase in sputum volume
- Increase in sputum purulence
- Increase in dyspnoea
- Fever (T ≥ 37.3°C)

Clinical scores

- CRB-65
- In the past 1 year
- Hospitalisation因为 of an AECOPD

Past medical history

- Asthma
- Hypertension
- Diabetes
- Coronary artery disease
- Left heart failure
- History of smoking

CT emphysema evaluation

- LAA% > 7.5%

*Factors related to the prognosis with \( P < 0.1 \) in the univariate analysis, which were selected for multivariate Cox regression analysis. AECOPD, acute exacerbation of COPD; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRB-65 score, confusion, respiratory rate ≥ 30/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years; LAA%, the percentage of low-attenuation areas (emphysema) on CT imaging during an AECOPD using a threshold of -950 Hounsfield units; RR, risk ratio of death in 1 year; T, body temperature.

In the stratified analysis, the relationship between LAA% and mortality was more significant in patients with a history of smoking and without a history of left heart failure or asthma (Table S6).

In the univariate Cox proportional hazard regression, higher CRB-65 scores, ageing, absence of fever during the exacerbation and LAA% > 7.5% were significantly related to mortality (Table 2).

After performing a multivariate Cox regression using CRB-65, LAA%, presence of fever and presence of increase in cough, the following were mortality predictors: higher CRB-65 scores (RR = 2.836, \( P = 0.001 \)) and LAA% > 7.5% (RR = 3.891, \( P = 0.039 \)) (Table 3).

The severity of symptoms after stabilisation and LAA%

LAA% was significantly correlated with mMRC grade (\( r = 0.285, P = 0.008 \)), performance status (\( r = 0.397, P < 0.001 \)) and CAT score (\( r = 0.27, P = 0.017 \)) at the 3-month follow up; and mMRC grade (\( r = 0.405, P < 0.001 \)) and performance status (\( r = 0.377, P < 0.001 \)) at the 1-year follow up (Table 4). However, the correlations were not significant between LAA% and the CAT score at the 1-year follow up, exacerbation frequency, severity of cough or severity of sputum (Table 4). In the stratified analysis, relationships between LAA% and dyspnoea symptoms after stabilisation were more significant in men, patients with smoking histories and patients without histories of left heart failure or asthma (Table S6).

In univariate analyses, age, absence of increase in cough during the exacerbation, CRB-65 score,

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RR</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRB-65</td>
<td>2.836</td>
<td>0.001</td>
<td>1.55–5.19</td>
</tr>
<tr>
<td>LAA% &gt; 7.5%</td>
<td>3.891</td>
<td>0.039</td>
<td>1.07–14.1</td>
</tr>
<tr>
<td>Fever (T &gt; 37.3°C)</td>
<td>0.259</td>
<td>0.085</td>
<td>0.06–1.21</td>
</tr>
</tbody>
</table>

AECOPD, acute exacerbation of COPD; CI, confidence interval; CRB-65 score, confusion, respiratory rate ≥ 30/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years; LAA%, the percentage of low-attenuation areas (emphysema) on CT imaging during an AECOPD using a threshold of -950 Hounsfield units; RR, risk ratio of death in 1 year; T, body temperature.

Table 3 A multivariate Cox regression analysis of risk factors for 1-year mortality in patients who came to the emergency department for an AECOPD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RR</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRB-65</td>
<td>2.836</td>
<td>0.001</td>
<td>1.55–5.19</td>
</tr>
<tr>
<td>LAA% &gt; 7.5%</td>
<td>3.891</td>
<td>0.039</td>
<td>1.07–14.1</td>
</tr>
<tr>
<td>Fever (T &gt; 37.3°C)</td>
<td>0.259</td>
<td>0.085</td>
<td>0.06–1.21</td>
</tr>
</tbody>
</table>

AECOPD, acute exacerbation of COPD; CI, confidence interval; CRB-65 score, confusion, respiratory rate ≥ 30/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years; LAA%, the percentage of low-attenuation areas (emphysema) on CT imaging during an AECOPD using a threshold of -950 Hounsfield units; RR, risk ratio of death in 1 year; T, body temperature.

Table 4 The correlation between LAA% during an AECOPD and COPD symptoms at follow up

<table>
<thead>
<tr>
<th>3-month follow up</th>
<th>1-year follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-month follow up</td>
</tr>
<tr>
<td></td>
<td>t</td>
</tr>
<tr>
<td>mMRC grade</td>
<td>0.285</td>
</tr>
<tr>
<td>Performance status</td>
<td>0.397</td>
</tr>
<tr>
<td>CAT score</td>
<td>0.27</td>
</tr>
<tr>
<td>Severity of cough</td>
<td>0.018</td>
</tr>
<tr>
<td>Severity of sputum</td>
<td>0.051</td>
</tr>
<tr>
<td>Frequency of exacerbations</td>
<td>0.128</td>
</tr>
<tr>
<td>Frequency of hospitalisations for exacerbations</td>
<td>0.219</td>
</tr>
</tbody>
</table>

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; LAA%, the percentage of low-attenuation areas (emphysema) on computed tomography imaging during an AECOPD using a threshold of -950 Hounsfield units; mMRC, modified Medical Research Council Dyspnoea Scale.

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AECOPD-related hospitalisations in the past year and LAA% > 7.5% predicted poor mMRC grades and performance statuses at follow up. A history of left heart failure also predicted a poor mMRC grade; an increase in dyspnoea, and no increase in sputum volume during exacerbations also predicted a poor performance status at follow up (Tables 5, 6).

In the multivariate analysis, LAA% > 7.5% remained a significant predictor of higher mMRC grades at the 3-month (odds ratio (OR) = 3.195, \( P = 0.036 \)) and 1-year follow ups (OR = 3.414, \( P = 0.028 \)), and poor performance statuses at the 3-month (OR = 3.619, \( P = 0.014 \)) and 1-year follow ups (OR = 4.751, \( P = 0.017 \)) (Tables 5, 6).

**Discussion**

Previous studies significantly correlated emphysematous extent on CT with disease severity and prognosis.\(^5, 6\) However, this is the first study that compared emphysema severity on CT during an exacerbation and prognosis to our knowledge. In the present study, there was a very good correlation and no significant difference between LAA% measured during the exacerbation and in the stable phase. This suggested that LAA% during an AECOPD has a similar prognostic predictive effect as LAA% during the stable phase. CT is more often performed for patients with exacerbations to evaluate lung consolidation, differentiate from pneumothorax or other processes, and guide treatment decisions.
hydrothorax and screen for post-obstructive pneumonia caused by neoplasms. Emergency CT imaging is inexpensive and readily available at our hospital.

The LAA% of patients who died between 1 month and 1 year was even higher than those who died within 1 month (although not statistically significant). LAA% may reflect the mid-term risk of death to a greater extent than the short-term risk. That is, patients without obvious emphysema (LAA% ≤ 7.5%) may have better reversibility. LAA% differs from other indices mainly related to the risk of death within 1 month.

In the present study, mMRC grade, performance status and CAT score at follow up were registered as end-points in addition to mortality. The mMRC scale is a 5-point scale to evaluate COPD-related dyspnoea severity, recommended by GOLD guidelines.1 and correlates significantly with respiratory symptom severity, disability18 and mortality.19 Performance status is a 6-point scale formulated by the Eastern Cooperative Oncology Group to evaluate performance and disability, formerly used in patients with malignant tumours and validated to be a predictor of mortality in COPD.20,21 In the present study, LAA% was correlated with mMRC grade and performance status at both the 3-month and 1-year follow ups, suggesting that LAA% is correlated with COPD severity and mortality for more extended durations.

The correlation was not significant between LAA% and chronic bronchitis symptoms, such as cough and sputum

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>M12 mMRC (increment by 1)</th>
<th>M12 PS (increment by 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
<td>Multivariate ordinal logistic regression</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>P</td>
</tr>
<tr>
<td>Age (increment by 1 year)</td>
<td>1.070</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.949</td>
<td>0.368</td>
</tr>
<tr>
<td>Male</td>
<td>1.679</td>
<td>0.301</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in cough</td>
<td>0.130</td>
<td>0.007</td>
</tr>
<tr>
<td>Increase in sputum volume</td>
<td>0.197</td>
<td>0.019</td>
</tr>
<tr>
<td>Increase in sputum purulence</td>
<td>0.632</td>
<td>0.255</td>
</tr>
<tr>
<td>Fever (T &gt; 37.3°C)</td>
<td>0.747</td>
<td>0.477</td>
</tr>
<tr>
<td>Clinical scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRB-65 (increment by 1)</td>
<td>6.521</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In the past 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations ≥ 2</td>
<td>1.644</td>
<td>0.230</td>
</tr>
<tr>
<td>Hospitalisation due to an AECOPD</td>
<td>2.945</td>
<td>0.038</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0.800</td>
<td>0.702</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.026</td>
<td>0.949</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.071</td>
<td>0.917</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.837</td>
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</tr>
<tr>
<td>Left heart failure</td>
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<td>0.001</td>
</tr>
<tr>
<td>History of smoking</td>
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<td>0.220</td>
</tr>
<tr>
<td>CT emphysema evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAA% &gt; 7.5%</td>
<td>3.987</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The multivariate logistic regression was performed only on influencing factors related to the mMRC grade or performance status in the univariate analyses with P < 0.1. Age was not utilised in the multivariate logistic regression because it was embodied in the CRB-65 score. Odds ratios (OR) refer to the change in OR ratios of PS or mMRC grade at least 1 unit higher at follow up with an increase in the predictor variables by 1 unit. Bold values refer to the OR of the independent prognosis predictors. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; CRB-65 score, confusion, respiratory rate ≥ 30/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years; LAA%, the percentage of low-attenuation areas (emphysema) on CT imaging during an AECOPD using a threshold of -950 HU; M3, 3-month follow up; M12, 1-year follow up; mMRC, the modified Medical Research Council Dyspnoea Scale; PS, performance status; T, body temperature.

Emphysema during AECOPD and prognosis

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after stabilisation, or between LAA% and exacerbation frequency. These results agree with findings of previous studies showing that chronic bronchitis symptoms\textsuperscript{22} and exacerbation risks\textsuperscript{5} are more related to bronchial wall thickening than emphysematous changes.

The CAT is an 8-item measure of health status impairment from COPD, correlates closely with health status measured by the St George’s Respiratory Questionnaire, and is reliable and responsive.\textsuperscript{1,14} The correlation between LAA% during exacerbations and CAT scores at the 3-month follow up was limited but significant, while the correlation between LAA% and CAT scores at the 1-year follow up was not significant. There are two possible reasons for this: first, the CAT includes each aspect of COPD symptoms, while LAA% correlates to dyspnoea rather than chronic bronchitis symptoms. Second, many patients completed the CAT questionnaire with the help of others because of low education and weakness, which may have caused errors; this problem was also described previously.\textsuperscript{5}

The median LAA% (6.6%) and criterion for obvious emphysematous change (7.5%) in the present research were much lower than in other cohorts, such as in Haruna's study (22.1% and 32.3% respectively).\textsuperscript{9} This may be because, first, patients with thickened bronchial walls rather than severe emphysema tend to suffer from frequent exacerbations.\textsuperscript{6,24} Second, the present study was based on emergency department patients, some of whom did not manifest severe dyspnoea in the stable phase\textsuperscript{2} and did not regularly seek treatment for COPD, and therefore were not registered in an outpatient department-based cohort. Third, the severity of emphysema differs among ethnic groups, even with similar lung function impairment.\textsuperscript{25} The COPD patients with hereditary alpha-1 antitrypsin deficiency, who often manifest severe emphysema, are extremely rare in China.\textsuperscript{26} Since we screened almost all AECOPD patients who visited our emergency department without selection, and the mortality was only a little lower than in other cohorts,\textsuperscript{3,4,17} we consider that this cohort covered a wide range of GOLD categories and different degrees of emphysema.

In the present study, we diagnosed COPD based on clinical presentation and bedside spirometry in addition to previous diagnoses, because only a few patients with COPD had been diagnosed previously in China, especially those with mild COPD.\textsuperscript{27} Patients with a history of asthma or left heart failure in addition to COPD were not excluded, because we consider them to be representative of some COPD patients. Many who reported to be suffering from asthma (‘xiao chuan’ in Chinese) were actually suffering from COPD. In some patients with chronic asthma, COPD may coexist.\textsuperscript{7} The incidence of concomitant COPD and asthma was reported to be 2604/6059 in a Medicaid population.\textsuperscript{28} Left heart failure is another common COPD comorbidity. Left ventricular dysfunction was found in 32% of COPD patients with symptomatic deterioration.\textsuperscript{29} Even in patients with stable COPD and without a cardiologist-confirmed diagnosis of heart failure, roughly 30% had heart failure to some extent.\textsuperscript{30} Although the cardinal symptoms of COPD and left heart failure are similar, dyspnoea and exercise intolerance, left heart failure does not cause obstructive airflow limitation.\textsuperscript{31} Therefore, FEV1/FVC < 70% indicates the existence of COPD, regardless of the presence of left heart failure.

Patients with radiographic consolidation were not excluded, because pneumonia is a common AECOPD complication. In previous studies, 15–36.5% of inpatients with an AECOPD had radiographic consolidation\textsuperscript{12,15} and were not excluded from a state audit.\textsuperscript{3,33} Furthermore, only a portion (12%/15%) would be diagnosed with pneumonia based on paired radiographs.\textsuperscript{22}

In the present study, the CRB-65 score was one of the best predictors of mortality, severity of dyspnoea and disability after stabilisation. The CRB-65 is a 4-point score, originally used for risk stratification in community-acquired pneumonia. Recently, CRB-65 was reported to predict in-hospital and 30-day mortality, but not 1-year mortality.\textsuperscript{12,34} In our study, the CRB-65 score predicted 1-year mortality, mMRC grade and performance status at the 1-year follow up. This may be because those enrolled in the previous study were inpatients, while the CRB-65 score and CURB-65 score are portions of the admission criteria.\textsuperscript{35} The present study enrolled almost all AECOPD patients who visited the emergency department without selection, thereby including different levels of severity, making the predictive ability of the CRB-65 score more obvious.

The present study showed that a history of left heart failure predicts a higher mMRC grade at the 3-month and 1-year follow ups independently. It is suggested that left heart failure may aggravate dyspnoea in COPD, which confuses severity assessments using the mMRC grade. Indeed, the widely used New York Heart Association functional classification for left heart failure is similar to the mMRC scale.\textsuperscript{36} These findings suggest the necessity of grading criteria to assess COPD-related dyspnoea and left heart failure separately.

Limitations

The present study had some limitations. First, some prognostic predictors, such as blood gas analyses and lung function tests were not analysed in this study, because only a few patients completed these tests in the emergency department. Thus, it remained undetermined...
whether the LAA% is a prognostic factor independent of the blood gas analysis and lung function test. Second, the CRB-65 score could not be calculated because of missing data in some patients. However, there were no significant differences in LAA% and prognosis between the patients with or without CRB-65 score. Among the patients with CRB-65 score, the LAA% was proven to be a prognosis predictor independent of CRB-65. Third, only a few patients underwent the follow-up CT with the same parameter. Therefore, the CT manifestation of exacerbation could hardly be analysed in detail in this study. The relationship between CT imaging and the aetiology of exacerbation awaits further investigation. The impact of the relationship between CT imaging and the aetiology of exacerbation on emphysema progression, as shown in a previous study,37 could not be analysed in the present study. Fourth, among the several CT indices, only LAA% was analysed in the present study. Thus, it remains unclear whether other CT indices were prognostic factors. Lastly, the sample size of the present study was small. Despite these limitations, the LAA% was still proven to be associated with the prognosis, even after adjustment for other co-variables.

Conclusions

The severity of emphysematous change on CT during an acute exacerbation of COPD was correlated with the risk of death in 1 year, and the severity of dyspnoea and disability at 3 months and 1 year after exacerbation. Obvious emphysema on CT during an AECOPD is an independent predictor of a poor prognosis.

References


Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Figure S1** The questionnaire used during an acute exacerbation of COPD.

**Figure S2** The questionnaire used at the 3-month and 1-year follow ups after an acute exacerbation of COPD.

**Figure S3** The correlation between the LAA% on computed tomography (CT) during exacerbations and stable phases (Pearson’s correlation). LAA%: the percentage of low-attenuation areas (emphysema) on CT imaging during an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) using a threshold of –950 HU.

**Table S1** Comparisons between patients with and without a CRB-65 score.

**Table S2** Main pulmonary function test data at follow up and during an exacerbation.

**Table S3** Complete pulmonary function test data at the 3-month follow up.

**Table S4a** Comparisons between patients with and without asthma.

**Table S4b** Comparisons between patients with and without infiltration.

**Table S5** Comparisons between patients who died within 1 month, who died between 1 month–1 year and survivors at 1-year follow up.

**Table S6** The correlation between low-attenuation areas (LAA%) during an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and COPD symptoms at follow up stratified by other factors.
Efficacy of non-invasive mechanical ventilation in the general ward in patients with chronic obstructive pulmonary disease admitted for hypercapnic acute respiratory failure and pH < 7.35: a feasibility pilot study

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Abstract

Aim: To date non-invasive (NIV) mechanical ventilation use is not recommended in chronic obstructive pulmonary disease (COPD) patients with acute respiratory failure (ARF) and pH < 7.30 outside a ‘protected environment’. We assessed NIV efficacy and feasibility in improving arterial blood gases (ABG) and in-hospital outcome in patients with ARF and severe respiratory acidosis (RA) admitted to an experienced rural medical ward.

Methods: This paper is a prospective pilot cohort study conducted in the General Medicine Ward of Budrio’s District Hospital. Two hundred and seventy-two patients with ARF were admitted to our Department, 112, meeting predefined inclusion criteria (pH < 7.35, PaCO2 > 45 mmHg). Patients were divided according to the severity of acidosis into: group A (pH < 7.26), group B (7.26 ≤ pH < 7.30) and group C (7.30 ≤ pH < 7.35). ABG were assessed at admission, at 2–6 h, 24 h, 48 h and at discharge.

Results: Group A included 55 patients (24 men, mean age: 80.8 ± 8.3 years), group B 31 (12 men, mean age: 80.3 ± 9.4 years) and group C 26 (15 men, mean age: 78.6 ± 9.9 years). ABG improved within the first hours in 92/112 (82%) patients, who were all successfully discharged. Eighteen per cent (20/112) of the patients died during the hospital stay, no significant difference emerged in mortality rate (MR) within the groups (23%, 16% and 8%, for groups A, B and C, respectively) and between patients with or without pneumonia: 8/29 (27%) versus 12/83 (14%). On multivariable analysis, only age and Glasgow Coma Scale had an impact on the clinical outcome.

Conclusion: In a non-‘highly protected’ environment such as an experienced medical ward of a rural hospital, NIV is effective not only in patients with mild, but also with severe forms of RA. MR did not vary according to the level of initial pH.

Introduction

Acute respiratory failure (ARF) with decompensated respiratory acidosis represents a frequent reason for hospital admission of patients with chronic obstructive pulmonary disease (COPD).1 Recent research has shown that COPD is very often associated with different comorbidities that considerably impact on the management and the prognosis of these patients.2,3 Despite the burden that COPD is increasing and that it will be the third cause of death in a few years, the number of patients admitted to the intensive care unit (ICU) has
decreased in the last decades. This may be partly due to better pharmacological and rehabilitative strategies but also to the early use of non-invasive mechanical ventilation (NIV) outside of a highly protected environment like an ICU or a respiratory ICU (RICU). The early use of such a therapeutic approach, when appropriate, may prevent clinical deterioration of these patients, reducing risk of endotracheal intubation (ETI) and mortality. However, the pH level has been reported to be a crucial factor in determining the NIV success rate.6,7 Although the confidence of healthcare providers with NIV has progressively improved and although NIV has been applied with success also outside the critical care environment,6,7 to date NIV is not recommended outside ICU in patients with severe hypercapnic ARF and a pH < 7.30.8 In particular, it was shown that NIV treatment failed in approximately 50–60% of COPD-exacerbated subjects with a baseline pH < 7.25. Indeed, concerns were also placed on treating these patients outside a protected environment when they are affected by comorbidities.

We have prospectively performed a feasibility pilot study with the aim to assess efficacy of NIV on mortality rate in the ‘every day clinical practice’ at the General Medical Ward of a small rural Italian hospital without ICU, focusing our analysis on patients presenting acute or acute-on-chronic respiratory failure and severe respiratory acidosis (pH < 7.35). Secondary outcomes were the influence of acute and chronic comorbidities on patients’ outcomes. Therefore, the results may be useful to calculate sample sizes for future definitive studies.

**Methods**

We performed a prospective-cohort study in the General Medicine Ward of Budrio’s District Hospital with the ‘external’ support of the RICU of S. Orsola-Malpighi Hospital at Bologna. If the patient met the intubation criteria, it was agreed to transfer her/him promptly to that unit, which is approximately 15 km far away.

Budrio District Hospital is a rural hospital of 80 beds with medicine and surgery units as well as emergency department but without ICU.

We enrolled consecutive COPD patients with hypercapnic ARF or with exacerbations on chronic RF (AHRF) admitted to our medical ward over a 13-month period (from 1 January 2013 to 31 January 2014). All these patients were first admitted to our emergency room, and if they showed signs of AHRF, they were sent to the doctor on duty at the medical ward. Only the patients who met the inclusion criteria (see below) were therefore consecutively enrolled.

**Inclusion criteria** were pH < 7.35 and PaCO₂ > 45 mmHg, in association with a respiratory rate > 25 breaths/min and massive activation of accessory (or secondary) respiratory muscles. The patients were subsequently divided into three groups according to the severity of acidosis:

- **Group A** included 55 patients with pH < 7.26;
- **Group B** included 31 patients with pH between 7.26 and 7.299;
- **Group C** included 26 patients with pH ≥ 7.30.

Exclusion criteria included multiple organ failure, haemodynamic instability, acute ischaemic heart disease, cerebrovascular accident, facial deformity preventing adequate mask fitting, upper airway obstruction, any causes of metabolic acidosis: gastrointestinal bleeding or surgery, severe psychiatric conditions with psychomotor agitation, cardiac or respiratory arrest with need of urgent intubation and NIV refusal. Any type of metabolic acidosis was excluded on the basis of the ‘classical’ arterial blood gases (ABG) criteria that is the presence of pH < 7.35 and pCO₂ < 45 mmHg with bicarbonate lower than the normal range. In addition, we enrolled in our study only patients with a body mass index < 30, to minimise the chances that patients with overlap syndrome could be included. Seven patients (four in group A, two in group B and one in group C) had previously been treated with NIV for an episode of acute COPD exacerbation, whereas no patient was enrolled in a home care NIV programme. COPD diagnosis was performed, according to a 1987 American Thoracic Society statement on the basis of pulmonary function tests (PFT) in 68% of our patients, whereas in the remaining subset, it was carried out based on the ‘usual criteria’ employed in most of the published NIV trials4,5,8 to define COPD in absence of PFT, which includes clinical history, physical examination and imaging data, such as chest radiograph or high-resolution computed tomography scan. In addition, health status of each patient was assessed by Charlson Index comorbidity score at hospital admission based on the clinical history and patient’s previous and actual records.10 The protocol was approved by our local Ethical Committee and written consent was obtained from all patients. Before starting NIV treatment, COPD patients received a standard medical treatment, including aerosolised bronchodilator drugs, intravenous steroid and, when necessary, furosemide and antibiotics.

**NIV settings**

Patients were treated with pressure support ventilation with a fixed back-up rate (12 breaths/min) (Resmed VSIII, ResMed, Sydney, NSW, Australia) supplied by means of a double-tube circuit through an oro-nasal non-vented mask (Performatrack total mask Respironics, Pittsburgh, PA, USA).
Different sizes of interfaces were available at patients’ bedside during NIV start. Peak inspiratory pressure was initially set at 14 cmH₂O and gradually increased to a maximum of 34 cmH₂O (median value was 22 cmH₂O, range 14–34 cmH₂O) to obtain an expired tidal volume of 7–8 mL/kg, according to patients’ tolerance, whereas the positive end-expiratory pressure was initially set at 4 cmH₂O and increased to a maximum of 8 cmH₂O or reduced to resolve patients’ hypoxaemia or decrease their discomfort respectively (median value was 6 cmH₂O, range 4–8 cmH₂O). An arterial oxygen saturation ranging between 90% and 95% was obtained with oxygen supply by means of an adequate FiO₂ setting. NIV was started directly in the emergency department by the respiratory physician on call. Patients were then transferred (average time 2.4 ± 2.1 h) to the medical ward, where four beds may be monitored and are utilised for very critically ill patients. NIV was always prescribed and started by the attending physician. The nurses were in charge to fix the interfaces and to monitor the patients. NIV was applied intermittently, for periods of at least 4 h, with a minimal duration of 8 h per day, or continuously in case of hypercapnic coma and was maintained until improvement of clinical signs and ABG parameters were obtained.

During NIV treatment in absence of clinical worsening, both in day and night-time, each patient was examined every 30 min by the attending nurses and every hour by the attending physician, whereas arterial blood pressure, oxygen saturation, respiratory rate and electrocardiogram were continuously monitored. NIV was discontinued when considered clinically indicated (see Measurements section).

Since we started the use of NIV in our unit several years ago, our medical and nursing staff received a specific training for NIV delivery with periodic retraining by a chest physician from our unit. The median nurse/patient ratio in our unit is equal to 1:12. Lacking an ICU, the decision to intubate the patient was taken by the attending anaesthetist (24 h on duty) according to our hospital guidelines (i.e. respiratory arrest, gasping for air, deterioration or no improvement of ABG after 2 h of NIV, sensorium deterioration, severe dyspnoea with sign of incipient muscle fatigue). The adoption of limits on life support and treatment (e.g. do not intubation order) was left to patient’ or his relatives’ decision, in accordance with the anaesthesiologist, because no specific Italian law regulates this topic. Intubated patients were eventually transferred to our ‘back-up’ RICU.

Measurements

The data recorded at hospital admission were age, sex and Glasgow coma Scale at admission. Number and types of acute and chronic non-respiratory comorbidities were defined, according to the CI, ABG levels at admission and within 2 h, 24 h, 48 h after NIV start and at discharge, as well as the length of in-hospital stay and in-hospital mortality. The following pathological conditions were considered as causes of acute RF in the enrolled patients: (i) acute exacerbations of COPD; (ii) cardiogenic pulmonary oedema or congestive heart failure; (iii) pneumonia; (iv) pneumothorax; and (v) pulmonary embolism.

In accordance with previous studies, objective criteria were used to define when to start the discontinuation process of NIV: an increase in pH value ≥ 7.35, a decrease in pCO₂ of >15–20% and in respiratory rate ≥20%, with oxygen saturation ≥90% in comparison with spontaneous breathing. SaO₂ and ECG were continuously monitored.9 Lung function test was carried out in 70/112 of patients in the preceding year.11

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) and categorical data as count and percentages. Baseline data and characteristics of A, B and C groups of patients were compared with one-way analysis of variance and Bonferroni post-hoc test for continuous variables and with Chi-squared test for categorical data. The repeated measures analysis of variance has been performed in order to study the changes of pH, pCO₂ and pO₂/FiO₂ across time intervals until patient hospital discharge or death. Risk factors of in-hospital all cause mortality have been assessed by univariate and multivariable logistic regression analysis. No correlated variables reaching a P-value less than 0.1 at univariate analysis were included in the multivariable analysis. All P-values refer to two-tailed tests of significance; P-values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata/SE 12.1 (StataCorp LP, College Station, TX, USA). The aim of the study was to assess the feasibility of NIV to improve ABG and in-hospital outcomes in these subjects. Therefore, in this pilot study, we did not perform a power calculation.

Results

The flow chart of the study is shown in Figure 1.

A total of 112 COPD patients with hypercapnic RF, meeting predefined inclusion criteria was enrolled in the trial and then divided into three groups according to the level of their acidosis. Among the COPD patients, who were excluded by the study, 15 refused NIV, 39 had pH ≥ 7.35 and were treated with only medical therapy, whereas four required immediate intubation and were
transferred. Baseline characteristics of enrolled patients and causes of acute RF are reported in Table 1. Obviously the severity of hypercapnia was significantly worse in the more acidotic group together with the level of consciousness. Numbers and types of acute and chronic comorbidities, according to the Charlson Index, are shown in Table 2. Overall the number of chronic comorbidities did not differ between A, B and C groups. All patients were ventilated at least one night after their in-hospital admission.

Patients who responded initially well to NIV were 101 of 112 (first few hours), but six of them deteriorated their pH after 48 h of NIV, and three died during NIV because of stroke (n.2) and myocardial infarction (n.1). Eighty-two per cent (92/112) of patients were therefore discharged alive and considered NIV treated with success: 42/55 (76%) in group A, 26/31 (84%) in group B, 24/26 (92%) in group C. None of these patients was considered intolerant to NIV. Overall 20/112 (18%) subjects died (NIV failure): 13 in group A, five in group B and two in group C. (P = 0.21). None of them required ETI because eight had a ‘do not intubation’ order (three patients discontinued NIV for intolerance), whereas, in the remaining 12 (four subjects discontinued NIV for intolerance), ETI was considered inappropriate by the attending anaesthetist, according to our hospital guidelines, because it was considered futile. The causes of death in these patients were: stroke (two patients in group A), myocardial infarction (one in group A), congestive heart failure (four in group A, four in group B and one in group C), refractory hypoxia due to pneumonia (six in group A, one in group B and one in group C) and are reported in Table 3. Table 4 depicts the changes in ABG during the time course in the patients of the three groups. A progressive improvement of arterial pH and pCO2 levels were observed in the subjects of the three groups (Fig. 2).

Pneumonia was the cause of in-hospital admission in 29/112 (26%) patients (16 in patients with pH < 7.26, eight in patients with pH between 7.26 and 7.299 and five patients with pH ≥ 7.30, P = 0.64); 8/29 individuals with pneumonia died versus 12/83 without pneumonia (P = 0.19). None of our patients developed pneumonia during their in-hospital stay. The left side of Table 5 shows the results of the univariate analysis to predict the NIV failure (NIVF). Remarkably, renal failure was not entered into the multivariable model due to the very strong association with in-hospital survival. Only age and GCS had an increased risk of NIVF, whereas, the prevalence of diabetes was higher in subjects with a better clinical outcome, although this difference was not significant (P = 0.08). Interestingly, the presence of comorbidities, pneumonia and Charlson Index were not associated with an increased probability of death in our study. The right side of Table 5 illustrates the results of the multivariate analysis: age and GCS were independently associated with NIVF and/or death, whereas a history of diabetes was associated with a better trend in clinical outcome.

In-hospital stay was similar in the three groups (14.1 ± 10.71 in group A vs 16.6 ± 11.51 days in group B vs 14.6 ± 6.8, P = 0.52).
Discussion

To our knowledge, our prospective observational pilot study reports, for the first time in a rural hospital, the feasibility and effectiveness of NIV in improving the outcome of COPD patients with moderate to severe acidosis (pH < 7.35) outside a protected environment. Based on the data obtained in the present investigation, with the assumption to have an expected proportion of death equal to 10% in the subset of patients at lower risk (group C) and 25% in the subsets of patients at higher risk, we need to enlist about 150 patients per group.

In the past few years, NIV use has been increased worldwide, and it has become the ‘standard of care’ for the treatment of most episodes of acute exacerbations in COPD-hospitalised patients. A recent study performed in the United States over a time span of 11 years, with the aim of assessing the prevalence and trends of NIV for acute COPD using data from the Healthcare Cost and Utilisation Project’s Nationwide Inpatient Sample, has shown that the use of this type of respiratory support has surpassed that of invasive mechanical ventilation.

Data from this investigation did not allow depiction of the location where patients were treated or their severity at admission. However, it is very likely that not all the 612,000 patients requiring mechanical support were ventilated in a protected environment like an ICU or RICU, and that a subset of individuals was also admitted nationwide in tertiary care hospitals. Most of the studies published in the literature were either conducted by an experienced team and/or in large hospitals with an ICU, and this may not reflect the ‘daily life’ situation of most of the rural or small district hospitals.

The International Consensus Conference of NIV dated back in 2000 was not specific in defining the ideal location according to patients’ severity since it was stated that the optimal environment depends on the capacity for adequate monitoring, staff skill and experience.

In a multicentre randomised study, Plant et al., compared NIV with conventional medical therapy to treat early an episode of ARF in COPD patients, using a ‘simple’ NIV ventilator, minimal monitoring and with a median 1:11 patient/nurses ratio. NIV was initiated and maintained by the ward staff according to a strict

<table>
<thead>
<tr>
<th>Characteristics at enrolment</th>
<th>Patients with pH &lt; 7.26 (group 1): 55</th>
<th>Patients with pH between 7.26–7.299 (group 2): 31</th>
<th>Patients with pH ≥ 7.30 (group 3): 26</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>80.8 ± 8.3</td>
<td>80.3 ± 9.4</td>
<td>78.6 ± 9.9</td>
<td>0.6</td>
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<td>24/31</td>
<td>12/19</td>
<td>15/11</td>
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<tr>
<td>Glasgow Coma Scale</td>
<td>10.6 ± 3.0*</td>
<td>12.0 ± 2.6</td>
<td>13.0 ± 1.8</td>
<td>0.0009</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>32.3 ± 3.6</td>
<td>31.2 ± 2.2</td>
<td>30.4 ± 3.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Charlson Index</td>
<td>3.54 ± 1.27</td>
<td>3.48 ± 1.41</td>
<td>2.23 ± 1.06</td>
<td>0.0001</td>
</tr>
<tr>
<td>PaO2/FiO2</td>
<td>244.4 ± 93.9</td>
<td>230.3 ± 66.3</td>
<td>221.8 ± 69.2</td>
<td>0.47</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>84.7 ± 21.9*</td>
<td>66.3 ± 13.4</td>
<td>65.6 ± 10.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Length of in-hospital stay</td>
<td>16.6 ± 11.5</td>
<td>14.1 ± 10.71</td>
<td>14.6 ± 6.8</td>
<td>0.52</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>29.9 ± 7.7</td>
<td>31.8 ± 11.8</td>
<td>33.8 ± 4.9</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Bonferroni multiple-comparison test: *P < 0.05 group 1 versus group 3. §P < 0.05 group 1 versus group 2. ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease.
protocol and after extensive training. Using prospectively defined criteria, NIV reduced the need for ETI and hospital mortality. However, in a subgroup analysis, patients with a pH \(< 7.30\) after 4 h of therapy reported a prognosis worse than that seen in comparable studies conducted in the ICU and not better than in the conventional treatment group.

This study raised the concern that NIV could not be safely used in the presence of moderate to severe acidosis outside a protected location. For example in the NIV guidelines, the British Thoracic Society confirmed that ‘patients with more severe acidosis (pH \(< 7.30\)) should be managed in a higher dependency area such as a high dependency unit or ICU, as should those in whom improvement in clinical state and arterial blood gas tensions is not seen after 1–2 h of NIV on a respiratory ward’.16

Interestingly in the same Country (UK) a survey on more than 200 units revealed that NIV was initiated in several non-ICU locations, including the emergency department (54.6% of hospitals), respiratory wards (51.4%) and general medical wards (18.8%), but once more there was no mention about the severity of the episode of ARF.17

To our knowledge, the only two large-sized investigations that tried to assess the percentage and clinical outcome of patients with severe respiratory failure, who were treated with NIV outside the wall of a protected location, were performed in UK and Canada. The first one was an audit on 232 hospital units obtaining data on 9716 patients, 20% of those with gases recorded on admission were acidotic and among the 1077 receiving NIV, 55% had a pH \(< 7.26\). Hospital mortality

### Table 2

<table>
<thead>
<tr>
<th>Charlson comorbidities</th>
<th>Patients with pH (&lt; 7.26) (group 1)</th>
<th>Patients with pH between 7.26–7.299 (group 2)</th>
<th>Patients with pH (\geq 7.30) (group 3)</th>
<th>Charlson comorbidities</th>
<th>Patients with pH (&lt; 7.26) (group 1)</th>
<th>Patients with pH between 7.26–7.299 (group 2)</th>
<th>Patients with pH (\geq 7.30) (group 3)</th>
</tr>
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</table>

AIDS, acquired immune deficiency syndrome.

### Table 3

| Causes of death in the three groups of patients, according to pH arterial blood (pH \(< 7.26\), pH between 7.26–7.299 or pH \(\geq 7.30\)) |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Patients with pH \(< 7.26\) (group 1): 55                      | Patients with pH between 7.26–7.299 (group 2): 31             | Patients with pH \(\geq 7.30\) (group 3): 26 | P-value               |
| Acute myocardial infarction                                   | 1                                                             | 0                                             | 0                      | 0.59               |
| Acute ischaemic stroke                                        | 2                                                             | 0                                             | 0                      | 0.35               |
| Pneumonia                                                     | 6 (2 patients with NIV early and 1 with NIV late failure)     | 1 (1 subject with NIV late failure)           | 1 (1 subject with NIV late failure) | 0.31               |
| Congestive heart failure                                      | 4 (2 patients with NIV early and 1 with NIV late failure)     | 4 (1 patient with NIV early and 1 with NIV late failure) | 1 (1 subject with NIV late failure) | 0.44               |

NIV, non-invasive.

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was 25% in these ventilated patients, and only 5% of all acidicotic patients in only 91 of 232 secondary care centres received ETI. These data suggest that a large number of units do not have in their hospitals ICU availability or receive adequate critical care support.

The second study performed in a Canadian tertiary care hospital showed that 13% and 23% of their COPD or Cardiogenic Pulmonary Oedema patients received NIV in the ward general or the observation ward respectively. Indeed, 23 of 68 patients had a baseline pH ≤ 7.25 prior to NIV initiation, 17 of whom had a pH from 7.15 to 7.24. Of these patients, 16 improved after treatment, suggesting the feasibility of NIV outside a protected area even in the case of severe acidosis.

Another interesting approach to treat patients with life threatening ARF is that proposed by Cabrini et al. that demonstrated how, under the supervision of a Medical Emergency Team in our institution, NIV could be applied in a wide variety of settings, outside the ICU, with a high success rate and with few complications. Some years ago, a previous study carried out in an ED had also suggested that NIV is effective in the treatment of patients with severe acidosis, due to acute hypercapnic COPD.

Our study systematically showed the feasibility of NIV even in patients with severe acidosis hospitalised in a general ward with minimal instrumentation and monitoring, and with a patient : nurse rate similar to what was described by Plant et al.

However, it is important, to describe better the environment where this study was conducted. The rural hospital of Budrio is located in the bigger Bologna area, serving alone a total of 100 000 inhabitants, and the distance from the referring RICU is 15 km that can be usually covered, in the case of need in <15 min by ambulance. The Budrio’s hospital team has three pulmonologists in its staff and a nursing team that initiated the use of NIV a decade ago. In 2011, the hospital initiated a strict collaboration with the Respiratory and Critical Care Unit of the Sant’Orsola Malpighi Hospital, which included formal training of nurses and doctors not only on the use of NIV ventilators and interfaces, but also life supporting manoeuvres.

The encouraging data obtained in this study should therefore not be generalised but placed in this particular context.

In fact, the about-20% rate of NIV failure is in keeping with most of the randomised controlled trial (RCT) studies performed with a similar degree of acidosis. Rather surprisingly though, we did not observe any statistical difference between the three groups of patients divided according to their severity of pH. For example, in patients with a mean pH of 7.17, Squadrone et al. reported a higher (>50%) failure rate than that reported in group A of the present study (25%) with a similar initial pH. However, they did not record the number and types of comorbidities of their COPD patients. Several studies have shown that coexisting comorbidities have a high prevalence in patients with COPD, with percentages ranging from 40% to 95%, and that they represent independent risk factors both for death in clinically stable COPD individuals and for in-hospital mortality in COPD patients after episodes of acute exacerbation.
and number of comorbidities in our three groups of patients were very similar, and this may well explain the similar outcomes of our patients despite the higher level of acidosis and more severely compromised level of consciousness. Comorbidities have been shown to be one of the major determinants of NIV success or failure. Very few studies have considered the Charlson Index to assess the overall severity of these patients, but interestingly the mean index of our study (between 2.5 and 3.5, according to the different groups) is rather similar to that described by others and the overall NIV failure was fairly constant (around 10–15%). The question of whether management of patients with a pH < 7.30 in a non-high dependency setting has equivalent outcomes to a high dependency setting can be solved only with a RCT is very difficult to perform.
We also seek to find potential variables associated with NIV failure. This has already been the objective of several studies, but mostly performed in the ICU or RICU. Changes in ABG after 1 or 2 h, respiratory rate and lack of sensorium impairment were the most powerful predictors of success. We confirm the predictive power of ABG and the rather surprising matter of age. An increasing age was associated with an elevated risk of NIV failure. This appears to be in contrast with most of the previous studies that showed a quite high success rate in old patients, but it is of note that the average baseline pH of the studies by Benhamou et al.28 and Nava et al.29 was 7.28 and 7.30, respectively, and that the mean age was 79 years and 81 years. Hence, overall the subjects enrolled in the present study were more acidotic and older.

The overall results obtained in our study may have important clinical and organisational implications. The implementation of a NIV service in a tertiary hospital without an ICU may decrease the number of urgent admissions in a large community hospital where bed availability in the critical care area, at least in some countries, may be problematic. Quite often, ICU admission is denied in old patients especially when they have a chronic illness or several comorbidities.30 The implementation of NIV in a hospital with limited resources should be carefully evaluated, depending on the geographical position, the expected number of patients to be treated in 1 year, the possibility of having a ‘back-up ICU’ in case of a patient’s deterioration, dedicated equipment and most important, adequate training for the doctors and nurses to bring together, as in our case, an enthusiastic team of motivated people.

In our hospital, we periodically meet (every 3 months) for an audit aimed to update knowledge and to discuss the problems that occurred in that time frame. Nurses and doctors participate in national and international courses on NIV. Lastly, we have specific protocols for monitoring patients’ vital signs and tolerance and to avoid nasal or skin abrasions.

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Our study presents important limitations. In this study, we did not record the effective hours of ventilation during nighttime, but it has been recently shown that the amount of time that NIV is effectively applied in ‘every day clinical practice’ is greater overnight than during the day, with air leaks, disconnections and desaturations not different between day and night.31 A relatively small number of patients was enrolled in a single centre for a limited amount of time (1 year). Indeed, despite the anaesthesiologist on duty who should theoretically follow the internal guidelines for intubation, it is well possible that other factors may have influenced his/her decision, such as the patient’s refusal and severity/prognosis of related diseases. Therefore, all these factors raise the possibility of a type 2 error. However, at least from a general point of view, our study has the merit to represent a snapshot of the ‘every day clinical practice’ in a rural hospital, where usually RCT are not performed.

**Conclusion**

Our pilot study confirms the hypothesis that NIV is a feasible and effective treatment also for patients with severe forms of acute exacerbations of COPD, admitted to a general ward of a rural hospital without dedicated critical care beds. However, the data need to be confirmed in larger studies and in different geographical locations.

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**Table 5. Predictors of in hospital mortality at logistic regression analysis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
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<tr>
<td>Age (years)</td>
<td>1.13 (1.05–1.22)</td>
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</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>0.82 (0.69–0.97)</td>
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<tr>
<td>pH</td>
<td></td>
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</tr>
<tr>
<td>7.26–7.299</td>
<td>3.30 (0.40–13.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>&lt;7.26</td>
<td>3.71 (0.77–17.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Tumours</td>
<td>1.44 (0.35–5.82)</td>
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</tr>
<tr>
<td>Sex</td>
<td>0.97 (0.37–2.57)</td>
<td>0.96</td>
</tr>
<tr>
<td>Charlson Index</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>0.16 (0.02–1.24)</td>
<td>0.08</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>1.71 (0.54–5.42)</td>
<td>0.36</td>
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<td>History of myocardial infarction</td>
<td>1.02 (0.31–3.44)</td>
<td>0.96</td>
</tr>
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<td>Cerebrovascular disease</td>
<td>1.35 (0.26–7.03)</td>
<td>0.72</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>2.44 (0.41–14.37)</td>
<td>0.32</td>
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CI, confidence interval; OR, odds ratio.
Acknowledgements


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References


Prevalence and significance of CYP2C19*2 and CYP2C19*17 alleles in a New Zealand acute coronary syndrome population

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Key words
platelet activation; drug effect, acute coronary syndrome, ticlopidine; analogue and derivative, ticlopidine therapeutic use, ethnicity.

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Abstract

Background: High on-treatment platelet reactivity has been associated with poor outcomes following acute coronary syndromes (ACS). Both the loss of function CYP2C19*2 allele and the gain of function CYP2C19*17 allele along with a range of clinical characteristics have been associated with variation in the response to clopidogrel.

Aim: The study aims to examine the frequency of CYP2C19 variants and understand the factors associated with on-treatment platelet reactivity in a New Zealand ACS population.

Methods: We prospectively enrolled 312 ACS patients. We collected clinical characteristics and measured on-treatment platelet reactivity using two validated point-of-care assays, VerifyNow and Multiplate. DNA was extracted and CYP2C19*2 and *17 alleles were identified using real-time polymerase chain reaction.

Results: CYP2C19*2 or CYP2C19*17 alleles were observed in 101 (32%) and 106 (34%) of patients, respectively, with significant differences in distribution by ethnicity. In Maori and Pacific Island patients, 47% (confidence interval (CI) 31–63%) had CYP2C19*2 and 11% (CI 4–19%) CYP2C19*17 compared with 26% (CI 19–32%) and 41% (CI 32–49%) in white people. Carriage of CYP2C19*2 alleles was associated with higher levels of platelet reactivity measured by either assay, but we observed no relationship between platelet reactivity and CYP2C19*17. In multivariate analysis diabetes, clopidogrel dose and CYP2C19*2 status were all significant independent predictors of platelet reactivity.

Conclusions: Both CYP2C19*2 and *17 were common in a New Zealand ACS population, with CYP2C19*2 observed in almost half the Maori and Pacific Island patients. CYP2C19*2, diabetes and clopidogrel dose were independent contributors to on-treatment platelet reactivity.
Introduction

There is considerable variability in the level of platelet inhibition observed in patients treated with clopidogrel and aspirin following acute coronary syndromes (ACS).\(^1\)\(^-\)\(^3\) Patients with high levels of platelet reactivity on clopidogrel have an increased risk of death, myocardial infarction and stent thrombosis.\(^4\)\(^-\)\(^5\) In a New Zealand context, we have previously demonstrated that high levels of platelet reactivity are common, particularly in Maori and Pacific Island patients.\(^2\)

Previous studies have suggested that the variability in clopidogrel’s pharmacodynamics is multifactorial in origin. Clinical variables, such as diabetes and smoking,\(^6\) drug interactions including those with proton pump inhibitors,\(^7\) functional genetic polymorphisms, most importantly those in the hepatic CYP2C19 enzyme,\(^8\) and variation in the level of pretreatment platelet reactivity,\(^9\) have all been implicated in contributing to the variability in the response to clopidogrel. CYP2C19 is one of the enzymes involved in converting clopidogrel to its active metabolite. The CYP2C19*2 allele is a loss of function (LOF) variant associated with reduced blood levels of the active metabolite, while the *17 allele is a gain of function variant associated with higher levels of the active metabolite.\(^8\)\(^-\)\(^10\) CYP2C19*2 has been associated with an increased risk of adverse cardiovascular outcomes.\(^8\)\(^-\)\(^10\)\(^11\)

Understanding the frequency of the CYP2C19 variants in a New Zealand ACS population and how this relates to on-treatment levels of platelet reactivity is important in determining optimal antiplatelet therapy in this population.

Methods

Patient population

Patients presenting to Wellington Regional Hospital with ACS between January and December 2012 were eligible for inclusion in the study if there was an invasive approach (coronary angiography ± percutaneous coronary intervention (PCI)) planned. All participants were adequately pretreated with aspirin and clopidogrel. To ensure the necessary statistical power to assess the impact of ethnicity, we recruited 282 ACS patients (232 white people, 40 Maori and Pacific Islanders) and enriched the population with an additional 30 Maori and Pacific Island ACS patients. Exclusion criteria included a platelet count less than \(100 \times 10^9/\text{L}\), known platelet function disorder, administration of a fibrinolytic agent within 24 h of enrolment, use of a glycoprotein IIb/IIIa receptor antagonist within 7 days, or administration of an oral antiplatelet agent other than aspirin or clopidogrel within 2 weeks of enrolment. The study was reviewed and approved by the Lower Regional South Ethics Committee (LRS/11/09/035). All patients provided written informed consent.

Definitions

An ACS was defined as symptoms suggestive of myocardial ischaemia lasting >10 min and either troponin elevation or ≥21 mm of new ST segment deviation or T wave inversion on an electrocardiogram in at least two contiguous leads.\(^12\) Adequate pretreatment was defined as chronic therapy (≥7 days) with aspirin (≥275 mg) and clopidogrel (≥75 mg) and/or loading with aspirin ≥300 mg at least 2 h and clopidogrel ≥300 mg at least 6 h prior to enrolment. The clopidogrel dose was defined as ‘high’ if patients had received a 600 mg loading dose followed by a 150 mg daily maintenance dosing. Intermediate dose was defined as either a 600-mg loading dose followed by 75-mg daily maintenance dose, or a 300-mg loading dose coupled with 150 mg maintenance dose. Low dose was defined as a 300-mg loading dose followed by 75-mg daily maintenance dose or chronic therapy with 75-mg daily of clopidogrel.

Platelet function testing

Blood samples for platelet function testing were taken prior to angiography. On average, this was 4 ± 2 days after hospital presentation with ACS. The level of on-treatment platelet reactivity was quantified using the VerifyNow P2Y\(_{12}\) assay (Accumetrics, San Diego, CA, USA) and the Multiplate analyser (Dynabyte, Munich, Germany), both of which have been shown to be predictive of clinical outcomes.\(^4\)\(^-\)\(^5\) The VerifyNow P2Y\(_{12}\) assay, a turbidimetric-based optical detection system, was used according to the manufacturer’s instructions. This device uses fibrinogen-coated microbeads, an agonist of adenosine diphosphate (20 mM ADP), and light transmittance through whole blood, to measure platelet agglutination. An optical signal, reported as P2Y\(_{12}\) reaction units (PRU), was recorded. The Multiplate analyser is a multiple electrode impedance aggregometer that assesses platelet function in whole blood as previously described.\(^13\) Briefly, whole blood was added to the test cuvettes, diluted (1:2 with 0.9% NaCl solution), stirred and warmed to 37°C. ADP was added to a final concentration of 6.4 mM, and aggregation was then continuously recorded for 6 min.
Aggregation values are quantified as area under the aggregation curve expressed as aggregation units × minutes (AU). All material used for platelet function testing was obtained from the manufacturer (Dynabyte).

High on-treatment platelet reactivity (HPR) was defined as >208 PRU for VerifyNow and >47 AU for Multiplate measurement, while low on-treatment platelet reactivity (LPR) was defined as <85PRU for VerifyNow and <19 AU for Multiplate measurement of platelet reactivity.14

Genotyping

Genomic DNA was isolated from EDTA blood, followed by identification of CYP2C19*2, and *17 using validated real-time polymerase chain reaction (PCR) high-resolution melting assays. The assay for CYP2C19*2 was based on the method described by Temesvari et al.15 For testing the presence of CYP2C19*17, a 62-base-pair PCR product was amplified with 0.2 μM each of the primers AAATTTGGTCTTCTTTCTCACA and TGCCCATCGTG GCCCATTAT;16 in a 10-μL reaction mixture containing 1x reaction buffer B1, 1.5 mM Mg2+, 0.2 mM of each dNTP, 1.5 mM SYTO 9 Green Fluorescent Nucleic Acid Stain (Life Technologies, Carlsbad, CA, USA), 0.5 U of HOT FIREPol DNA Polymerase (Solis BioDyne, Tartu, Estonia), and 50 ng of input DNA. Thermal cycling was preceded by 95°C for 10 min, then 45 cycles of 95°C for 10 s, 52°C for 15 s and 72°C for 15 s. High-resolution melting profile was obtained by initial heating at 95°C for 15 s, re-annealing at 55°C for 15 s, and final denaturation with gradual heating to 95°C, during which fluorescence data were collected every 0.1°C. CYP2C19*2 and *17 genotyping for most samples was performed twice. Ambiguous genotype calls were resolved by Sanger sequencing or restriction digest.

Statistical analysis

Data are presented as mean (SD) for continuous variables that were normally distributed and as counts (%) for categorical variables. Differences in platelet reactivity by genotype were examined using analysis of variance. In univariate analysis using student t test, analysis of variance and correlation, we identified the factors associated with at least one of the platelet function assay measurements at P < 0.10. These variables were then examined using multivariate linear regression analysis with calculation of the adjusted β coefficient and coefficient of determination (R²) to identify the independent contribution of each to the inter-individual variability in on-treatment platelet reactivity as measured with the Multiplate assay and the VerifyNow assay.

Results

Of the 312 patients enrolled in the study, 58 (18%) presented with ST-segment elevation myocardial infarction, 239 (77%) with non-ST segment elevation myocardial infarction and 15 (5%) with unstable angina. The mean age of the population was 65 (±10) years old, and 225 (72%) were male. The majority (237, 76%) of the population were white people, with 70 (22%) of the patients identifying as Maori or of Pacific Island descent.

There were 101 patients (32%) with carriage of at least one CYP2C19*2 allele, and this more likely in Maori and Pacific Island patients than white people (47%, confidence interval (CI) 31–63% compared with 26% CI 19–32%). There were 106 patients (34%) with at least one CYP2C19*17 allele. Maori and Pacific Island patients were less likely than white people to have a CYP2C19*17 allele (11% CI 4–19% compared with 41% CI 32–49%).

We examined platelet reactivity by CYP2C19*2 status (Fig. 1), and the presence of the CYP2C19*17 allele (Fig. 2). The presence of the CYP2C19*2 allele was associated with significant differences in platelet reactivity with both platelet function assays. VerifyNow levels of platelet reactivity were 174 (93), 210 (81) and 224 (68) PRU in the no CYP2C19*2 alleles, 1 allele and 2 CYP2C19*2 alleles groups respectively (P = 0.001). Bonferroni’s multiple comparison showed significant differences between no and 1 CYP2C19*2 allele groups, but not between the other pairs. Multiplate levels of platelet reactivity were 39 (23), 43 (23) and 64 (41) AU in the no CYP2C19*2 alleles, 1 allele and 2 CYP2C19*2 alleles groups respectively (P = 0.0003). Bonferroni’s multiple comparison showed significant differences between 2 CYP2C19*2 alleles and both 1 allele and no CYP2C19*2 alleles, but not between the 1 allele and no CYP2C19*2 alleles groups. There were no significant differences in platelet reactivity measured by either assay and the presence of the CYP2C19*17 allele.

On the basis of VerifyNow measurement, 138 (44%) had HPR, and this was associated with CYP2C19*2 allele carriage, with an observed rate of 26% in no CYP2C19*2, 54% with 1 CYP2C19*2 allele and 70% with 2 CYP2C19*2 alleles (P = 0.01, chi-squared test). Multiplate measurements led to the classification of 116 (37%) of the patients as having HPR, and this was also associated with CYP2C19*2 allele carriage, with a rate of 32% in the no CYP2C19*2 allele group, 44% with one allele and 58% with two CYP2C19*2 alleles (P = 0.03, chi-squared test). LPR was observed in 53 (17%) and 56 (18%) patients assessed by VerifyNow and Multiplate criteria, respectively, and this did not differ by CYP2C19*17 allele status with either assay (P = 0.95 and P = 0.69, respectively, for VerifyNow and Multiplate assays, chi-squared test).
We examined clinical characteristics of the groups by CYP2C19*2 allele status (Table 1). There were significant differences in ethnicity between the three groups, with higher rates of Maori and Pacific Island patients in 1 allele and 2 CYP2C19*2 alleles groups. There were also significantly more diabetic patients in the 2 CYP2C19*2 alleles group (0.02). There were no other significant differences between the three groups.
There were 14 variables that had a univariate relationship with either Multiplate or VerifyNow measured platelet reactivity at $P < 0.10$, and these were included in the multivariate analysis shown in Table 2. CYP2C19*2 status, platelet count, diabetes and clopidogrel dose were all significant independent predictors of Multiplate measured platelet reactivity, while genotype, male gender, diabetes and clopidogrel dose were predictors of VerifyNow measured platelet reactivity. The proportion of platelet reactivity predicted on the basis of CYP2C19*2 alone was low for both assays (Table 3), but improved the overall predictive value above the use of clinical variables alone for each assay.

**Discussion**

Both CYP2C19*2 and *17 had high prevalence in a New Zealand ACS population. The frequency of these polymorphisms differed significantly in Maori and Pacific Island patients when compared with white people, with higher CYP2C19*2 and lower CYP2C19*17 frequency in Maori and Pacific Island patients. CYP2C19*2 alleles had a modest impact on platelet reactivity, with diabetes and clopidogrel dose having a greater influence. Clinical factors and genotype combined only explained 20–21% of the observed variance in on-treatment platelet reactivity.

The observed frequency of CYP2C19*2 and *17 alleles in this study were 32% and 34% respectively. The percentage of patients with CYP2C19*2 and *17 alleles in the white people subpopulation, 26% and 41% respectively, was within the range of previous studies, where 10–28% with CYP2C19*2 and 21–41% with CYP2C19*17 have been described. The proportion of Maori and Pacific Island patients with CYP2C19*2 was 47%. The only previous study to examine the incidence of CYP2C19*2 in...
Maori reported results in terms of allele frequency rather than proportion of patients carrying the allele. Using this measure, Lea et al. reported a frequency of 24%,20 and our calculated frequency was similar at 29%. This is the first study that we are aware of to examine the prevalence of CYP2C19*17 in Maori and Pacific Island patients, where only 11% demonstrated this allele.

Several previous studies have demonstrated striking differences in the proportion of patients with CYP2C19 variants.3 Within a Japanese cohort CYP2C19*2 was observed in more than 57% of patients.3 A Korean study reported 44% of patients had CYP2C19*2.21 This level of variance between populations in a genotype known to affect responsiveness to a commonly used drug and to be associated with poor clinical outcomes highlights the importance of examining clinically relevant genotypes in a New Zealand population.

Table 3 Percentage of the variability in on-treatment platelet reactivity explained

<table>
<thead>
<tr>
<th>R² (%)</th>
<th>P-value</th>
<th>R² (%)</th>
<th>P-value</th>
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<tr>
<td>Multiplate ADP assay</td>
<td>VerifyNow P2Y12 assay</td>
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</table>

The high prevalence of diabetes in Maori and Pacific Island patients2 contributed to the high rate of diabetes in the 2 CYP2C19*2 alleles group. Our previous observation that on-treatment platelet reactivity was higher in Maori and Pacific Island patients2 did not include genetic analysis, and so did not allow us to examine CYP2C19*2 alleles and diabetes as covariates along with ethnicity. All three were univariate predictors of platelet reactivity in the current study. However, in the multivariate analysis, only diabetes and CYP2C19*2 alleles but not ethnicity were independent contributors to platelet reactivity, suggesting that the ethnic differences are largely driven by these factors.

The observed relationship between diabetes and platelet reactivity is consistent with previous reports.6,7,22 Similarly, lower doses of clopidogrel leading to lower levels of active metabolite have been previously described as a significant contributor to on-treatment platelet reactivity, as observed in our cohort.7

The two different platelet function assays produced slightly different models accounting for platelet reactivity. Platelet count was associated with platelet reactivity measured with the Multiplate system. Previous studies have reported a relationship between platelet count and platelet reactivity.7 The Multiplate assay is known to be sensitive to platelet count,21 but whether this reflects a more accurate assessment of how platelets behave in blood or is an artefact of measurement is unclear. Male gender has also been previously associated with higher levels of platelet reactivity,7 consistent with the results from the VerifyNow assay in our study.
A large meta-analysis examining CYP2C19*2 allele carriage reported a significant increased risk of the composite end-point of cardiovascular death, myocardial infarction and stroke associated with this allele. Several studies have similarly reported a relationship between HPR and death, myocardial infarction, and stent thrombosis. The findings of these studies raise the possibility that the high prevalence of CYP2C19*2 in Maori and Pacific Island patients observed here, and the previously described high rate of HPR in Maori and Pacific Island patients, may contribute to the poor outcomes observed in this patient group.

We did not observe a relationship between CYP2C19*17 and platelet reactivity in the current study, despite a high prevalence of this allele. Larger studies than ours have reported a lower rate of platelet reactivity in patients with this genotype and an increased associated bleeding risk, suggesting that our failure to observe any relationship here may be due to a lack of statistical power. However, there are large studies that have failed to demonstrate a relationship between CYP2C19*17 and bleeding risk.

Alternative antiplatelet therapies are now available. Ticagrelor and prasugrel are more potent P2Y₁₂ receptor antagonists, both of which have been associated with improved clinical outcomes in ACS patients. Switching from clopidogrel to prasugrel or ticagrelor effectivel reduces the rate of HPR, while simply increasing the dose of clopidogrel appears to be a less effective strategy. In substudies from both PLATO and TRITON-TIMI, the adverse event rate was significantly higher in the clopidogrel arm of the trials in subgroups with CYP2C19*2 alleles. While a significant benefit remained for ticagrelor compared with clopidogrel in those without LOF alleles, there was no difference in the event rate between those without LOF alleles treated with clopidogrel compared with those treated with prasugrel. These studies raise the possibility that at least a portion of the benefits associated with prasugrel and ticagrelor could be achieved through a tailored strategy based on genotype.

Given that clinical characteristics, medications and genotype combined in this study to predict only 20% of the measured platelet reactivity, it would appear that there is considerable additional information that can be gained from platelet function testing. However, it is not currently clear how this information should best be used.

Tailored therapy driven by platelet function testing has not been successful to date. The three largest randomised trials using platelet function testing to tailor antiplatelet therapy, the GRAVITAS trial, the ARCTIC study and the TRIGGER-PCI trial, all failed to demonstrate any benefit from this approach. In the GRAVITAS study, patients with high levels of platelet function were given higher dose of clopidogrel rather than a more potent P2Y₁₂ receptor antagonist, and this strategy has limited effectiveness. This was also the case for the majority of the ARCTIC study, with only 3.3% of patients switched to prasugrel. The TRIGGER-PCI trial was halted early due to a lower than expected event rate, suggesting that it was not going to be adequately powered. A relatively small (n = 600) randomised controlled trial that personalised antiplatelet therapy on the basis of CYP2C19 genotype demonstrated that this approach reduced MACE at 6 months in a Chinese population. This suggests that using CYP2C19 status rather than phenotype to direct therapy may have merit.

In the New Zealand environment, currently both clopidogrel and ticagrelor are available and being used to treat patients with ACS. Given that nearly half the Maori and Pacific Island patients in this study had a CYP2C19*17 allele and we previously observed just over half had HPR, it is reasonable to suggest that Maori and Pacific Island patients with ACS are likely to have an increased benefit from the use of ticagrelor and should be preferentially treated with this agent.

There are several limitations to this study. The sample size of 312 patients was relatively small, and as a consequence our power to observe significant contributors within a multivariate model was limited. This is seen in the reasonably large CI around the βₐ coefficients in Table 2. Platelet function testing was performed prior to angiography. The time between symptom onset, presentation and loading with antiplatelet agents will have varied in the population, and we cannot exclude the possibility that this contributes to the variance in on-treatment platelet reactivity observed. We have not measured platelet reactivity prior to treatment, and so cannot examine how this relates to on-treatment variability. Other clinical variables that may contribute to platelet reactivity, such as left ventricular function, were not routinely measured. We have combined Maori and Pacific Island patients into a single ethnic group within this study, and this may be inappropriate as there may be significant differences between Maori and Pacific Island patients in terms of the frequency of CYP2C19 alleles.

Conclusion

Both CYP2C19*2 and *17 had high prevalence in a New Zealand ACS population, and CYP2C19*2 was observed in almost half the Maori and Pacific Island patients. While CYP2C19*2 demonstrated a modest contribution to the observed levels of platelet reactivity, we did not detect a relationship between CYP2C19*17 and platelet reactivity. Diabetes and clopidogrel dose were the most significant
contributors to on-treatment platelet reactivity, but 80% of the observed variance in platelet reactivity was not accounted for.

References


Safety of coadministration of ezetimibe and statins in patients with hypercholesterolaemia: a meta-analysis

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Key words
ezetimibe, statin, hypercholesterolaemia, adverse event, meta-analysis.

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Abstract

Background: Hypercholesterolaemia is a pivotal risk factor for cardiovascular and cerebrovascular disease and is treated with many effective lipid-lowering agents. Statins are often used alone or in combination with ezetimibe. Combination therapy is more effective because of its complementary approach, which has major benefits for patients with unmanageable lipid levels. Extensive application of combination therapy has resulted in an increased incidence of side-effects, which has raised our concern.

Aim: To evaluate the evidence associated with the safety of coadministration of ezetimibe with statins.

Methods: Three electronic databases were searched (PubMed, EMBASE and Cochrane Library) from January 2002 to October 2014. Two independent reviewers critically identify randomised controlled trials (RCT), extracted the data and assessed trial quality. A total of 20 RCT met inclusion criteria, including 14 856 patients. A fixed-effects model was used for meta-analysis to assess the safety of combination therapy.

Results: Coadministration of ezetimibe and statins did not result in significant increases in total adverse events (30% vs 29%, \( P = 0.34 \)), serious adverse events (2% vs 1.6%, \( P = 0.81 \)), treatment discontinuations (3.5% vs 2.9%, \( P = 0.22 \)), gastrointestinal adverse events (5% vs 4%, \( P = 0.08 \)), allergic reactions or rashes (0.9% vs 1.3%, \( P = 0.33 \)), creatine kinase > 10 × upper limit of normal (ULN) (0.2% vs 0.2%, \( P = 0.86 \)), alanine aminotransferase > 3 × ULN (0.5% vs 0.4%, \( P = 0.96 \)) and aspartate aminotransferase > 3 × ULN (0.4% vs 0.4%, \( P = 0.58 \)).

Conclusion: The incidence of adverse events was similar between ezetimibe–statin combination therapy and statin monotherapy; thus, we recommend combination therapy for patients with hypercholesterolaemia at high risk for cardiovascular and cerebrovascular disease.

Introduction

Statins are inhibitors of hydroxymethylglutaryl-CoA (HMG-CoA) reductase, which lowers cholesterol through inhibiting the sterol biosynthetic pathway and are first-line lipid-altering medications. Ezetimibe is a cholesterol-absorption inhibitor that potently and selectively reduces intestinal absorption of dietary and biliary cholesterol, which is an option for patients with hypercholesterolaemia. The complementary mechanisms of action of statins and ezetimibe have greater lipid-altering efficacy than either agent alone, which is an option for patients at high cardiovascular and cerebrovascular risk whose lipid levels do not reach the recommended standard of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III. However, in addition to lipid-modifying efficacy, the safety of coadministration of ezetimibe with statins has been a major concern. This meta-analysis aimed to examine critically the evidence for safety by analysing trials comparing ezetimibe–statin combination therapy with statin monotherapy.

Methods

We searched PubMed, EMBASE and Cochrane Library databases from January 2002 to October 2014, using the following terms ‘ezetimibe’, ‘zetia’, ‘ezetrol’, ‘statin’,

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Conflict of interest: None.

Studies were included if they met the following criteria: (i) double-blind RCT; (ii) patients >18 years of age diagnosed with hypercholesterolaemia, whose low-density lipoprotein cholesterol (LDL-C) levels were above NCEP ATP III guidelines; (iii) comparison of safety of coadministration of ezetimibe and statins versus statins monotherapy; and (iv) treatment duration >4 weeks. Any disagreement about the inclusion of an article was resolved by discussion.

Identified articles were screened to ensure that they met the predetermined inclusion criteria. Titles were reviewed initially, followed by abstracts and then full-text publications. Detailed information of whole articles was acquired by two reviewers independently. The detailed data were extracted as follows: study characteristics (first author’s name, publication year, number of participants), invention and control measures (type and dosage of active drug, duration of follow up), individual characteristics (number of patients with hypertension or diabetes mellitus) and outcome indicators (numbers of serious adverse events, treatment discontinuations, allergic reactions or rashes, patients with alanine aminotransferase (ALT) >3 × upper limit of normal (ULN), patients with aspartate aminotransferase (AST) >3 × ULN, gastrointestinal adverse events and patients with creatine kinase (CK) >10 × ULN.

We put the Cochrane Risk of Bias tool into effect, including assessing random sequence generation; allocation concealment; participant, personnel and outcome assessor blinding; incomplete outcome data; selective outcome reporting; and other bias. In addition, risk of bias was not used as an exclusion criterion for individual studies in the meta-analysis. The risk of bias was demonstrated graphically: blank means not clear; red means high risk, and green means low risk; that is, the greener the graph, the higher quality the trials.

For evaluation of safety, we analysed the total number of adverse events, and the numbers of serious adverse events, treatment discontinuations, allergic reactions or rashes, patients with ALT >3 × ULN, patients with AST >3 × ULN, gastrointestinal adverse events, and patients with CK >10 × ULN in each group, and compared the values between the two groups. The statistical analysis was performed by Software Review Manager 5.2 (Cochrane Collaboration, Oxford, UK). To assess heterogeneity for RCT, \( \chi^2 \) test and its results, \( P \) value and \( I^2 \) statistics were analysed to assess the incidence of adverse events. Fixed-effects models were used for the meta-analysis. The \( P \) values were two tailed, and statistical significance was set at \( P = 0.05 \).

Results

A flow diagram of the selection process for the meta-analysis is shown in Figure 1. A total of 568 studies was hit initially, and 49 articles were retrieved for evaluation at length; and finally, 20 RCT that satisfied the inclusion criteria were analysed. The characteristics of these 20 studies are listed in Table 1.© The quality of the reporting is shown in Figure 2; 13 trials had complete information for assessing randomisation, and five trials had adequate blinding. Results of the quality assessment for individual studies are shown in Figure 3.

Total adverse events were reported in 16 studies, with 1165 events occurring in 3856 patients (30%) treated with ezetimibe and statins, compared with 1198 events in 4171 patients (29%) treated with statins alone. There was no significant difference in the two arms (95% confidence interval (CI), 0.85–1.06; \( P = 0.34 \); \( F = 0\% \)), as shown in Figure 4. In the subgroup analysis of ezetimibe with atorvastatin, incidence of total adverse events in the combination therapy and statin monotherapy arms was...
27.6% and 27.7%, respectively, which did not represent a significant difference (95% CI, 0.77–1.19; \( P = 0.69; I^2 = 0\%\)) (Fig. 4). In the subgroup analysis of simvastatin, four trials reported the occurrence of total adverse events during follow up. There were no treatment differences in the proportion of patients reporting total adverse events in both groups (95% CI, 0.65–1.20; \( P = 0.22; I^2 = 0\%\)) (Fig. 4). This lack of significance persisted in the subgroup analysis of other statins (95% CI, 0.85–1.13; \( P = 0.75; I^2 = 27\%\)) (Fig. 4). Total adverse events were generally similar between the treatments in both groups.

Eighteen studies were assessed in terms of treatment discontinuation, 169 of 4818 patients (3.5%) discontinued treatment with ezetimibe and statins and 148 of 5142 patients (2.9%) discontinued statins alone. There was no significant difference between combination therapy and statin monotherapy (95% CI, 0.92–1.44; \( P = 0.22; I^2 = 0\%\)), as shown in Figure 5. In a subgroup analysis of atorvastatin, discontinuation in the combination therapy and atorvastatin monotherapy arms was 2.2% and 2.6%, respectively. There was no significant difference in discontinuation between the groups (95% CI, 0.45–1.43; \( P = 0.46; I^2 = 0\%\)) (Fig. 5). In the subgroup analysis of simvastatin, there were six trials that reported the proportion of patients with treatment discontinuation during follow up, although there was no significant

Table 1 Characteristics of included studies.

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num, number; PHC, primary hypercholesterolaemia; HC, hypercholesterolaemia; CHD, coronary heart disease; CAD, coronary artery disease; DM, diabetes mellitus; MS, metabolic syndrome; AS, atherosclerosis; E, ezetimibe; S, simvastatin; A, atorvastatin; R, rosuvastatin; L, lovastatin; P, pravastatin; F, fluvastatin; w, week; NR, not reported.
difference when comparing combination therapy with simvastatin monotherapy (95% CI, 0.81–1.58; \( P = 0.48; I^2 = 0\%\)) (Fig. 5). This lack of significance persisted in the subgroup analysis of other statins (95% CI, 0.95–1.94; \( P = 0.10; I^2 = 18\%)\) (Fig. 5).

Serious adverse events were reported in 13 studies, with 76 events occurring in 3997 patients (2%) treated with ezetimibe and statins, compared with 69 events in 4301 patients (1.6%) treated with statins alone. This end point was not higher with combination therapy compared with statin monotherapy (95% CI, 0.75–1.45; \( P = 0.81; I^2 = 0\%\)) (Fig. 6). In the subgroup analysis of atorvastatin, incidences of serious adverse events in the combination therapy and atorvastatin monotherapy arms were 2.1% and 1.5%, respectively, although this difference was not significant (95% CI, 0.58–3.09; \( P = 0.49; I^2 = 0\%\)) (Fig. 6). In the subgroup analysis of simvastatin, five trials reported the proportion of patients with serious adverse events during follow up. Both treatments had similar tolerability and safety profiles (95% CI, 0.68–1.78; \( P = 0.7; I^2 = 0\%\)) (Fig. 6). Incidence of serious adverse events was generally similar between treatments in the subgroup analysis of other statins (95% CI, 0.49–1.52; \( P = 0.60; I^2 = 38\%\)) (Fig. 6).

Nine studies were assessed for gastrointestinal adverse events. A total of 123 events occurred in 2446 patients (5%) treated with ezetimibe and statins, compared with 122 events in 2957 patients (4%) treated with statins alone. There was no significant difference between combination therapy and statin monotherapy (95% CI, 0.97–1.63; \( P = 0.08; I^2 = 24\%\)), as shown in Figure 7. In the subgroup analysis of atorvastatin, the incidences of gastrointestinal adverse events in the combination therapy and atorvastatin monotherapy arms were 4% and 5% respectively, which did not represent a significant difference (95% CI, 0.31–1.35; \( P = 0.46; I^2 = 53\%\)) (Fig. 7). In the subgroup analysis of other statins, there were five trials that reported the occurrence of gastrointestinal adverse events during follow up. Treatment with other statins alone was associated with a significant reduction in gastrointestinal adverse events compared with combination of ezetimibe and statins (95% CI, 1.10–2.02; \( P = 0.01; I^2 = 0\%\)) (Fig. 7).

Six trials reported allergic reactions or rashes. Seventeen events occurred in 1903 patients (0.9%) treated with ezetimibe and statins, compared with 31 events in 2391 patients (1.3%) treated with statins alone. There was no significant difference between the groups (95% CI, 0.41–1.35; \( P = 0.33; I^2 = 0\%\)) (Fig. 8).

CK >10×ULN was reported in 11 studies. Eleven events occurred in 5579 patients (0.2%) treated with ezetimibe and statins, compared with 10 events in 5850 patients.
(0.2%) treated with statins alone. There was no significant difference between the groups (95% CI, 0.51–2.23; P = 0.86; I² = 0%), as shown in Figure 9. In the subgroup analysis of atorvastatin, the incidence of CK >10 × ULN in the combination therapy and statin monotherapy arms was 0.3% in both. There was no significant difference between the groups (95% CI, 0.25–2.88; P = 0.79; I² = 0%) (Fig. 9). Both treatments had generally similar tolerability and safety profiles in the subgroup analysis of other statins (95% CI, 0.48–3.06; P = 0.68; I² = 0%) (Fig. 9).

The incidence of ALT ≥3 × ULN was reported in 11 studies and did not reach statistical significance when compared between the combination therapy and statin monotherapy groups (95% CI, 0.58–1.77; P = 0.96; I² = 0%) (Fig. 10). In the subgroup analysis of atorvastatin, 6 events occurred in 629 patients (1%) treated with ezetimibe and atorvastatin, and 4 in 625 patients (0.6%) treated with atorvastatin alone. There was no significant difference between the groups (95% CI, 0.42–5.33; P = 0.54; I² = 0%) (Fig. 10). There were generally similar rates reported for the occurrence of ALT ≥3 ULN in the subgroup of other statins (95% CI, 0.49–1.72; P = 0.80; I² = 28%) (Fig. 10).

Seven trials reported the proportion of patients with AST ≥3 × ULN. A total of 17 events occurred in 3864 patients (0.4%) treated with ezetimibe and statins,
compared with 16 events in 4335 patients (0.4%) treated with statins alone. There was no significant difference between the groups (95% CI, 0.61–2.39; P = 0.58; I² = 35%) (Fig. 11).

**Discussion**

Hypercholesterolaemia is one of the risk factors for atherosclerosis and has an indirect relationship with severe complications of atherosclerosis, such as transient ischaemic attacks, acute myocardial infarction and thrombotic stroke, which can have a poor prognosis. Elevated plasma LDL-C, especially, is a major risk factor in the development and prevention of atherosclerotic coronary heart disease and cerebrovascular disease. Reduction in LDL-C levels in individuals with pre-existing coronary heart disease has been shown to reduce cardiovascular and cerebrovascular disease morbidity and total mortality.

Statins have pleiotropic activities, including lowering cholesterol level and stabilising atherosclerotic plaques on the blood vessel walls, which can help to prevent
ischaemic events. Statins have also made a major contribution to the treatment of hypercholesterolaemia and play a key role in comprehensive strategies for treating cardiovascular diseases in the 21st century. In addition, statins are the most commonly prescribed lipid-lowering drugs for patients with elevated plasma LDL-C and play a major part in the reduction of cardiovascular and cerebrovascular disease morbidity.

Ezetimibe has been shown to be the first selective inhibitor of cholesterol absorption by reducing overall delivery to the liver, and the mean decrease in LDL-C with ezetimibe was 19.1% versus placebo. Phase III studies have shown a mean additional decrease of LDL-C (12.1–13.8%) and increase in high-density lipoprotein cholesterol (1.4–4.5%) with ezetimibe and various statins at increasing dosages (vs pooled statins). Coadministration of ezetimibe and statins results in greater reductions in LDL-C, which is similar to using the highest dose of statin monotherapy.

Several studies have found that when the dosage of statin is doubled, the decrease in LDL-C increases by 5–6%, along with efficacy; patients' perceived intolerance of statin therapy increases, which is often dose related and may include elevations in blood levels of liver or muscle enzymes. A previous meta-analysis found that intensive-dose statin therapy was associated with an increased risk of adverse drug events, compared with moderate dose therapy. Many patients at high risk for coronary heart disease and cerebrovascular disease fail to...
reach LDL-C targets with statin monotherapy, and several patients cannot tolerate high doses of statins, because of dose-related adverse events.33

In addition to efficacy, safety is an important issue influencing the selection of ezetimibe for combination with a statin. Ezetimibe and statins are associated with liver function test abnormalities and can cause rhabdomyolysis and myositis. Although the incidence of adverse effects was low, the elevation of liver enzymes was observed more frequently in ezetimibe–statin combination therapy than statin monotherapy in the overall population. These rates for statin monotherapy (0.4%)
and ezetimibe-statin combination therapy (1.4%) were consistent with those reported in the prescribing information.34

Based on these studies, our meta-analysis clarifies the evidence for safety from RCT comparing ezetimibe–statin combination therapy with statin monotherapy. In our study, combination therapy and monotherapy generally had a similar incidence of total adverse events (30% vs 29%, \(P = 0.34\)), serious adverse events (2% vs 1.6%, \(P = 0.81\)), treatment discontinuations (3.5% vs 2.9%, \(P = 0.22\)), gastrointestinal adverse events (5% vs 4%, \(P = 0.08\)), allergic reactions or rashes (0.9% vs 1.3%, \(P = 0.33\)), CK >10×ULN (0.2% vs 0.2%, \(P = 0.86\)), ALT ≥3×ULN (0.5% vs 0.4%, \(P = 0.96\)) and AST ≥3×ULN (0.4% vs 0.4%, \(P = 0.58\)). The incidence of adverse effects with coadministration of ezetimibe and statins did not differ significantly from those with statin monotherapy.

### Conclusion

The present meta-analysis shows that ezetimibe–statin combination therapy is tolerated as well as statin monotherapy. Our meta-analysis shows that the addition of ezetimibe to statins is safe, and the safety profile is similar between coadministration and monotherapy. Combination therapy has greater efficacy through differing mechanisms of action, can lower doses of individual drugs and alleviate adverse effects generated with high doses of single agents. Thus, we recommend combination therapy for patients with hypercholesterolaemia at high risk for cardiovascular and cerebrovascular disease.

### Acknowledgement

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### 6.1.1 Atorvastatin

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<td></td>
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<tr>
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**Heterogeneity:** \(\chi^2 = 1.61\), df = 2 (\(P = 0.45\)); \(I^2 = 0\%\)

**Test for overall effect:** \(Z = 0.62\) (\(P = 0.54\))

### 6.1.2 Other Statin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Odds Ratio</th>
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<td>Weight</td>
<td>M-H Fixed. 95% CI</td>
</tr>
<tr>
<td>Ballantyne et al. 2005(^{11})</td>
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<td>10</td>
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</tr>
<tr>
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<td>221</td>
<td>0</td>
<td>219</td>
</tr>
<tr>
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<td>1437</td>
<td>2</td>
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<tr>
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<tr>
<td>Foooy et al. 2010(^{22})</td>
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<tr>
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<td>1</td>
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</tr>
<tr>
<td>Robinson et al. 2009(^{20})</td>
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<td>442</td>
<td>2</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td>Total events</td>
<td>16</td>
<td>20</td>
<td></td>
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</tr>
</tbody>
</table>

**Heterogeneity:** \(\chi^2 = 9.71\), df = 7 (\(P = 0.21\)); \(I^2 = 28\%\)

**Test for overall effect:** \(Z = 0.25\) (\(P = 0.80\))

Figure 10 Forest plots to show the number of patients with alanine aminotransferase (ALT) \(>3\times\) upper limit of normal (ULN). CI, confidence interval; OR, odds ratio.

### 6.1.1 Aspartate Aminotransferase

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
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<tr>
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<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H Fixed. 95% CI</td>
</tr>
<tr>
<td>Ballantyne et al. 2003(^{6})</td>
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<td>255</td>
<td>1</td>
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<tr>
<td>Ballantyne et al. 2005(^{11})</td>
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<td>7</td>
<td>939</td>
</tr>
<tr>
<td>Catapano et al. 2006(^{16})</td>
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<tr>
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<td>93</td>
<td>2</td>
<td>94</td>
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<td>Foooy et al. 2010(^{22})</td>
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<td>500</td>
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<td>Melanie et al. 2007(^{3})</td>
<td>1</td>
<td>204</td>
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</tr>
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<tr>
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<tr>
<td>Total events</td>
<td>17</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** \(\chi^2 = 9.18\), df = 6 (\(P = 0.16\)); \(I^2 = 35\%\)

**Test for overall effect:** \(Z = 0.55\) (\(P = 0.58\))

Figure 11 Forest plots to show the number of patients with aspartate aminotransferase (AST) \(>3\times\) upper limit of normal (ULN). CI, confidence interval; OR, odds ratio.
References

17. Leiter LA, Bays H, Conard S, Bird S, Rubino J, Hanson ME et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with up titration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. Am J Cardiol 2008; 102: 1495–501.
Crescentic glomerulonephritis: data from the Spanish Glomerulonephritis Registry

B. Quiroga, A. Vega, F. Rivera and J. M. López-Gómez, on behalf of all members of the Spanish Registry of Glomerulonephritis

Key words age, crescentic glomerulonephritis, Goodpasture, vasculitis, registry.

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Received 17 November 2014; accepted 1 February 2015.

doi:10.1111/imj.12725

Abstract

Background: Crescentic glomerulonephritis (CGN) is a histological finding that implies rapid deterioration of renal function and can be related to different diseases, such as type 1 or anti-glomerular basement membrane antibody (Goodpasture) disease, type 2 or immune complex CGN and type 3 or pauci-immune disease.

Aim: The present study describes CGN and its characteristics based on the data from the Spanish Glomerulonephritis Registry.

Methods: An analysis was made of all native renal biopsies obtained from patients during 1994–2013 and classified as CGN. A patient epidemiological and clinical data questionnaire was completed by the 120 centres involved.

Results: A total of 21,774 biopsies was performed, of which 2089 (8.1%) corresponded to CGN (211 type 1, 177 type 2 and 1701 type 3). Renal function was poorer in type 1 compared with types 2 and 3, and proteinuria was higher in type 2 compared to types 1 and 3. Patients diagnosed with CGN type 3 were older than those with types 1 and 2, but less hypertensive than the type 2 patients. No differences in the urine test findings were found between types 1 and 2. Microhaematuria was the most frequent feature in general, as well as in type 3 compared with types 1 and 2. The main indication for biopsy was acute renal injury. Age was the only difference between type 1 patients with and without alveolar haemorrhage (53 [33–67] vs 64 [46–73], P = 0.008).

Conclusion: Although classified as the same entity, the different types of CGN have different features that must be taken into account.

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Conclusion: Although classified as the same entity, the different types of CGN have different features that must be taken into account.
Introduction

Crescentic glomerulonephritis (CGN) is defined by the presence of more than 50% of glomerular crescents in a renal biopsy. These histological findings imply rapid deterioration of renal function, but can be related to different diseases with different clinical, diagnostic, treatment and prognostic features. There are three main types of CGN: type 1 or anti-glomerular basement membrane (GBM) antibody (Goodpasture) disease; type 2 or immune complex CGN; and type 3 or pauci-immune disease. Recently, a double-antibody positive disease has been accepted as CGN type 4. The disease typically manifests as impaired renal function, proteinuria (usually <3 g/day) and haematuria. Types 1 and 3 usually also show systemic symptoms. Although included within the same type of glomerulonephritis (GN), CGN is not a specific disease and can be caused by different mechanisms. Furthermore, the differences among them have not been fully described. At present, immunological tests, including anti-neutrophil cytoplasmic antibodies (ANCA) and anti-GBM antibodies, can help clinicians to assess patient diagnosis, relapse and treatment response.

Renal biopsies are the gold standard for diagnosing kidney diseases. Histopathological data give nephrologists important information regarding not only the diagnosis but also the prognosis, with a view to making appropriate management decisions. CGN and its pathological features are very important for establishing proper management, because treatment includes aggressive drugs, such as immunosuppressive agents. In the early stages, inflammatory cells and the expression of cytokines (interleukin-1 and tumour necrosis factor alpha) are the main findings. Based on the natural history of the disease, the next step is the confirmation of glomerular crescents that are firstly epithelial and lead to fibrosis and irreversible renal failure. The presence of crescents in a biopsy usually implies rapid progression of the disease and also the need to decide treatment. Only if irreversible changes are found in the biopsy (e.g. fibrosis) should non-aggressive immunosuppressive therapy be chosen.

Medical registries and networks are useful tools for describing diseases, due to the large number of centres involved and the important size of the samples. Studies of diseases that are not particularly frequent, such as GN, stand to benefit most from such registries. The United States, Brazil, Europe (Spain, Italy, the Czech Republic, France and Hungary) and Asia have their own biopsy registries. The Spanish Glomerulonephritis Registry has been collecting data in this regard since 1994, and now has registered over 20 000 biopsies. Thanks to the large records of biopsies, we now know that the natural history of GN exhibits a changing pattern. Immunosuppressive drugs are improving, and histological techniques supported by serum tests yield prompt results, thereby allowing treatments to be started earlier. Descriptions of these changes and the evaluation of correlations between clinical data and histological patterns are essential in order to improve outcomes in serious diseases, such as GN.

Aims

Based on the data of the Spanish Glomerulonephritis Registry covering the period between 1994 and 2013, the present study describes and analyses the different types on CGN, including their incidence, epidemiological data, clinical manifestations and laboratory features.

Methods

We analysed all native renal biopsies obtained from patients classified as corresponding to CGN and included in the Spanish Glomerulonephritis Registry between 1994 and 2013, together with the corresponding clinical indications. Each sample was analysed by pathologists from the 120 participating hospitals using specific techniques, mainly light microscopy and direct immunofluorescence (IgG, IgA, IgM, C3, C1q, fibrinogen and light-chain antibodies). For sending the biopsies to the registry (through www.senefro.org, official webpage of the Spanish Society of Nephrology) a questionnaire (available only in Spanish) was sent by the participant centres (including year, hospital, name of the sender, age of the patient, gender, renal function (serum creatinine, estimated glomerular filtration rate, proteinuria, description of the sediment), main syndrome of the patient, history of hypertension and data regarding the biopsy (number of glomeruli and main diagnosis). The registry only included the main diagnosis, so superimposed syndromes could not be identified. Also, in the registry the diagnosis was codified, but we do not have access to the pathological description.

A questionnaire on the patient epidemiological and clinical data was completed. The following definitions were established: (i) acute renal injury: rapid deterioration of the glomerular filtration rate (GFR), with or without oligoanuria or rapidly progressive renal failure, including a worsening of chronic kidney disease, (ii) nephrotic syndrome: proteinuria >3.5 g/day/1.73 m2 and serum albumin <2.5 g/dL, (iii) acute nephritic syndrome, oliguric acute renal injury with oedema, haematuria and hypertension, (iv) asymptomatic urinary abnormalities: proteinuria <3.5 g/day and/or haematuria with more...
than three red blood cells per field, in the absence of clinical manifestations, (v) arterial hypertension: blood pressure >140/90 mmHg or antihypertensive treatment irrespective of blood pressure and (vi) chronic kidney disease: persistent serum creatinine >1.5 mg/dL.

The questionnaire was applied to obtain the following information: identification code, date of birth, gender, hospital, presence of hypertension and/or antihypertensive treatment, serum creatinine (mg/dL), 24-h urine creatinine clearance (mL/min), proteinuria (g/day) and urinary sediment. We also noted the main renal syndrome, the histological methods applied to the sample and the number of glomeruli obtained. CGN was defined as the presence of crescents in >50% of the glomeruli, and was classified as follows:

• Type 1: accompanied by anti-glomerular basal membrane antibodies, with or without alveolar haemorrhage.
• Type 2: presence of immune complexes.
• Type 3: necrotising GN with or without ANCA or systemic vasculitis symptoms.

As this registry exists from 1994, and no changes in definitions have been performed to avoid confusion in data, some of them are outdated. The cut-off of 50% of crescent formation for achieving the definition was due to definition of the entity in 1994.16,17 No data regarding the type of crescent are available in this registry.

 Statistical analysis

The data were entered in a Microsoft Access database. Values are expressed as the mean (SD) or median (interquartile range). The normal distribution of the samples was determined using the Kolmogorov–Smirnov test. Categorical data were compared using the chi-squared test or the Fisher’s exact test, while continuous variables were compared using the Student t-test or Mann–Whitney U-test. Analysis of variance was used when several parameters of the two groups were compared. Statistical analysis was performed using the SPSS version 16.0 statistical package for Microsoft Windows (SPSS, Chicago, IL, USA). Statistical significance was considered for \( P < 0.05 \).

Results

Baseline characteristics are shown in Table 1. The frequencies of each type of CGN and the overall percentages divided into five periods of 4 years each are shown in Figure 1. Taking into account all the renal biopsies performed \( (n = 21\,774) \), 8.1% \( (n = 2089) \) corresponded to CGN; 0.8% \( (n = 211) \) corresponded to type 1, 0.7% \( (n = 177) \) to type 2, and 6.5% \( (n = 1701) \) to type 3. CGN type 1 was characterised by poorer renal function than types 2 and 3. Proteinuria was higher in CGN type 2 than in types 1 and 3. In turn, patients diagnosed with CGN type 3 were older than those with types 1 and 2 disease, but less hypertensive than patients with CGN type 2.

The urine test results are shown in Table 2. The most frequent characteristic in all types of CGN was microhaematuria. We found no significant differences...
between CGN types 1 and 2. At diagnosis, CGN type 3 had less gross haematuria, but microhaematuria was more frequent than in the other two types.

Clinical features are shown in Table 3. The main indication of biopsy was acute renal injury, followed by nephritic syndrome. At diagnosis, hypertension was more frequent as the indication of biopsy in CGN type 3 in comparison to types 1 and 2. Also, chronic kidney disease was a more frequent indication of biopsy in CGN type 3 than in type 1 disease.

A comparison between Goodpasture syndrome with and without alveolar haemorrhage (Table 4) only identified differences in age (older patients presenting less alveolar haemorrhage) \( (P = 0.008) \).

The results among the elderly patients were analysed, stratifying age into three groups \( (<65 \text{ years}, 65–75 \text{ years} \text{ and} >75 \text{ years}) \). We found 61.7% of the patients diagnosed with CGN type 1 to be under 65 years of age; 22.9% were between 65–75 years of age, and 7.3% were over 75 years of age. In patients with CGN type 2, 62.8% were under 65 years of age, 21.6% were between 65–75 years of age and 15.5% over 75 years of age. Lastly, among the patients who developed CGN type 3, 44.6% were under 65 years of age, 32.7% were between 65–75 years of age, and 22.6% were over 75 years of age. The differences in the distribution were statistically significant when comparing CGN type 3 with types 1 and 2 \( (P < 0.0001 \text{ for both}) \).

## Discussion

Considering the large number of biopsies included in our study, this is the largest series of CGN published to date. A total of 8.1% of the biopsies included in the Spanish Glomerulonephritis Registry corresponded to CGN. Of these cases, 10% corresponded to CGN type 1, 8% to type 2 and 81% to type 3. Considering a minimum of 10 glomeruli as adequate to the effects of diagnosis, our series presented a median of 13 (all biopsies included).

In coincidence with previous studies, \(^ {19}\) patients developing CGN types 1 and 2 were younger, with a median age of 58 and 60 years, respectively, when compared with type 3 (66 years). On analysing the patients stratified by age, and focusing on the elderly, we found that patients over 75 years of age developed CGN type 3 more often than the other groups. We recently published data regarding the elderly \( (>75 \text{ years of age}) \), showing a higher prevalence of CGN type 3 in comparison to types 1 and 2.\(^ {18}\) No gender differences were found between groups \( (56.1–64.4\% \text{ were males}) \), though males tended to be less frequent in CGN type 3.\(^ {20}\)

Since the introduction of laboratory tests to assess ANCA/anti-GBM antibodies, biopsies for establishing a diagnosis have decreased in number. In this context, biopsies are presently more relevant for defining a prognosis, quantifying epithelial and fibrotic crescents to decide whether to continue with immunosuppression...

<table>
<thead>
<tr>
<th>Table 2 Urine test findings at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ((n = 2089))</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Gross haematuria</td>
</tr>
<tr>
<td>Microhaematuria</td>
</tr>
<tr>
<td>Leukocyturia</td>
</tr>
<tr>
<td>Cylindruria</td>
</tr>
<tr>
<td>Telescoped sediment</td>
</tr>
<tr>
<td>Normal</td>
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</tbody>
</table>

CGN, crescentic glomerulonephritis; NS, non-significant.

<table>
<thead>
<tr>
<th>Table 3 Clinical features at diagnosis</th>
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</thead>
<tbody>
<tr>
<td>Total ((n = 2089))</td>
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<td>----------------------------------------</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
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<tr>
<td>Nephritic syndrome</td>
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<td>Hypertension</td>
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<tr>
<td>Asymptomatic urinary abnormalities</td>
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</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

CGN, crescentic glomerulonephritis; NS, non-significant.
therapy or to prescribe more conservative treatment. However, while the mentioned immune tests yield high (99%) positive predictive values, the negative predictive values are only in the order of 80% (and even lower in older patients). A renal biopsy is therefore mandatory if CGN is suspected.1

CGN is one of the leading histopathologically diagnosed aetiologies underlying acute or rapidly progressive renal injury.22 The indication of a renal biopsy for this reason was registered in 58% of the cases, followed by nephritic and nephrotic syndrome (16.6% and 6.9% respectively). Interestingly, as shown in Table 3, hypertension accounted for 8.9% of the indications of biopsy in CGN type 3, showing significant differences with respect to types 1 and 2. Hypertension usually precedes flare-up or relapse in ANCA-associated vasculitis, and renal biopsy may be useful for diagnosing and starting treatment before renal injury has developed.19 Chronic kidney disease accounted for 6% and 6.7% of the indications in CGN types 2 and 3 versus only 1% in CGN type 1 – thus showing that this disorder usually debuts more aggressively than the other two types. This condition is confirmed by the fact that renal function is poorer in type 1 than in types 2 and 3, as a consequence of the higher frequency of crescent formation at the time of diagnosis.23 The strongest predictor for renal and survival outcomes in CGN is renal function at the time of diagnosis, which is correlated to the histological findings.23,24

Probably, as a result of the introduction of serum tests, renal function at debut or onset has improved when compared with previous reports.1,19

Important deterioration of renal function can lead to low levels of proteinuria, and this is probably the main reason for finding of sub-nephrotic protein excretion in CGN.25 Our results indicate a median proteinuria of 1.7 g/day, with higher protein urinary excretion in CGN type 2 (median 3.0 g/day) compared with the other disease types. Haematuria is a constant finding in all types of CGN16 and also in our series, with 85% of the patients presenting gross haematuria, microhaematuria or telescoped sediment. However, the kind of haematuria differs between groups. In this sense, microhaematuria appears frequently in CGN type 3, unlike gross haematuria, which is more often seen in types 1 and 2.

As observed in other series, anti-GBM antibody disease could be associated with pulmonary bleeding in one-half of all cases.5,17 The presence of lung bleeding was more common in young patients, as published elsewhere; however, no differences were observed in terms of gender, clinical features, urine test findings or renal function.17,25

Our study has a series of limitations. First, biopsy complications were not recorded. Second, no data were collected on more complex analytical parameters, such as autoimmunity and the presence of ANCAs. Lastly, the clinical questionnaire accompanying each renal biopsy

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison between Goodpasture syndrome with and without alveolar haemorrhage</th>
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<tbody>
<tr>
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<td>Age (years)</td>
<td>53 (33–67)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>55 (64.7%)</td>
</tr>
<tr>
<td>Hypertension (presence)</td>
<td>41 (51.3%)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>7 (3.5–9.9)</td>
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<tr>
<td>24-h creatinine clearance (mL/min)</td>
<td>10 (5–19.5)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>2.1 (0.7–4.8)</td>
</tr>
</tbody>
</table>

Urine test findings

| Gross haematuria | 22 (28.6%) | 25 (30.1%) | NS     |
| Microhaematuria | 39 (50.6%) | 44 (53%) | NS     |
| Leukocyturia | 0 | 0 | NS     |
| Cylindruria | 1 (1.2%) | 1 (1.2%) | NS     |
| Telescoped sediment | 12 (15.5%) | 11 (13.3%) | NS     |
| Normal | 2 (2.6%) | 2 (2.4%) | NS     |

Clinical features

| Nephrotic syndrome | 6 (7.1%) | 6 (7.1%) | NS     |
| Nephritic syndrome | 15 (17.6%) | 19 (22.6%) | NS     |
| Hypertension | 2 (2.4%) | 1 (1.2%) | NS     |
| Asymptomatic urinary abnormalities | 0 | 0 | NS     |
| Acute renal failure | 58 (68.2%) | 54 (64.3%) | NS     |
| Chronic kidney disease | 0 | 3 (3.6%) | NS     |
| Others | 4 (4.7%) | 1 (1.2%) | NS     |

NS, non-significant.
did not include treatment or patient outcome. CGN type 4 is not included in the registry, since it dates from 1994.

Conclusion

Although the three types of CGN are usually classified as the same entity, some features, such as patient age at presentation, renal function, degree of proteinuria and the urine test characteristics differ.

Acknowledgements

The authors thank the participating hospitals for submitting the results of their renal biopsies.

References

Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand

P. N. Britton, K. Eastwood, B. Paterson, D. N. Durrheim, R. C. Dale, A. C. Cheng, C. Kenedi, B. J. Brew, J. Burrow, Y. Nagree, P. Leman, D. W. Smith, K. Read, R. Booy and C. A. Jones on behalf of the Australasian Society of Infectious Diseases (ASID), Australasian College of Emergency Medicine (ACEM), Australian and New Zealand Association of Neurologists (ANZAN) and the Public Health Association of Australia (PHAA)

Key words
encephalitis, guideline, Australia, New Zealand.

Correspondence
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Abstract
Encephalitis is a complex neurological syndrome caused by inflammation of the brain parenchyma. The management of encephalitis is challenging because: the differential diagnosis of encephalopathy is broad; there is often rapid disease progression; it often requires intensive supportive management; and there are many aetiologic agents for which there is no definitive treatment. Patients with possible meningoencephalitis are often encountered in the emergency care environment where clinicians must consider differential diagnoses, perform appropriate investigations and initiate empiric antimicrobials. For patients who require admission to hospital and in whom encephalitis is likely, a staged approach to investigation and management is preferred with the potential involvement of multiple medical specialties. Key considerations in the investigation and management of patients with encephalitis addressed in this guideline include: Which first-line investigations should be performed?; Which aetiologies should be considered possible based on clinical features, risk factors and radiological features?; What tests should be arranged in order to diagnose the common causes of encephalitis?; When to consider empiric antimicrobials and immune modulatory therapies?; and What is the role of brain biopsy?

Introduction
Encephalitis is a complex condition caused by brain inflammation that is challenging to manage. The diagnosis is rarely confirmed by brain biopsy and instead is inferred by the presence of acute central nervous system (CNS) dysfunction, fever and/or inflammation in the cerebrospinal fluid (CSF) and/or on neuroimaging. Differentiation from encephalopathy due to other causes is difficult. There is a wide variety of presentations and a myriad of possible aetiologies but in most cases a cause is not identified. There is often no definitive treatment and a high rate of mortality and morbidity. The investigation and management of encephalitis worldwide are of...
variable quality. While several international guidelines exist and the International Encephalitis Consortium consensus included Australian authors, a concise guideline for Australian and New Zealand clinicians is required due to differences in the epidemiology of encephalitis.

Methods
We reviewed the literature and sought expert opinions in the development of the Consensus guidelines. The guidelines were peer reviewed by the Australasian Society for Infectious Diseases Encephalitis Special Interest Group and Guidelines Committee, the Public Health Association of Australia (PHAA), the Australian and New Zealand Association of Neurologists (ANZAN), and the Australasian College of Emergency Medicine (ACEM).

Epidemiology
In Australia, the annual hospitalisation rate for encephalitis has been calculated as 5.2/100 000 and case fatality rate is estimated to be 4.6%. The highest admission rates are observed in males, and those aged less than 9 or over 60 years of age. This is similar to international findings.

Case definition
The international case definition of encephalitis (Box 1) requires the presence of altered mental status lasting at least 1 day, and exclusion of encephalopathy from other causes (Box 2). Confirmed diagnosis requires meeting additional criteria such as CSF pleocytosis, neuroimaging and electroencephalography (EEG) changes consistent with encephalitis, and the presence of seizures and new onset of focal neurological signs. Of note, in individual cases, expected features of encephalitis such as headache, fever and CSF pleocytosis may be absent.

Aetiology
Multiple infectious agents have been associated with encephalitis, but the syndrome is an uncommon manifestation of most. Viruses are the most commonly identified agent in all settings. Immune-mediated aetiologies are increasingly recognised in up to one third of cases, and are important because they are often treatable.
Box 3 Selected immune-mediated encephalitides

**ADEM**

Acute disseminated encephalomyelitis is an inflammatory, multi-focal, demyelinating condition of the central nervous system. It presents with encephalopathy and multi-focal neurological deficits. It is most common in children (mean age 5–8 years old), with a slight male predominance. Rarely it may occur in adults. A temporal association following infection or, less commonly, vaccination is often identified. Magnetic resonance imaging (MRI) is central to the diagnosis. Features include multi-focal, high signal lesions most evident on T2 weighted and fluid-attenuated inversion recovery (FLAIR) sequences involving the sub-cortical, central and periventricular white matter and deep grey matter. Approximately one quarter of children with ADEM will have serum antibodies to myelin oligodendrocyte glycoprotein (MOG). Persistence of anti-MOG IgG is associated with recurrent central nervous system demyelination in this group. Corticosteroids are the established first-line therapy, with other immune-modulatory therapies used in refractory cases. Acute haemorrhagic leuко-encephalopathy (AHLE) is a rare, hyper-acute form of ADEM that overlaps with cerebral vasculitis.

**Anti-NMDAR**

Anti-N-methyl-D-aspartate receptor encephalitis has been shown to be one of the principal causes of encephalitis in recent large prospective studies. It typically presents with psychiatric symptoms, seizures, memory loss and mutism. The syndrome evolves to include movement disorders, dysautonomia and sometimes hypoventilation. Although initially described as a para-neoplastic disorder with ovarian teratoma in young adults (usually female), this tumour association is uncommon in young children where the female gender predominance is also less pronounced. MRI is most often normal. It is diagnosed by identifying CSF or serum antibodies against the NR1 subunit of the NMDA receptor. Anti-NMDAR can be identified in a proportion of relapsing HSV encephalitis, in particular if associated with chorea. Immuno-modulatory therapy improves outcomes.

**Anti-VGKC**

Anti-voltage-gated potassium channel-complex (including antibodies against leucine-rich glioma-inactivated 1 protein (Lgi1) and contactin-associated protein 2(Caspr2)) encephalitis includes a broad clinical spectrum. In adults it typically presents in older male (>40 yrs) patients with ‘limbic encephalitis’; sub-acute evolution of memory loss, confusion, medial-temporal lobe seizures and psychiatric features; hyponatraemia is common. Lgi1 antibodies are often identified and it is rarely associated with malignancy. In children it presents as temporal lobe focal seizures, status epilepticus and encephalopathy (behavioural disturbance, hallucinations) and cognitive decline. Specific Lgi1 or Caspr2 antibodies may not be identified. Diagnosis is by identifying serum antibodies that bind to the VGKC-complex, although low titre antibodies are of questionable significance. Immuno-modulatory therapy should probably be similar to NMDAR encephalitis although there is less evidence.

**Para-neoplastic ‘limbic encephalitis’**

‘Limbic encephalitis’ (see above for clinical features) occurring in adults is often associated with malignancy. The encephalitis may occur prior to the diagnosis, or during the course of cancer treatment. The tumours most often associated with limbic encephalitis are small cell lung carcinomas (SCLC), testicular germ cell tumours, breast cancer, ovarian teratoma, Hodgkin lymphoma and thymoma. The most commonly identified antibodies in this group are against intracellular neuronal antigens: anti-Hu, anti-Ma2(Ta), anti-CV2 CRMP5, and anti-amphiphysin. A spectrum of neurological syndromes may overlap with ‘limbic encephalitis’ including features of brainstem encephalopathy, basal ganglia syndromes, cerebellar ataxia and peripheral neuropathies. Specific antibodies associate with specific tumours, clinical features and neurological outcome; for example, anti-Hu with SCLC, isolated limbic encephalitis and poorer prognosis, and anti-Ma2 with testicular tumour, brainstem features and better prognosis. Treatment is directed towards the underlying tumour; immuno-modulatory treatments are often used adjunctively.

**Other**

Increasing numbers of serum auto-antibodies are being associated with paraneoplastic and non-paraneoplastic limbic encephalitis. These include: anti-Ri, anti-Yo, anti-glutamic acid decarboxylase (GAD), anti-gamma-aminobutyric acid B receptor (GABA-B-R), anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R), anti-glycine receptor (GlyR), anti-dipeptidyl-peptidase-like protein-6 (DPPX), anti-metabotropic glutamate receptor 5 (mGlu-R5). 

An algorithm addressing approaches to testing and management has been recently published. 

These include acute disseminated encephalomyelitis (ADEM), primarily seen in children and antibody-mediated encephalitides (e.g. anti-N-methyl-D-aspartate receptor (NMDAR) and anti-voltage-gated potassium-channel (VGKC) complex). Aetiology varies with age, immune status, geography, climate and pathogen endemcity, and has changed over time due to changes in immunisation, changing behaviours (Box 4), improved testing and discovery of novel aetologies. Herpes simplex virus (HSV), varicella zoster virus (VZV), toxoplasma, ADEM and enteroviruses are the most commonly identified encephalitides from studies based on hospital admission records. These studies also demonstrate that deaths from toxoplasmosis, HSV and measles-related encephalitis and subacute sclerosing panencephalitis (SSPE) have declined in recent decades.

A confirmed laboratory diagnosis is frequently not obtained. Almost 70% of cases in a retrospective Australian study did not have an identified aetiology, although
**Box 4 Clinical, risk factor and radiologic pointers to direct targeted (second line) investigation**

### Clinical features
- Psychosis, movement disorder, hypventilation: anti-NMDAR.
- Cognitive dysfunction, seizures: anti-VGKC, anti-NMDAR, HSV, HHV6, anti-GAD, anti-Hu, anti-Ma (other antibody mediated see Box 3).
- Subacute behavioural/personality change: HSV, anti-NMDAR, anti-VGKC, HIV, *Treponema pallidum* (syphilis), Whipple disease, trypanosomiasis, SSPE, anti-GAD, anti-Hu, anti-Ma (other antibody mediated see Box 3).
- Hydrophobia, hypersalivation, delirium: rabies, ABLV.
- Parkinsonian features: flaviviruses (esp. JEV), anti-DR2 (basal ganglia encephalitis).
- Brainstem dysfunction: enteroviruses (esp. EV71, flaviviruses (esp. MVEV, JEV, KUNV), Nipah†, *Listeria monocytogenes*, *Burkholderia pseudomallei*, MTB, anti-Hu, anti-Ma (other paraneoplastic see Box 3).
- Associated limb weakness (flaccid paralysis) or tremor: enteroviruses (esp. EV71, poliovirus), flaviviruses.
- Parotitis, testicular pain: mumps.
- Cervical lymphadenopathy: EBV, CMV.
- SIADH: anti-VGKC, SLEV†.
- Chronic symptoms: HIV, JCV, BKV, trypanosomiasis, SSPE, *T. pallidum* (syphilis), Whipple disease.
- Cranial nerve palsy: neuroborreliosis†.

### Risk factors
- >60 years: *L. monocytogenes*, VZV, HSV.
- Female: anti-NMDAR.
- Immunocompromised patient: HHV6, CMV, EBV, measles, VZV, LCMV, toxoplasma, cryptococcus, JCV, BKV, *Bartonella* sp.
- Tropical Australia: JEV, dengue, MVEV, KUNV, *B. pseudomallei*.
- Travel history‡
  - Asia: JEV, dengue, malaria, MTB, Nipah, *Angiostrongylus cantonensis*.
  - Pacific: JEV, dengue, malaria, MTB, *Angiostrongylus cantonensis*.
  - North America: WNV, LCV, SLEV, EFV, EEEV, neuroborreliosis, *Rickettsia rickettii* (RMSF), ehrlichiosis (HME), anaplasmosis (HGA), babesiosis, coccidiodymycosis.
  - South America: WNV, VEEV, dengue, MTB, trypanosomiasis (Chagas).
  - Europe: TBEV, TOSV, neuroborreliosis, anaplasmosis (HGA).
  - Africa: malaria, trypanosomiasis, MTB.
- Animal exposure
  - Monkeys: herpes B, rabies†.
  - Bats: rabies†, ABLV.
  - Dogs and other canids outside Australia: rabies.
  - Cats: *Bartonella henselae*.
  - Horse: Hendra, KUNV.
  - Rodents: LCMV, leptospirosis.
  - Snails/other moluscs: *Angiostrongyulus cantonensis*.
  - Swine: Nipah.
  - Mosquito or Tick bite history.
- Recreational
  - Sexually transmitted: HIV.
  - Fresh water§: leptospirosis, *Naegleria fowleri*.
  - Soil/mud§: *Balamuthia mandrillis*.
- Occupational
  - Animal husbandry, farming: *C. burnetii* (Q fever), leptospirosis.
  - Abattoir workers: *C. burnetii* (Q fever).
- Unvaccinated: measles, mumps, rubella, VZV.
testing for immune-mediated and vector-borne causes was limited. Rigorous implementation of systematic testing will likely reduce this proportion but in many cases the cause will remain unknown. In Australia, endemic viruses, including Hendra virus, Australian bat lyssavirus (ABLV), Murray Valley encephalitis virus (MVEV) and West Nile virus (WNV) (Kunjin clade (KUNV) – WNV/KUNV), should be considered as possible aetiologies as well as regional infections such as Japanese encephalitis virus, enterovirus 71 (EV71), dengue and Nipah virus. Key differences to note when applying this guideline in New Zealand are that there are currently no endemic flaviviruses, nor are Hendra virus, ABLV and Q fever endemic. Novel agents, particularly viruses, or a changing geographical distribution of diseases should be considered where unexplained encephalitis clusters occur.

Causality
Experts agree that identification of an infectious agent that is an established cause of encephalitis from a CNS specimen is strong evidence of causality. Identification of an encephalitic infectious agent outside of the CNS is less conclusive. Identification of a specific antibody response within the CSF in temporal association with an episode of encephalitis is more convincing evidence of causality than identification of a systemic antibody response, especially on a single specimen. Causality may be classified as confirmed/definite, probable or possible to reflect the level of evidence achieved. Investigation of patients may require specimens from multiple sites, with repeated sampling for pathogen identification and to identify a specific serologic response. This is necessary to avoid missing treatable causes, especially where there are two or more potential infectious agents and/or autoantibodies.

Clinical assessment
We present two algorithms to assist clinicians with diagnosis and management. The first (Fig. 1) will assist clinicians to: identify possible meningoencephalitis patients, consider differential diagnoses, initiate empiric acyclovir and antibiotic therapy, and discriminate between patients in whom encephalitis can be excluded from those where a more rigorous assessment is required. Table 1 details first-line investigations. The second algorithm (Fig. 2) follows on from the first and is applied when encephalitis is likely. It provides a multidisciplinary, staged approach to investigation and management.

History
Collecting a comprehensive history is essential to enable a diagnosis. The onset and evolution of altered consciousness, lethargy, cognition, behaviour or personality change, seizures, weakness, abnormal movements and

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Table 1

<table>
<thead>
<tr>
<th>Specimen/Investigation</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF†</td>
<td>Opening pressure, microscopy, Gram stain and bacterial culture</td>
</tr>
<tr>
<td></td>
<td>Cell count and type‡</td>
</tr>
<tr>
<td></td>
<td>Biochemistry: protein, glucose</td>
</tr>
<tr>
<td></td>
<td>PCR: HSV, VZV, enterovirus, V2V</td>
</tr>
<tr>
<td>Antibodies: oligoclonal bands, V2V IgG¶</td>
<td></td>
</tr>
<tr>
<td>Antigen: cryptococcal Ag</td>
<td></td>
</tr>
<tr>
<td>Other: VDRL (adult); consider cytology; to store</td>
<td></td>
</tr>
<tr>
<td>Serum‖</td>
<td>Serology: HIV††, flavivirus (Australia)‡‡, M. pneumoniae, EBV (child/adolescent), T. pallidum (syphilis – adult)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>PCR testing for enterovirus, influenza A and B, adenovirus</td>
</tr>
<tr>
<td>Faeces</td>
<td>PCR or antigen testing for enterovirus, adenovirus, rotavirus (child); enterovirus culture/typing</td>
</tr>
<tr>
<td>Skin swabs (where lesions present)</td>
<td>PCR testing for HSV 1/2, VZV, enterovirus</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>MRI (sequences to include: T1, T2, FLAIR, DWI, gradient-echo, gadolinium contrast) or if unavailable CT with contrast</td>
</tr>
</tbody>
</table>

†Collect up to 10 mL, if able, in four tubes in adults and children, and up to 5 mL in a small child (<2 years old). Formal cytological examination is required to reliably differentiate eosinophils from other leukocytes and identify malignant cells. ‡HSV PCR is highly sensitive (>95%) between days 3 and 7 of the illness, its sensitivity decreases slightly in the second week of the illness. False negatives prior to day 3 have been described. After day 10, CSF HSV IgG can be used to make a late diagnosis. ¶Where available, CSF VZV IgG may be more sensitive than PCR. Testing requires the demonstration of intrathecal synthesis of VZV IgG, that is a reduced serum/CSF ratio of VZV IgG (serum IgG, that is a reduced serum/CSF ratio of VZV IgG compared with the serum/CSF ratio of albumin. ††HIV is very uncommon in children in Australia, and encephalopathy is an uncommon presentation; some experts would still undertake HIV testing as the diagnosis impacts upon possible aetiologies of encephalitis, and is treatable. ‡‡Flaviviral IgM should be tested after 5 days of symptoms. A negative result makes the diagnosis unlikely. CSF IgG is specific for these viruses and should be performed in patients in whom the diagnosis is likely in terms of risk factors, clinical and radiologic features (see Boxes 4 and 5). Ag, antigen; CSF, cerebrospinal fluid; CT, computed tomography scan; DWI, diffusion-weighted imaging; EEG, electro-encephalogram; FLAIR, fluid-attenuated inversion recovery; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; V2V, varicella zoster virus; WBC, white blood cell.

Examination

Physical examination should include an objective assessment of the level of consciousness, and look for subtle seizure activity, meninges, abnormal movements (e.g. chorea, parkinsonism), weakness, sensory loss and cranial nerve involvement (including deafness and anosmia), noting any focal findings and for features suggesting other diagnoses (Box 2). Temperature and other vital signs should be assessed for features of raised intracranial pressure or autonomic dysfunction. Mental status examination should be recorded, particularly if there are psychotic features (hallucinations and delusions). A rash or other skin lesions (e.g. bite marks, eschar, mouth/palate ulcers, lymphadenopathy and shingles lesions), or other insect bites, animal exposures (wild, farm or domestic), and occupation and outdoor activities (e.g. hiking, camping, water sport). Public health authorities should be consulted about seasonal/epidemic activity of infectious agents (e.g. flaviviruses and other arboviruses, enteroviruses). Risk factors (Box 4) including age, immunisation and immune status (e.g. immune suppressive treatment, immunodeficiency virus (HIV) risk factors) should be considered.

Investigations

First-line investigation of all patients with suspected/probable encephalitis

Investigations to exclude differential diagnoses (Box 2) and guide initial management are listed in Table 1 and Figure 1. Blood cultures should be taken prior to the administration of empiric antibiotics. A lumbar puncture (LP) should be performed if there is no contraindication or following appropriate imaging and/or clinical observation. CSF analysis is needed to confirm encephalitis (Fig. 1) and identify a cause. Sufficient volumes should be sampled (Table 1) to enable microscopy and cell counts, Gram stain, bacterial culture (mycobacterial culture or fungal cultures if indicated), biochemistry (protein, glucose) and exclusion of HSV, Cryptococcus, VZV and syphilis in those patients meeting the more rigorous definition of encephalitis (Fig. 2). Where available, other biomarkers of CNS inflammation including CSF oligoclonal bands and CSF neopterin should be considered.
be considered. A serum specimen (Table 1) should be stored for testing with convalescent sera. All patients (Fig. 2) should have serology for HIV, mycoplasma and flaviviruses, and syphilis serology in adults and Epstein–Barr virus (EBV) serology in children. A respiratory tract specimen and stool for viral testing, and viral and bacterial swabs from any skin lesions should be collected. CNS imaging (Fig. 1) should be performed on all patients, by magnetic resonance imaging (MRI) wherever possible using T1, T2 and fluid-attenuated inversion recovery, diffusion-weighted imaging, gradient echo or similar sequences and gadolinium contrast. A chest X-ray is needed to detect associated lung disease (e.g. tuberculosis (TB) and Cryptococcus). EEG is highly sensitive in encephalitis, but often non-specific. It is particularly important in patients with chronic symptoms and those with psychiatric presentations to identify encephalopathy or to diagnose subtle seizure activity and non-convulsive status epilepticus.11,12 Localised EEG activity may suggest specific aetiologies (e.g. temporal localisation with HSV).

Targeted testing of patients with encephalitis

Where encephalitis is likely, second and third-line testing of patients should be guided by risk factors, clinical and radiologic features (Boxes 4, 5; Fig. 2) in consultation with specialists in neurology, infectious diseases, microbiology/virology and neuroradiology. Remote consultations (by telephone) may be necessary, and transfer to a referral centre considered.

Patient subgroups

Children

Encephalitis is challenging to identify in very young infants as features are non-specific (lachrymation, excessive irritability, poor feeding). Diagnosis requires a high index of suspicion and consultation with experienced clinicians. The most common causes of childhood encephalitis globally are HSV-1, VZV, enteroviruses and JEV in endemic regions. Other causes include: ADEM, EBV and adenovirus in children, and HSV-2 and parechovirus in neonates. Human herpesvirus (HHV)-6 and HHV-7 may be associated with febrile seizures and encephalopathy in immune-competent children and may uncommonly cause encephalitis in the immunocompromised.42 Mycoplasma pneumoniae has been associated with childhood encephalitis (less commonly in adults) when a positive M. pneumoniae IgM is detected in blood, although causality remains controversial without concurrent pathogen identification.31,43

Box 5 Tests of choice for the more common and regionally important aetiologies

For an extensive review of indicated tests for other aetiologies see Granerod et al., 2010 and Tunkel et al., 2008.11–14 Direct discussion with a medical microbiologist/virologist and local laboratory scientist is good practice before ordering uncommon tests.

HSV: CSF PCR 3–10 days into illness. May be negative < 3 days, repeat lumbar puncture and re-test CSF PCR (between days 3 and 10) if other features suggest HSV (see Fig. 2). CSF IgG (in combination with serum IgG) > 10 days.

Enteroviruses: CSF PCR, stool and upper respiratory tract specimens for PCR/viral culture.

VZV: CSF PCR, CSF IgG (in combination with serum IgG), Acute serum IgM, serum IgG acute/convalescent.

EBV/CMV/HHV-6: CSF PCR†. Acute serum IgM, serum IgG acute/convalescent‡.

Flaviviruses: CSF IgM after 5 days into illness, Acute serum IgM, serum IgG acute/convalescent‡.

WNV/KUNV: As for other flaviviruses and CSF PCR.

Dengue: As for other flaviviruses and acute blood NS1 Antigen, PCR.

Measles: CSF IgM, acute serum IgM and acute/convalescent serology, urine or upper respiratory specimen for PCR or antigen testing.

Rabies or ABLV: CSF PCR. Serum and CSF IgG. DFA on saliva, nuchal skin, corneal impression, brain.

Hendra or Nipah: PCR on CSF, serum, respiratory, urine specimens‡ serum IgM/G.

Ab-mediated: Serum and/or CSF anti-NMDAR Ab; serum anti-VGKC complex Ab; serum anti-Hu, anti-Ma2 Ab†.

‡Quantitative PCR may contribute to diagnosis. Exclusion of HHV6 chromosomal integration may be required to confirm its aetiological role.

†Convalescent for practical purposes is 2–4 weeks following symptom onset.

§Includes: Japanese encephalitis virus (JEV), Murray valley encephalitis virus (MVEV), West Nile virus/Kunjin virus (WNV/KUNV), dengue, St Louis encephalitis virus (SLEV), tick-borne encephalitis virus (TBEV). Other encephalitic arthropod-borne viruses (arboviruses) are investigated in the same way including togaviruses (eastern equine encephalitis virus (EEEV), western equine encephalitis virus (WEEV), Venezuelan equine encephalitis virus (VEEV)), bunyaviruses (Lacrosse virus (LACV), Toscana virus (TOSV)), and reoviruses (Colorado tick fever virus (CTFV)).

±Other serum antibodies that have been implicated in paraneoplastic and non-paraneoplastic limbic encephalitis include: anti-ampiphysin, anti-CV2/CRMP5, anti-Ri, anti-Yo, anti-glutamic acid decarboxylase (GAD), anti-gamma-aminobutyric acid A and receptor B (GABA-A-R, GABA-B-R), anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid receptor (AMPA-R), anti-glycine receptor (GlyR), anti-dipeptidyl-peptidase-like protein-6 (DPPX), anti-metabolotropic glutamate receptor 5 (mGlu-R5).

CSF, cerebrospinal fluid; DFA, direct fluorescent antibody test; HSV, herpes simplex virus; NMDAR, N-methyl-D-aspartate receptor; PCR, polymerase chain reaction; VGKC, voltage-gated potassium channel.
**Conditions that may present like meningo-encephalitis**

- Cerebral abscess
- Encephalitis
- Meningitis
- Seizures
- Raised intracranial pressure
- Vascular injury
- Metabolic

---

### Comprehensive history, including exposures, and examination (See box 4; Consider other causes)

- Detailed medical history, including exposures or travel (See box 1)
- Detailed family history
- Detailed past medical history
- Current drug regimen
- Past surgical history
- Presence of meningo-encephalitis

---

### Early Investigation and Management

- Blood: full blood count, electrolytes, glucose, urea, creatinine, calcium, liver function tests, blood culture, serum to store (5-10 mL). In adult consider early HIV testing with appropriate pre-test counselling
- Judicious fluid and electrolyte management as required
- Acute seizure management (follow local and state-based guidelines)
- Consider If lumbar puncture (LP) can be performed and role of preceding CT scan (see below)
- 1-tap vented LP or CT delayed - commence antibiotics promptly as per national guidelines

---

### Performance of LP and role of prior CNS imaging

CNS Imaging (most commonly CT) should be performed prior to lumbar puncture in the following circumstances:

- Impairment of consciousness, abnormal, fluctuating or declining GCS
- Signs of raised intracranial pressure (papilloedema, relative bradycardia with hypertension, coumadin effect or abnormal papillary reponse)
- Focal neurological deficits
- New onset sepsis until stabilised
- Immunocompromised state (HIV/AIDS, immunosuppressive therapy, transplantation)
- Previous history of a CNS lesion (mass lesion, stroke, or focal infection)
- LP is relatively contra-indicated in the following circumstances:
  - Haemodynamic instability or acute respiratory failure
  - Signs of raised intracranial pressure (papilloedema, relative bradycardia with hypertension, oculomotor palsy or abnormal pupillary response)

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- Haemodynamic instability or acute respiratory failure
- Signs of raised intracranial pressure (papilloedema, relative bradycardia with hypertension, oculomotor palsy or abnormal pupillary response)

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### Contraindication to LP or LP deferred pending CNS imaging or CT unavailable

- Bacterial meningitis possible. Commence antibiotics promptly
- For possible bacterial meningitis as per local and national guidelines
- Encephalitis is possible, start acyclovir (see doses below)
- Perform LP as soon as possible - if no radiologic confirmation of meningo-encephalitis is made

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### No clinical contraindication. LP performed

- Acyclovir dose:
  - Children: <3 months: 10mg/kg IV 8 hourly
  - <3 mo- 20mg/kg IV 8 hourly
  - Children: 10mg/kg IV 8 hourly
  - Adults/Children >12 years: 200mg/kg IV 8 hourly; adjust dose for renal function

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### Acute treatment

- LP performed:
  - Take 10mL (if able) in 4 tubes (1 - 2.5mL, ideally in 4 tubes)
  - Take 10mL if able (5mL in a small child <15kg); ideally in 4 tubes (1 - 2.5mL, ideally in 4 tubes)

**CSF Parameters (See Figure 2)**

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Lymphocytes</th>
<th>Neutrophils</th>
<th>RBC</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Neutrophils predominate</td>
<td>Lymphocytes predominate</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protein (g/L)</th>
<th>Normal</th>
<th>Low (&lt;0.4)</th>
<th>Very Low (&lt;0.3)</th>
<th>Normal-low</th>
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<tbody>
<tr>
<td>&lt;0.5</td>
<td>0.5-1.0</td>
<td>&gt;1.0</td>
<td>1.0-5.0</td>
<td>0.2-5.0</td>
</tr>
</tbody>
</table>

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**Who has “Suspected” meningo-encephalitis?**

An adult or child who presents with:

- Encephalopathy defined by some or all of the following features: altered level of consciousness, altered cognition, altered personality or behaviour and lethargy

### In combination with:

- Current or recent history of fever, and/or new onset seizures, and/or new onset focal neurological signs/symptoms and/or headache.

---

**Typical cerebrospinal fluid pattern**

<table>
<thead>
<tr>
<th>Opening pressure</th>
<th>Normal</th>
<th>Viral meningo-encephalitis</th>
<th>Bacterial meningitis</th>
<th>Tuberculous meningitis</th>
<th>Fungal meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25cm H2O</td>
<td>Normal</td>
<td>Normal-high</td>
<td>High</td>
<td>High</td>
<td>Very High</td>
</tr>
</tbody>
</table>

**Cell type**

- Lymphocytes: no neutrophils or RBC
- Lymphocytes predominate (neutrophils if early)
- Neutrophils predominate
- Lymphocytes predominate
- Lymphocytes predominate

**Glucose (CSF/plasma)**

<table>
<thead>
<tr>
<th>Glucose (mmol/L)</th>
<th>Normal</th>
<th>Low (&lt;0.4)</th>
<th>Very Low (&lt;0.3)</th>
<th>Normal-low</th>
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</thead>
<tbody>
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<td>&gt;0.5</td>
<td>0.5-1.0</td>
<td>&gt;1.0</td>
<td>1.0-5.0</td>
<td>0.2-5.0</td>
</tr>
</tbody>
</table>

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**Meningo-encephalitis**

- Meningo-encephalitis: defined by any one of the following features: altered level of consciousness, altered cognition, altered personality or behaviour and lethargy

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**MRI normal and CSF normal, but clinical findings persist, and no other diagnosis made.**

- Encephalitis probable. Commence acyclovir (see Figure 3)
- Arrange CNS imaging: MRI within 24-48h (CT with contrast if MRI unavailable)

---

**Encephalitis excludes.**

- Encephalitis excluded. Manage as per alternative diagnosis

---

**Alternative diagnosis negative.**

- Encephalitis excluded. Manage as per alternative diagnosis

---

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Immunocompromised hosts

The aetiology of encephalitis in the immunocompromised varies depending on the timing, nature and intensity of immunosuppression. CSF pleocytosis may be lacking in these patients. CNS reactivation of latent infection (e.g. VZV, cytomegalovirus (CMV), HHV-6, EBV) can occur, but is less common than systemic reactivation. HHV-6 post-transplant limbic encephalitis is now well described.44,45 VZV reactivation and primary infection in immunocompromised hosts causes a small vessel vasculitis. Encephalitis may be caused by opportunistic pathogens (e.g. Toxoplasma, Cryptococcus). HIV testing is essential as encephalitis may be the presenting illness of HIV/AIDS. A variety of neurological syndromes is associated with HIV; patients at highest risk are those with severe immune suppression (CD4 count < 200). Toxoplasma gondii, Cryptococcus neoformans and CMV are the most important pathogens. John Cunningham virus-associated progressive multifocal leucoencephalopathy (PML) can present in a variety of ways including fulminant encephalopathy.46,47 Initiation of anti-retroviral therapy can result in CNS immune reconstitution inflammatory syndrome (IRIS) encephalitis, including a non-pathogen-associated CNS IRIS, so-called CD8-positive encephalitis.48 The role of corticosteroids in this group should be discussed with an HIV specialist.

International travellers or immigrants

Overseas travellers may be exposed to a wide array of infections that can cause encephalitis. Common aetiologies as well as the exotic should be considered. Testing should be guided by a detailed history including timing of symptom onset in relation to travel, destination and in-location movements and activities, pre-departure immunisation, antimicrobial prophylaxis and adherence, animal and vector exposure, and ingestion of raw or unusual foods. Cerebral malaria is a potential cause in the febrile returned traveller with encephalopathy. Tuberculous meningoencephalitis should be considered, especially in young children and vector-borne pathogens (e.g. flaviviruses, Rickettsia spp.) after travel to overseas rural locations, especially in summer/spring. A history of insect bites is not always given. Immune suppression (CD4 count < 200) increases the risk of reactivation of latent pathogens. CNS Whipple disease, TB, PML and neurosarcoidosis may be diagnosed using biopsy in these circumstances.51–54 Other occult diagnoses can be made, for example, CNS Whipple disease, TB, PML and neurosarcoidosis.52 Liaison with histopathology and microbiology prior to sampling is essential to ensure correct specimen handling, transport and testing. A proportion of patients will not have an aetiological diagnosis made despite extensive investigation. Patients
Identify clinical features, risk factors, radiologic features (see Box 4) to guide second-line investigation:

- In consultation with neurologist, infectious diseases specialist, radiologist, microbiologist (Box 5).
- Especially note the following risk groups:
  - Children and neonates
  - Immunocompromised (including HIV/AIDS, immunosuppressive therapy, transplantation)
  - International travellers or immigrants
  - Those residing in or having travelled to tropical regions of Australia

**Encephalitis**

An adult or child with:

1. **Encephalopathy**, defined by the presence of some or all of the following features:
   - altered level of consciousness, altered cognition, personality/behavioural change, lethargy; lasting >24 h.
2. In combination with two or more of the following:
   - Fever or history of fever (≥38°C) within 72 h before/after presentation.
   - Generalised or partial seizures not fully attributable to a pre-existing seizure disorder.
   - New onset focal neurologic findings.
   - CSF pleocytosis (>5 WBC/μL).
   - Abnormal results of neuroimaging suggestive of encephalitis.
   - EEG abnormality consistent with encephalitis and not attributable to another cause.
3. **AND** no alternative cause identified/diagnosis made.

Arrange specialist consultation:

- Neurology
- Infectious Diseases
- Microbiology/Virology
- Radiology

Arrange first-line investigations if not performed already (see also Table 1):

- CSF: microscopy, culture, protein, glucose, HSV PCR, enterovirus PCR, VZV PCR and IgG, cryptococcal Ag, VDRL (adult), consider cytology.
- Serology: HSV, flavivirus (Australia), HIV, M. pneumoniae, EBV (child/adolescent), *T. pallidum* (Syphilis - adult).
- Respiratory viral testing: PCR or antigen testing for enterovirus, influenza A and B, adenovirus.
- Stool viral testing: PCR or antigen for enterovirus, adenovirus, rotavirus (child).
- MRI brain: sequences to include T1, T2, FLAIR, DWI, gradient-echo, gadolinium contrast or if unavailable CT with contrast.
- EKG X-ray.
- EEG (particularly useful in certain circumstances)

Consider addition of empiric antimicrobials for *Listeria monocytogenes* (penicillin or ampicillin) and rickettsiae (doxycycline in adults)

If no aetiology identified, consider empiric treatment of possible aetiologies, including immune therapy (corticosteroids and/or IVIG) based on clinical features, risk factors, radiologic features in consultation with neurologist and infectious diseases specialist (see Box 6).

Definitive treatment of aetiology if identified (see Box 6)

Where relevant, report case to public health or other statutory authorities and perform contact tracing

Consider third-line investigations if:

1. The patient remains unwell and other investigations are negative or
2. The patient is deteriorating and an aetiological diagnosis has not yet been made.
   - Repeat CSF sampling: microscopy, CSF wet mount, cytology, repeat HSV PCR, CSF immunoglobulin testing (HSV, VZV, flavivirus, IgG index, ABLV (Australia) and other epidemiologically relevant viruses if international travel).
   - Repeat MRI brain: sequences to include T1, T2, FLAIR, DWI, gradient-echo, gadolinium contrast. It is essential to liaise with a (neuro)radiologist with regards to planning these and any additional sequences.
   - All patients in this circumstance should be tested for anti-NMDAR, anti-VGKC and in Australia, ABLV.
   - Brain biopsy: it is essential to liaise with histopathology and microbiology prior to sampling with regards to specimen handling, transport and testing – especially note that specimens should not be formalin fixed prior to transfer to the laboratory.

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Britton et al.
Box 6 Directed management of viral and immune-mediated encephalitis

For an extensive review of antimicrobial treatments for other aetiologies see Tunkel et al., 2008.96

**HSV**: Minimum 14 days intravenous acyclovir for immunocompetent patients and 21 days for immunocompromised patients (adults and children > 12 years: 10 mg/kg 8 hourly; children <3 mo 20 mg/kg 8 hourly; 3 mo-12 y 500 mg/m² 8 hourly). Consider repeat lumbar puncture for CSF HSV PCR at planned completion of treatment especially in immunocompromised and children.

**VZV**: Consider 7-14 days intravenous acyclovir (adults and children > 12 years: 10 to 12.5 mg/kg 8 hourly; children: 500 mg/m² 8-hourly (approximately 20 mg/kg for child 5 years or less. 15 mg/kg for child 5-12 years)) with or without corticosteroids in consultation with an infectious diseases specialist.

**Enterovirus**: Intravenous immunoglobulin if hypogammaglobulinaemic. Intravenous immunoglobulin is used widely in Asia for enterovirus 71.

**CMV/HHV6**: Reduce immunosuppression and consider ganciclovir or foscarnet in consultation with infectious diseases specialist.

**Rabies or ABLV**: Consider Milwaukee protocol95 in consultation with infectious diseases specialist.

**ADEM**: Methyprednisolone 30 mg/kg daily in children up to 1000 mg (adult daily dose) for 3–5 days in consultation with a neurologist. Second-line treatments in consultation with a neurologist.

**Ab-mediated**: Immunosuppressive therapy in consultation with a neurologist. Investigation for underlying tumour and removal (where indicated). Ongoing tumour surveillance.

**Pleconaril**: For enteroviral encephalitis has limited documented efficacy and is not widely available. Intravenous immunoglobulin is used, without strong evidence of efficacy, to treat chronic enteroviral infections in antibody deficient hosts. It is increasingly being used as adjunctive therapy for other encephalitides. Corticosteroids have an established role in the management of ADEM, although this is not based on high-quality evidence18,66; intravenous immunoglobulin and plasma exchange may be used where there is steroid resistance.18 Evidence of benefit from immune suppression in NMDAR encephalitis in increasing21 and similar approaches are recommended for other immune-mediated encephalitides.57 An extensive search for an underlying malignancy should be performed whenever NMDAR encephalitis is diagnosed84 and in adults with “limbic encephalitis”99 (Box 3). There is no evidence that antimicrobials are beneficial in *M. pneumoniae*-associated encephalitis.

**Directed management of encephalitis with an identified aetiology (Box 6)**

When a cause is identified, directed therapy (Box 6) should be determined in consultation with relevant specialists and national/international antimicrobial guidelines.10

With the exception of the herpesviruses, most viral causes have no specific treatment. For HSV and VZV encephalitis, guidelines regarding acyclovir duration and corticosteroids vary.57-66 as does advice regarding antivirals for CMV or HHV-6 encephalitis.10 Antivirals are not recommended for EBV encephalitis.10 Pleconaril for enteroviral encephalitis has limited documented efficacy and is not widely available. Intravenous immunoglobulin is used, without strong evidence of efficacy, to treat EV71-associated encephalomyelitis,43 and also for chronic enteroviral infections in antibody deficient hosts. It is increasingly being used as adjunctive therapy for other encephalitides. Corticosteroids have an established role in the management of ADEM, although this is not based on high-quality evidence18,66; intravenous immunoglobulin and plasma exchange may be used where there is steroid resistance.18 Evidence of benefit from immune suppression in NMDAR encephalitis in increasing21 and similar approaches are recommended for other immune-mediated encephalitides.57 An extensive search for an underlying malignancy should be performed whenever NMDAR encephalitis is diagnosed84 and in adults with “limbic encephalitis”99 (Box 3). There is no evidence that antimicrobials are beneficial in *M. pneumoniae*-associated encephalitis.

with ‘cryptic’ encephalitis should be tested for anti-NMDAR and anti-VGKC complex encephalitis and in Australia for ABLV.

**Management (Figs 1, 2; Box 6)**

**Supportive and empiric**

Seizure control, management of raised intracranial pressure (occasionally by surgical decompression), circulatory and respiratory support, fluid and electrolyte balance, nutritional support, skin integrity and pressure area care, and prevention of hospital-acquired infections should all be addressed.

Patients with ‘suspected meningo-encephalitis’ should be commenced on acyclovir. Antibiotics for possible meningitis or sepsis should be administered promptly as per local and national guidelines (ACEM advise within 20 min of presentation) and should not be delayed if LP is contraindicated or neuroimaging delayed.

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Outcome, prognosis and follow-up

Overall mortality of encephalitis is approximately 10%,1,2,3,17 Up to 50% of patients experience short-term deficits with 20% experiencing severe sequelae; long-term outcome is poorly characterised, and neurocognitive sequelae likely underestimated.20,21 Depression of consciousness at presentation is the main adverse prognostic feature; poor outcome has also been associated with refractory status epilepticus, intensive care unit admission, local neurologic signs, abnormal MRI findings, extremes of age and immune compromise, a diagnosis of HSV in adults, and JEV or Mycoplasma pneumoniae in children,2 or delay in the initiation of directed therapy.

Recovery from encephalitis reaches a plateau at approximately 6–12 months. Rehabilitation assessment (medical and non-medical) should be considered, especially in those with neurological or neuropsychological deficits at discharge. We recommend early formal discharge planning to facilitate referrals and follow-up including development and learning in children, and seizure management.

Conclusion

Further research is needed to inform better local management guidelines; however, many patients will benefit from the optimal application of existing knowledge.

References

21 Titulaer MJ, McCracken L, Gahleonde L, Armanigue T, Glaser C, Itukra T et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis; an
BRIEF COMMUNICATIONS

Survey of infection control and antimicrobial stewardship practices in Australian residential aged-care facilities

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Key words
residential care, infection control, antibiotic stewardship.

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Abstract
This study assessed infection prevention and antimicrobial stewardship (AMS) practices in Australian residential aged-care facilities (RA CF). Two hundred and sixty-five surveys (15.6%) were completed with all states represented and the majority (177 (67.3%)) privately run. Only 30.6% RAC F had infection control trained staff on site. Few facilities had AMS policies, only 14% had antimicrobial prescribing restrictions. Most facilities offered vaccination to residents (influenza vaccination rates >75% in 73% of facilities), but pneumococcal vaccination was poor.
The term residential aged-care facilities (RACF) refers to a group of residential facilities designed to meet the needs of the elderly. These include nursing homes, skilled nursing facilities and assisted living facilities. The population in RACF is vulnerable to infection due to frailty, poor functional status, multiple comorbidities and compromised immune systems. Bed-bound residents are at greater risk of skin and soft tissue infections, while those with urine and/or faecal incontinence have an increased risk of urinary tract infections. In addition, close living proximity and frequent carer-resident contact facilitate the spread of organisms among RACF residents. This, coupled with frequent transfers to the acute hospital setting, promotes a higher infection burden among residents in RACF compared to those living at home.

Although the infection burden among the RACF population has long been recognised, infection prevention efforts are often limited to sentinel infection surveillance activity. Of particular concern is the widespread empiric antibiotic prescribing in RACF that may lead to the emergence of antibiotic resistance. Studies have reported increasing use of broad-spectrum oral antibiotics, such as fluoroquinolones, among this population, with up to 75% of use judged to be inappropriate. In an era where multidrug-resistant organisms (MDRO) are emerging in the community, RACF residents have been increasingly identified as important reservoirs of such bacteria.

In Australia, RACF are operated by not-for-profit organisations, church and charitable organisations, commercial organisations and some state and governments. To receive Australian Government subsidies, RACF are required to be accredited and meet four Accreditation Standards. ‘An effective infection control programme’ and ‘care recipients’ medication is managed safely and correctly’ are two of the 44 expected outcomes.

The aim of this study was to document the infection prevention and antimicrobial stewardship practices in RACF around Australia. This will, in-turn, lend itself to developing an understanding of gaps to inform an ongoing research agenda.

All RACF caring for low or high-level care residents (as defined by the Aged Care Funding Instrument) and having more than 50 beds were identified from a database held by the Commonwealth Department of Health. Managers of these facilities were contacted by email, and then a follow-up phone call, to ask if they would like to be involved in the survey. Details of contact numbers and email addresses for these sites are all publicly available on the Commonwealth Department of Health web site.

The survey could be completed online or on paper and mailed back to the principal investigator. Surveys were sent to all available addresses, but we were unable to confirm that the intended addressee received the email unless they responded. Completion and submission of the survey implied consent.

The survey was developed to enable RACF to answer questions in a de-identified manner on aspects of infection control and antimicrobial stewardship, that the members of the working group felt important. This included questions (in a checkbox format) on the population demographics of residents, the expertise and availability of infection control personnel, the availability of policies and procedures around infection control and antimicrobial stewardship, the type of infection surveillance that was undertaken in the facility and whether vaccination programmes were available for staff and residents. There were 40 questions in total, with the survey taking 5–10 min to complete. The RACF were invited once to complete the survey, there were no inducements offered for completion. Analysis was descriptive. The Commonwealth Departmental Ethics Committee approved the project.

There were 265 surveys returned from a possible total pool of 1700 RACF (15.6%) with the majority (177 (67.3%)) being from private facilities. All States were represented with 81 (30.6%), 88 (33.2%), 43 (16.2%), 22 (8.3%), 16 (6%) and 14 (5.3%) of returned surveys coming from New South Wales, Victoria, Queensland, South Australia, Western Australia and Tasmania respectively. This total number of RACF beds per facility ranged from 50 to 250 (mean 90, median 77 beds). The total number of RACF beds covered by the survey was 22 335, with 15 725 (70.4%) being high care. Occupancy at the time of the study was 95% (range 45–100%; median 98%). Male residents accounted for 7230 occupants (32.4%) with 13 972 (62.6%) being greater than 85 years of age. Over the entire cohort, there were 776 residents (3.5%) with urinary catheters in situ and 22 (0.1%) with a vascular catheter in place, while 910 (4.1%) had been in an acute care facility in the previous 30 days.

Two hundred and forty-two (91.3%) facilities had designated infection control personnel although only 30.6% (74) of these staff had any certification in infection control. Two hundred and sixteen (81.5%) facilities had an infection control committee. The availability of poli-
cies or procedures within the facility and the surveillance performed are outlined in Table 1.

Alcohol-based hand rub (ABHR) was available in all publically accessible areas in 246 (95.4%) of facilities and resident bedrooms in 72 (27.9%). While four facilities (1.6%) did not have ABHR available at all.

Antimicrobial prescribing was the role of general practitioners in all facilities, while 88 (33.6%) also had specialist consultants prescribing. Notification to the medical officer about resident illness and need for antibiotics was made by telephone in 254 (98.5%) via a communication book in 118 (45.7%) and in 16 cases (6.2%), the facility waited until the doctor made a routine visit. Notably, policies for antibiotic use were only available in 106 (40.3%) of facilities (Table 1), with only 36 (13.9%) stating there were any restrictions to prescribing. Local private pharmacies dispensed the majority of medications (222, 86%) with the remainder distributed through a hospital-associated pharmacy.

Vaccination for residents and staff is summarised in Table 2. Influenza vaccination was available in 245 (96.1%) of facilities with vaccination rates in 2012–2013 reported as >75% in 190 (72.8%) facilities, 50–75% in 45

<table>
<thead>
<tr>
<th>Procedure availability</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Management/isolation of MRSA carriers</td>
<td>226 (85.9)</td>
</tr>
<tr>
<td>Management/isolation of VRE carriers</td>
<td>206 (78.3)</td>
</tr>
<tr>
<td>Management/isolation of MDR-GN</td>
<td>174 (66.2)</td>
</tr>
<tr>
<td>Wound management</td>
<td>259 (98.5)</td>
</tr>
<tr>
<td>Management of urinary catheters</td>
<td>250 (95.1)</td>
</tr>
<tr>
<td>Management of vascular catheters</td>
<td>73 (27.8)</td>
</tr>
<tr>
<td>Management of enteral feeding</td>
<td>218 (82.9)</td>
</tr>
<tr>
<td>Standard precautions</td>
<td>253 (96.2)</td>
</tr>
<tr>
<td>Management/isolation of gastroenteritis</td>
<td>258 (98.1)</td>
</tr>
<tr>
<td>Management/isolation of Clostridium difficile</td>
<td>156 (59.3)</td>
</tr>
<tr>
<td>Cleaning rooms of MRO carriers</td>
<td>228 (86.7)</td>
</tr>
<tr>
<td>Hand hygiene</td>
<td>256 (97.3)</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>106 (40.3)</td>
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<table>
<thead>
<tr>
<th>Surveillance undertaken</th>
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<tbody>
<tr>
<td>Non-catheter-associated urinary tract infection</td>
<td>240 (92.7)</td>
</tr>
<tr>
<td>Catheter-associated urinary tract infection</td>
<td>211 (81.5)</td>
</tr>
<tr>
<td>Blood stream infection</td>
<td>171 (66)</td>
</tr>
<tr>
<td>Common coldpharyngitis</td>
<td>195 (75.3)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>229 (88.4)</td>
</tr>
<tr>
<td>Lower respiratory tract infection/pneumonia</td>
<td>242 (93.4)</td>
</tr>
<tr>
<td>Skin and soft tissue infection</td>
<td>242 (93.4)</td>
</tr>
<tr>
<td>Skin condition, wounds and ulcers</td>
<td>251 (96.9)</td>
</tr>
<tr>
<td>Eye infection</td>
<td>250 (96.5)</td>
</tr>
<tr>
<td>Gastrointestinal infection</td>
<td>242 (93.4)</td>
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<tr>
<td>Clostridium difficile infection</td>
<td>151 (58.3)</td>
</tr>
<tr>
<td>MRSA infection</td>
<td>197 (76.1)</td>
</tr>
<tr>
<td>VRE infection</td>
<td>182 (70.3)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Use of transmission-based precautions where appropriate</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Contact (single room, gloves, gown)</td>
<td>239 (91.6)</td>
</tr>
<tr>
<td>Droplet (single room, surgical mask)</td>
<td>213 (70.1)</td>
</tr>
<tr>
<td>Airborne (negative pressure room, N95/P2 mask)</td>
<td>34 (13)</td>
</tr>
<tr>
<td>None</td>
<td>23 (8.8)</td>
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<table>
<thead>
<tr>
<th>Resident vaccinations available</th>
<th></th>
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<tbody>
<tr>
<td>Influenza</td>
<td>245 (96.1)</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>170 (66.7)</td>
</tr>
<tr>
<td>Tetanus/diphtheria/pertussis</td>
<td>11 (4.3)</td>
</tr>
<tr>
<td>Varicella-zoster</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>No vaccines available</td>
<td>10 (3.9)</td>
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<tr>
<th>Staff vaccines available</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>217 (86.5)</td>
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<tr>
<td>Tetanus/diphtheria/pertussis</td>
<td>21 (8.4)</td>
</tr>
<tr>
<td>Varicella-zoster</td>
<td>77 (30.7)</td>
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<tr>
<td>Hepatitis B</td>
<td>20 (8)</td>
</tr>
<tr>
<td>Measles/mumps/rubella</td>
<td>26 (10.4)</td>
</tr>
<tr>
<td>Quantiferon Gold/Mantoux testing</td>
<td>16 (6.4)</td>
</tr>
<tr>
<td>No vaccines available</td>
<td>31 (12.4)</td>
</tr>
</tbody>
</table>

| MDR-GN, multidrug resistant Gram negative; MDRO, multidrug resistant organism; MRSA, methicillin resistant Staphylococcus aureus; VRE, vancomycin-resistant enterococcus. |

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Align accreditation of RACF with national standards for the acute sector</td>
<td>Include a focus on infection prevention and control</td>
</tr>
<tr>
<td>Develop database of policies and procedures for facilities to access</td>
<td>• MRSA colonisation</td>
</tr>
<tr>
<td>Develop surveillance programme for MDRO</td>
<td>• VRE colonisation</td>
</tr>
<tr>
<td>Enhanced immunisation</td>
<td>Increase vaccination rates</td>
</tr>
<tr>
<td>Develop education packages for nursing staff</td>
<td>• Respiratory tract infection</td>
</tr>
<tr>
<td>Hand hygiene</td>
<td>• Skin and soft tissue infection</td>
</tr>
<tr>
<td>Cleaning and disinfection</td>
<td>• Urinary sepsis with and without indwelling catheter</td>
</tr>
<tr>
<td>MDRO, multidrug resistant organism; MRSA, methicillin resistant Staphylococcus aureus; RACF, residential aged-care facilities; VRE, vancomycin-resistant enterococcus.</td>
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<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Include a focus on infection prevention and control</td>
<td>• Antimicrobial stewardship</td>
</tr>
<tr>
<td>Standardised procedures for managing</td>
<td>• Immunisation</td>
</tr>
<tr>
<td>• Management of urinary catheters</td>
<td>• Multidrug-resistant Gram-negative colonisation</td>
</tr>
<tr>
<td>• Clostridium difficile</td>
<td>• Clostridium difficile</td>
</tr>
<tr>
<td>Suggested</td>
<td>• Respiratory tract infection</td>
</tr>
<tr>
<td>• Skin and soft tissue infection</td>
<td>• Skin and soft tissue infection</td>
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<tr>
<td>• Urinary sepsis with and without indwelling catheter</td>
<td>• Urinary sepsis with and without indwelling catheter</td>
</tr>
<tr>
<td>• Multidrug-resistant Gram-negative bacteria</td>
<td>• Pneumococcal vaccine – residents</td>
</tr>
<tr>
<td>• MRSA and VRE</td>
<td>• Pneumococcal vaccine – residents</td>
</tr>
<tr>
<td>• Clostridium difficile</td>
<td>• Influenza – healthcare workers</td>
</tr>
<tr>
<td>• Multidrug-resistant Gram-negative bacteria</td>
<td>• Pneumococcal vaccine – residents</td>
</tr>
<tr>
<td>Diploma opportunities</td>
<td>• Influenza – resident</td>
</tr>
<tr>
<td>• Nurse practitioner role in RACF</td>
<td>• Infection control in RACF</td>
</tr>
<tr>
<td>• Guideline development specific for RACF</td>
<td>• Infection control in RACF</td>
</tr>
</tbody>
</table>

578
(17.3%) and <50% in 26 (11%) of facilities. Although 170 (66.7%) facilities claimed that pneumococcal vaccination was available for residents, only 46 (20.7%) reported vaccination rates >75%, with 99 facilities (44.6%) reporting that the pneumococcal vaccination rate for residents was unknown. Staff influenza vaccination rates were >75% in 35 (13.6%), 50–75% in 66 (25.7%), 20–50% in 105 (40.9%) and <20% in 51 (19.8%) of facilities.

This large survey of infection control and antimicrobial stewardship practices in RACF across Australia is the first of its kind to our knowledge. Infection control resources were evident across the services; however, most facilities did not have nursing staff possessing a higher certification in this area. Hand hygiene education and ABHR availability across all but a few facilities implies the importance placed on this as an infection control intervention, similar to that seen in the acute care sector.11 Surveillance activities for common infections in RACF was also generally undertaken although a lack of surveillance for Clostridium difficile was notable given the increasing concern there is for this disease.12 Additionally, we were unable to assess if standardised criteria were used for surveillance in these facilities – an area that requires further work.

While the majority of facilities had procedures in place for common infections, the currency of these documents was not assessed in this study. In fact, some services commented that it would be beneficial for Australian RACF to have access to a bank of policies and procedures that could be modified to suit individual facilities. This could be an area for future investment and one that may assist RACF accreditation. The survey did not address auditing of these procedures.

Antimicrobial stewardship is recognised as a vital component of infection control activities and has become part of National Standards for Accreditation in the Australian acute health sector. Recognition of AMS importance is also growing in residential care with increasing studies showing an urgent need for research in this area.13,14 Our survey supports the need to develop guidelines for antimicrobial use in RACF, to support facilities to enforce restrictions on prescribing and to develop a nationwide infection surveillance programme for MDRO.

Improving influenza vaccination rates in the elderly decreases lower respiratory tract infection and decreases hospitalisation.14 This survey has shown room for improvement with 28% facilities declaring that <75% of their residents were vaccinated in the previous year. More concerning is the low influenza vaccination rates of healthcare worker in these facilities (only 13.6% achieving vaccination rates >75%). This is a trend seen Australia wide,15 but given that most evidence for the healthcare worker vaccine efficacy is in the residential care setting,16 it is an area that deserves urgent attention.

Pneumococcal vaccination is recommended for those >65 years of age,17 and it is concerning that RACF do not place importance on knowing if residents are vaccinated. More research in the area of vaccination in RACF is required. A summary of recommendations from this study is presented in Table 2.

A weakness of this study is the low response rate (15.6%) of total available services such as these data may not reflect all RACF across Australia. However, given that the survey does include 265 sites and over 22 000 beds, it is the largest study of its kind. Furthermore, the response rate is estimated from a possible pool of 1700 facilities with greater than 50 beds; however, we were not able to confirm that all facilities received the email invitation, thus the response rate is likely to be much higher.

In summary, this large survey has uncovered some important areas for future research and quality improvement in RACF, namely AMS, immunisation of both residents and staff and the role that accreditation changes may have in these areas.

References


Long-term follow up of paediatric liver transplant recipients: outcomes following transfer to adult healthcare in New Zealand

R. Harry,1 C. Fraser-Irwin,2 S. Mouat,2 E. Gane,1 S. Munn1 and H. M. Evans2

1New Zealand Liver Transplant Unit (NZLTU), Auckland City Hospital and 2Department of Paediatric Gastroenterology, Starship Hospital, Auckland, New Zealand

Key words
paediatrics, liver transplantation, transition to adult care, patient non-adherence.

Abstract
Poor outcomes are reported in young people with chronic health conditions. We performed a retrospective notes review of New Zealand paediatric liver transplant recipients transferred to adult services. Two patients were lost to follow up. Out of 20, 12 were non-adherent, and out of 12, 7 developed rejection. Other risk behaviours were common in the non-adherent group. We conclude that dedicated services for these young people may be needed to optimise outcomes.

Adolescents and young people who have chronic health conditions are at increased risk of poor health and social outcomes compared with those who do not.1,2,3 This has been demonstrated among young people who were recipients of solid organ transplants as children. Among young people who have received renal transplants in childhood, graft loss is reported as between 35% at 2 years following transfer to adult services4 and 67% at 4 years5. In liver transplant populations, others have shown adherence with investigations, clinic appointments and medication is compromised in patients who transfer to adult care.6 Such non-adherence is not uniform but has been shown to be associated with low infections in elderly residents of long-term care facilities. Arch Intern Med 1999; 159: 2058–64.

11 Grayson ML, Russo PL, Cruickshank M, Bear JL, Gee CA, Hughes CF et al.

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11 Grayson ML, Russo PL, Cruickshank M, Bear JL, Gee CA, Hughes CF et al.

socioeconomic status, single parenting, psychiatric diagnoses, school dropout, substance abuse and child abuse. Ultimately, non-adherence in liver transplant recipients may be associated with late rejection, graft loss, re-transplantation or death.

Young people with chronic illness are also more likely to engage in risk-taking behaviours such as smoking, drinking alcohol, taking drugs and unprotected sex and are more likely to come to harm as a result of them.

The long-term outcome of paediatric liver transplant recipients after transfer to adult services in New Zealand has not been previously reported.

As such, the clinical notes were reviewed retrospectively of New Zealand paediatric liver transplant recipients born before 1998 who had been planned to transfer to adult services prior to 31 December 2012 (i.e. aged over 14 years). Data were retrieved from New Zealand Liver Transplant Unit (NZLTU) and Starship Hospital databases whether transplanted in New Zealand or abroad. Prior to 2002, when the paediatric liver transplant service started at Starship Hospital, Auckland, paediatric liver transplant recipients underwent assessment and transplantation in Brisbane, Australia.

This was granted institutional approval by the Auckland DHB research review committee.

Demographic data were recorded from clinical record or NZLTU databases including ethnicity, age and diagnosis at transplant.

The following outcomes occurring following transfer to adult services were sought:

1. Non-adherence with medication as evidenced by undetectable tacrolimus levels, self-report or report by others of non-adherence in the clinical record or episodes of rejection attributed to non-adherence by treating physicians.
2. Health outcomes such as rejection (biopsy proven or as defined by treating physicians) admissions with rejection, mental health diagnoses, graft loss and death.
3. Social outcomes, such as drug and alcohol use, unplanned pregnancy and legal issues as reported in the clinical record.

The data are reported in two groups based on the presence or absence of evidence of non-adherence as median and ranges.

A total of 60 New Zealand paediatric liver transplant recipients who underwent liver transplantation before 1998 was identified from NZLTU and Starship Hospital databases. Of these, nine had died post-transplant, six had moved abroad, four had been lost to follow up (presumed to be abroad) and six were still in paediatric care. There were 13 young people in the process of transition through the newly established young person’s liver clinic.

The remaining 22 patients had planned to be transferred directly from paediatrics to adult health services without being involved in any formal transition pathway or youth specific service.

Data were available on 20 of these, as two were lost to follow up at or shortly after transfer. These data are summarised in Table 1.

A total of 16 young people was New Zealand European (NZE) and four were New Zealand Maori or Pacific Islander. The median time after transplant was 17 years (range 4–27 years) and the median age was 21.5 years (range 17–30 years).

Out of 20, 12 (60%) of these patients had evidence of non-adherence following transfer. The four non-NZE young people all had evidence of non-adherence in their record.

Of those who were non-adherent, 7/12 (58%) had either suspected or biopsy proven rejection. Three of these young people had multiple episodes of rejection requiring hospitalisation. Overall, 35% of the non-adherent group had evidence of rejection, whereas no patients who were thought to be adherent had late rejection. No patients in this series required re-transplantation or died.

Other risk behaviours, such as alcohol and substance use, are common in the group of patients with evidence of non-adherence and are not reported in the group presumed to be adherent (Fig. 1).

Young people in the non-adherent group were also suboptimally engaged with healthcare with 10 young people in the non-adherent group (83%) reported to be suboptimally adherent with attendance at clinics or monitoring blood tests. At the time of data collection, only 42% of the non-adherent group were receiving regular secondary or tertiary healthcare in New Zealand (Table 1).

Other health risks were reported in the non-adherent group. Of this group, 42% carried mental...
health diagnoses resulting in one intentional overdose. Six pregnancies are reported in four young women in the non-adherent group. Two young women had terminations aged 18 years, one also had an unplanned pregnancy at 19 years. Three live births were reported in patients aged 20, 22 and 22 years where intent related to pregnancy was not reported. In the group of patients with no evidence of non-adherence, there was one pregnancy reported to be intentional.

In conclusion, these data comprise a retrospective notes review of patients who underwent paediatric liver transplantation and were subsequently transferred to adult services. There are limitations to these data, including the under reporting of non-adherence and other risk behaviours that are inherent in retrospective clinical record reviews and the potential over reporting of risk behaviours in the non-adherent group, as these may have been specifically sought where they were not in the adherent group.

Notwithstanding the limitations of this retrospective study, we found that reported non-adherence with medication is common in paediatric liver transplant recipients following transfer to adult services in New Zealand. Non-adherence was reported in two out of three patients, of whom two out of three subsequently suffered harm as a consequence of rejection.

Despite the flaws in the data, we confirm that in this population, non-adherence occurs as part of a constellation of risk behaviours, including alcohol and drug use, unintentional pregnancy, mental health diagnoses and legal issues.

Dedicated services for young people have been shown to improve outcomes for paediatric renal transplant recipients in the UK. These data demonstrate that there may be a need for improved services for young people with chronic health conditions, including solid organ transplants, in New Zealand. A holistic approach that not only addresses the presenting medical condition, but also provides culturally and developmentally appropriate care may improve long-term medical and social outcomes for these young people.

References

Primary central nervous system posttransplantation lymphoproliferative disorder after heart and lung transplantation

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Key words
posttransplant lymphoproliferative disorder, central nervous system, lymphoma, heart, lung, transplantation.

Abstract
Primary central nervous system posttransplantation lymphoproliferative disorder (PCNS-PTLD) is uncommon, especially after heart or lung transplantation. Database analysis from a single heart and lung transplantation centre and a literature review pertaining to PCNS-PTLD was performed. In this study, the prevalence of PCNS-PTLD was 0.18% after heart and/or lung transplants. Of 1674 transplants, three cases of PCNS-PTLD developed 14 months, 9 years and 17 years posttransplant, and all were Epstein–Barr virus driven malignancies. Literature review of the topic revealed predominantly retrospective studies, with most reported cases after renal transplantation. The overall survival is poor, and it may be improved by early diagnosis and treatment. There are no published guidelines on the management of PCNS-PTLD; immune-chemotherapy in conjunction with reduction of immune suppression is preferred based on available evidence.

Primary central nervous system posttransplantation lymphoproliferative disorder (PCNS-PTLD) is uncommon, and its occurrence after heart or lung transplantation is unknown. PCNS-PTLD presents in a plethora of ways with broad differential diagnoses. Management of this condition in transplant recipients is challenging. There is no consensus on treatment due to its rarity. This report describes all identified cases of PCNS-PTLD in a single institution that performs heart and lung transplantation over 28 years and its prevalence. The approaches to the management of PCNS-PTLD based on published evidence are summarised.

Case 1: A 64-year-old man presented with urinary incontinence, dysphasia, personality changes and memory loss 14 months after heart transplantation for transthyretin amyloid cardiomyopathy. He was on prednisolone, mycophenolate and cyclosporin. Magnetic resonance imaging (MRI) revealed bilateral lesions in the fronto-temporal areas. Neurosurgery relieved the associated raised intracranial pressure and obtained histology; monomorphic PTLD, variant diffuse large B cell lymphoma (DLBCL) that was angioinvasive and Epstein-Barr virus (EBV)–encoded RNA (EBER) positive. There was no systemic involvement on computed tomography (CT) and positron electron tomography (PET). Cyclosporin and prednisone were reduced, mycophenolate replaced by everolimus. Intravenous rituximab was administered weekly for 4 weeks resulting in rapid clinical and radiological improvement. The patient then completed six cycles of high-dose methotrexate (HD-MTX). The patient remains alive at 18 months, with complete clinical recovery and no evidence of tumour on MRI and a normal functioning cardiac allograft.

Case 2: A 56-year-old man who received double lung transplantation for α1-antitrypsin deficiency developed gradual diplopia and ataxia 9 years posttransplant. He was immunosuppressed with prednisolone, tacrolimus and mycophenolate mofetil. Imaging showed a circumferential cerebellar lesion surrounding the fourth ventricle. Emergency decompressive neurosurgery to relieve raised intracranial pressure also provided a histological diagnosis of monomorphic PTLD, variant DLBCL. The lymphoma was angio-invasive and EBER positive. There was no systemic involvement CT and PET. Tacrolimus and mycophenolate were reduced and the patient received one dose of intravenous rituximab. The patient rapidly deteriorated and died within a month of his diagnosis.

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cases of PTLD occur within a year of transplantation, and seropositive donor. PTLD has a bimodal distribution; most seronegative patients receiving an allograft from an EBV-often remain heavily immunosuppressed, and in EBV-observed in lung transplantation recipients who negative, monomorphic and carry a worse prognosis. 3–5 that occur late are more commonly disseminated, EBV-infection.1 Higher incidences of PTLD are thus factors for PTLD are immunosuppression and primary immunosuppressive drugs were dosed according to pharmacokinetic measurement, with therapeutic ranges for heart and lung transplant for tacrolimus 10–15 ug/L; cyclosporin trough therapeutic level varied according to time after transplant, with a target of 100–180 ug/L a year after transplantation; mycophenolate mofetil 2.5–4.5 mg/L; sirolimus 3.5–15 ug/L.

In this single centre study of 1674 heart and/or lung transplantation recipients (857 heart, 151 single lung, 583 bilateral lung and 83 heart-lung), three were identified to have PCNS-PTLD during a 28-year period from 1984 to 2012, yielding a prevalence of 0.18%. The transplantation recipients are routinely reviewed in a multidisciplinary clinic with a prospectively maintained departmental database, and local registry, so that the prevalence is accurate. This study is the first to establish prevalence for PCNS-PTLD after solid organ transplant. PTLD ranges from polyclonal proliferations to monomorphic forms indistinguishable from those which occur in immunocompetent individuals. The major risk factors for PTLD are immunosuppression and primary EBV infection.1 Higher incidences of PTLD are thus observed in lung transplantation recipients who often remain heavily immunosuppressed, and in EBV-seronegative patients receiving an allograft from an EBV-seropositive donor. PTLD has a bimodal distribution; most cases of PTLD occur within a year of transplantation,1 and these cases are more likely to involve the allograft.2 PTLD that occur late are more commonly disseminated, EBV-negative, monomorphic and carry a worse prognosis.1–5

The incidence of PCNS-PTLD is unknown, and older series have included systemic PTLD with CNS involvement. In a series of 639 heart and/or lung transplantation recipients, two developed PCNS-PTLD.6 PCNS-PTLD in the published literature is predominantly reported in small case series after renal transplantation, the monomest solid organ transplanted. The interval from transplantation to diagnosis of PCNS-PTLD has been reported to range from 3 months to 5 years.3–9 The prognosis of PCNS-PTLD is varied and best described after renal transplantation. A case series of 25 patients reported overall survival of 40% with a median survival time of 26 months.7 In recent international reports, median survival was 47 months in a series of 34 patients,8 while the largest series of 84 PCNS-PTLD reported an overall survival of 43%.10

In the joint British Committee for Standards in Haematology and British Transplantation Society Guidelines for Management of PTLD in Adult Solid Organ Transplant Recipients,11 reduction in immunosuppression followed by local radiotherapy with or without steroids, and addition of HD-MTX for young, fit patients are recommended as grade C, level 3 evidence. Otherwise, survey of the literature yields neither guidelines nor consensus documents on how to treat PCNS-PTLD. It may not be unreasonable to extrapolate from the treatment of PCNSL to PCNS-PTLD. PCNSL is chemosensitive and radiosensitive, and its treatment has been rigorously studied. However, patients with PCNS-PTLD often have comorbidities precluding the application of standard PCNSL treatment protocols.

Recommendations for the treatment of systemic PTLD might be insufficient or inappropriate for PCNS-PTLD. Reducing immunosuppression in PTLD is recommended,1 as the attenuation or withdrawal of immunosuppression allows restitution of immunity, especially against EBV. Reducing immunosuppression alone has been reported to induce remission in low grade, systemic PTLD.12 Reduction of immunosuppression needs to be gradual to prevent allograft rejection, a timeframe that is not feasible in PCNS-PTLD due to raised intracranial pressure.

Surgery is directed at obtaining histological diagnosis and for cerebral decompression. It otherwise has little therapeutic role.

Whole-brain or focal radiation therapy is administered alone or in combination for treatment of PCNSL or to palliate symptoms.13 For PCNS-PTLD, radiation dosages and schedules have been extrapolated from PCNSL and human immunodeficiency virus and acquired immunodeficiency syndrome-related lymphoma. Acute and long-term neurotoxicity from radiation therapy limits this treatment.

Systemic chemotherapy has improved outcomes for PTLD, but the blood brain barrier limits the choice of agents for PCNS-PTLD. Extrapolating from PCNSL studies, HD-MTX and cytarabine have been successfully...
used to treat PTLD-CNS. Complex medical comorbidities and poor performance status prevent the administration of systemic chemotherapy in many PCNS-PTLD patients.

Therapy with intravenous rituximab has improved overall survival for patients who develop systemic PTLD. Although only a small fraction of the systemic dose is detectable in cerebrospinal fluid, rituximab remains effective as monotherapy in PCNSL because of its long half-life, resulting in low yet stable therapeutic concentrations over time. Sequential treatment of rituximab half-life, resulting in low yet stable therapeutic concentrations over time, is associated with all-cause mortality.

A small study showed that intrathecal rituximab was efficacious in heavily pretreated patients with non-Hodgkin lymphoma who have CNS disease. Intrathecal rituximab has been successful in some paediatric sufferers with PCNS-PTLD. However, accessing the intrathecal space might be inadvisable in patients with raised intracranial pressure. In summary, the current literature suggests that in conjunction with reduction in immunosuppression, immune-chemotherapy should be first line treatment due to its efficacy and minimisation of neurotoxicity.


References

LETTERS TO THE EDITOR

Clinical-scientific notes

Bilateral cordotomy post-failure of intrathecal analgesia in a palliative care setting

A 60-year-old man was referred to a tertiary palliative care unit with poorly controlled right hip pain. He was diagnosed in 2009 with a large solitary right hip metastasis from a poorly differentiated pulmonary neuroendocrine tumour. Over a 5-year period he was given seven lines of chemotherapy and three courses of radiotherapy (total of 121 Gy in 63 fractions) to this metastasis.

The patient’s analgesic regimens failed to stabilise his pain, despite opioid rotations and recognised co-analgesics. Unfortunately, analgesic up-titration caused increasing drowsiness, which limited his mobility. He also had an aversion to hospitals, exacerbated by anxiety, but increasing pain persuaded him to consent to inpatient intrathecal analgesia. Ongoing support from his family was vital during his admission.

An intrathecal catheter was inserted in late January 2014. While initially effective, the management lacked sustained efficacy despite significant dose increases. The infusion was ceased after 12 days, following a multidisciplinary plan for a cordotomy.

An open bilateral cordotomy via a T1/T2 laminectomy was performed with an excellent result. The patient had no right leg pain post-procedure, and only minor wound pain; postoperative analgesia is outlined in Table 1. Lower limb power remained intact; however, due to deconditioning, he was limited to stand-transfers and also developed urinary incontinence. Following a 5-week period of rehabilitation, he was discharged home with his family, remaining comfortable and with improved mobility. Unfortunately, after 2 months he deteriorated and required a 2-week hospital admission for end-of-life care.

Despite the best systemic management of cancer pain, up to 10% of patients have inadequate analgesia. Intrathecal catheter insertion and cordotomy are two analgesic procedures appropriate for medically refractory cancer pain. There is no current consensus of when and in whom cordotomies should be performed. However, medically refractory, unilateral nociceptive pain, where prognosis is less than 1 year is deemed appropriate. Holistic multidisciplinary care is essential to manage pain and recognise suitable cordotomy candidates. While percutaneous cordotomy is recognised as an effective and less invasive technique, the neurosurgical expertise at our centre is in open cordotomy. The open cordotomy procedure is performed under general anaesthetic via a laminectomy technique. Open surgical exposure allows mechanical interruption of the lateral spinothalamic tract at the upper thoracic level. In contrast, the percutaneous procedure is performed under local anaesthetic, where a radiofrequency heat lesion interrupts the lateral spinothalamic tract at the C1/C2 level. Open cordotomy is less commonly performed, causes more extensive lesions and is less selective than the percutaneous procedure; however, it decreases the risk of respiratory compromise. Complications of both procedures include: paresis or ataxia, worsening micturition control (as in the present case), post-cordotomy dysesthesia and mirror pain. The patient was appropriate for a bilateral approach given his high risk of developing contralateral
pain requiring a further cordotomy.6 This case study demonstrates the beneficial use of cordotomy, once intrathecal and other non-procedural analgesia have failed. Unfortunately, the availability of cordotomy remains dependent on appropriately skilled neurosurgeons.2 Further research should better elucidate the use of cordotomy in this important group of patients.

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Table 1 Analgesic requirements

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Pre-intrathecal max dose</th>
<th>Post-intrathecal Pre-cordotomy</th>
<th>3 days post-cordotomy</th>
<th>2 weeks post-cordotomy</th>
<th>EOLC – 3 months post-cordotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral morphine equivalent dose†</td>
<td>622.5‡</td>
<td>3307.75 mg (1489–9503 mg)</td>
<td>120 mg (90–180 mg)</td>
<td>176.5 mg (112–194 mg)</td>
<td>1230 mg (255–1500 mg)</td>
</tr>
<tr>
<td>Morphine (oral)</td>
<td>60 mg</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Morphine (subcut)</td>
<td>70 mg</td>
<td>11.25 mg (5–45 mg)</td>
<td>30 mg (20–40 mg)</td>
<td>20 mg (20–20 mg)</td>
<td>—</td>
</tr>
<tr>
<td>Morphine (intrathecal)</td>
<td>—</td>
<td>10 mg (4–30 mg)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hydromorphone (oral)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4.5 mg (1–8 mg)</td>
<td>—</td>
</tr>
<tr>
<td>Hydromorphone (subcut)</td>
<td>—</td>
<td>12 mg (0 mg–12 mg)</td>
<td>2 mg (2–4 mg)</td>
<td>—</td>
<td>82 mg (17–100 mg)</td>
</tr>
<tr>
<td>Bupivacaine – intrathecal</td>
<td>—</td>
<td>150 mg (120–200 mg)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Methadone – oral</td>
<td>75 mg</td>
<td>20 mg (50–40 mg)</td>
<td>—</td>
<td>20 mg (10–20 mg)</td>
<td>—</td>
</tr>
<tr>
<td>Midazolam (subcut)</td>
<td>—</td>
<td>20 mg (10–35 mg)</td>
<td>5 mg (0–5 mg)</td>
<td>—</td>
<td>47.5 mg (7.5–85 mg)</td>
</tr>
<tr>
<td>Midazolam (intrathecal)</td>
<td>—</td>
<td>10 mg (5–10 mg)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ketamine – CSCI</td>
<td>—</td>
<td>200 mg (0–200 mg)</td>
<td>150 mg (100–200 mg)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>50 mg</td>
<td>50 mg (50–75 mg)</td>
<td>100 mg (50–100 mg)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

†Morphine – oral : subcut: intrathecal = 3:1:0.01; hydromorphone : morphine = 1:5; methadone oral : morphine oral 1:4.7 (Knotkova, Fine & Portenoy—see references). ‡Calculated from admission notes – median dose not available. §All doses are presented as median dose and range unless otherwise specified. ¶Started post-intrathecal failure. CSCI, continuous subcutaneous infusion; EOLC, end-of-life care.

References

Serum creatinine is not the end-all, be-all of renal impairment

A 52-year-old African American man with no medical history presented as a referral to the nephrology clinic for evaluation of renal dysfunction. The patient was an active body builder in good health. He had blood pressure of 110/70 mmHg and heart rate of 70 b.p.m., and his physical examination was remarkable for an extremely muscular physique with no evidence of central obesity. He weighed 220 lb with a body mass index of 30.4 kg/m² and body surface area of 2.25 m². He reported taking injectable testosterone cypionate to build muscle for the past 1 year. Initial laboratory measurements revealed a blood urea nitrogen (BUN) of 3.9 mmol/L, a serum creatinine of 141.4 μmol/L and an estimated glomerular filtration rate (eGFR) of 50 mL/min/1.73 m².

Repeat serum BUN/creatinine/eGFR did not reveal a significant variation from the initial evaluation of renal function on day 1 (Table 1). Urinalysis was negative for haematuria, proteinuria or pyuria. Since the patient’s only abnormality was an elevated serum creatinine, we used several methods to measure his ‘true GFR’. First, the 24-h urine collection revealed a creatinine clearance of 131 mL/min (urine volume 1500 mL). Second, the GFR was estimated at 140.2 mL/min from a dynamic radionuclide study by measuring Tc-99m DTPA uptake within the kidneys. Last, cystatin C was measured at 0.76 mg/L (normal range 0.5–1.0 mg/L). These three independent measurements of a normal GFR confirmed our suspicion that this patient had an elevated serum creatinine in the absence of renal impairment.

In clinical practice, a serum creatinine greater than the upper limit of normal is taken as prima facie evidence of decreased GFR and therefore impaired renal function. The use of the modification of diet in renal disease (MDRD) equation to estimate GFR strengthens this interpretation since a high serum creatinine will invariably calculate a decreased GFR. The diagnosis of decreased GFR will label the patient as having chronic kidney disease, a diagnosis with significant clinical, psychological and financial repercussions.

The rate of creatinine production is directly associated with skeletal muscle mass and to a lesser extent with meat intake. For instance, cross-sectional studies in healthy adult males demonstrate that the mean ratio of skeletal muscle mass to 24-h creatinine excretion is 21.8 kg/g.1 Also, the administration of 3 mg/kg/week of testosterone increases the skeletal muscle mass and 24-h creatinine excretion by 20% within a short 12-week period.2 Furthermore, muscle mass is a strong determinant of eGFR in normal healthy male subjects, independent of body fat or protein intake.3 This is clearly exaggerated in our patient who had a significantly large muscle mass with a high 24-h creatinine excretion (Table 1). This concept is not accounted for in the widely used eGFR from the MDRD equation. In addition to the radioisotope studies and 24-h creatinine clearance measurements to measure GFR, cystatin C production is a better marker of renal function in these clinical scenarios since its measurement is independent of age, sex or muscle mass.4 The use of these other measures of GFR can often be neglected in the primary care setting, leading to the misdiagnosis of renal dysfunction in a given patient with elevated serum creatinine.

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Table 1 Laboratory parameters during clinic visit

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mmol/L)</td>
<td>3.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>141.4</td>
<td>141.4</td>
</tr>
<tr>
<td>Urine protein/creatinine ratio (mg/mmol)</td>
<td>6.7</td>
<td>6.7</td>
</tr>
<tr>
<td>24-h protein (mg/day)</td>
<td>157.5</td>
<td></td>
</tr>
<tr>
<td>24-h creatinine excretion (mmol)</td>
<td>26.5</td>
<td></td>
</tr>
<tr>
<td>24-h volume (L)</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>eGFR MDRD (mL/min/1.73 m²)</td>
<td>50.3</td>
<td>50.3</td>
</tr>
<tr>
<td>Tc GFR (mL/min)</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>24-h creatinine clearance (mL/min)</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>24-h creatinine clearance (mL/min/1.73 m²)</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>0.76</td>
<td></td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

References


General correspondence

Audit of inpatient referrals

I was very interested in the recent article by Brown et al. comparing specialty referrals made from inpatient general medical units in regional and metropolitan hospitals. The authors state that there is no available research on inpatient referrals published. In fact, there is one historical comparator which we published in the 1980s. This was a somewhat similar study but was done over a 6-month period prospectively when two units, both of which were general medical units with a special interest in respiratory medicine, recorded all of their inpatient and outpatient activity. There are some interesting comparisons with Brown et al.’s study. The Teaching Hospital unit in our study (consisting of one consultant, one senior registrar, one registrar and one intern) averaged 16.4 admissions per week compared with Monash’s 11.6 and the District General Hospital’s (one consultant, one registrar and one intern) 19.7 admissions as opposed to West Gippsland’s 10.7. In our study, there was no difference in the range of pathology seen between the two hospitals, but we also found a significant difference between the Teaching Hospital and the District General Hospital in the number of referrals made to other specialists. The Teaching Hospital averaged 0.26 referrals per admission (including geriatrics) compared with Monash’s 1.74 and the District General Hospital’s 0.13 compared with West Gippsland’s 0.69.

I would suspect that the units involved in Brown’s et al. study were more generously staffed than those in Yorkshire in the 1980s, and together with the much smaller number of admissions, this documents the reduction in clinical experience now offered to junior doctors. Brown et al. correctly point out the dangers of over-referral and speculate on possible causes including greater availability of subspecialists and fear of litigation. Our feeling in the 1980s was that this disparity largely reflected better general medical skills and greater confidence in dealing with a wider variety of conditions among physicians working in District General Hospitals rather than major metropolitan teaching centres, together with a reluctance to bother one’s busy colleagues with routine or banal medical conditions which any physician should be capable of managing.

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References


Author reply

We thank Simpson1 for commenting on our paper2 and also for alerting us to his historical comparator study, which has also compared inpatient referrals in a Teaching Hospital and District General Hospital in the 1980s. It is indeed interesting to note that this study also showed a significant difference between the Teaching Hospital and District General Hospital in the number of referrals made to other specialists. We agree that in the 1980s, this difference may have reflected greater confidence and general medical skills in dealing with a wide variety of conditions among physicians working in District General Hospitals rather than major teaching centres.

It is certainly interesting to note the change in patient load over the last two decades. We do not entirely agree with Simpson that this correlates with a reduction on clinical experience offered to junior doctors. There have certainly been important moves in recent years to ensure safer working hours for junior doctors that may in some ways have limited clinical exposure compared with two decades ago. However, we suspect that the change in patient load is more a reflection on the increasing complexity and expectation of patients along with advances in medicine, which have made management more complex as the years go by.

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Leprosy and Australia

While syphilis has been hailed as ‘the great imitator’, leprosy can also qualify, as illustrated by Turner et al.1 in a summary of cases treated in a tertiary centre in Victoria. The authors make the point that little has been published about aspects of the disease in developed settings. Some readers may be interested in two accounts of leprosy2,3 as seen in New South Wales from the 1950s to the 1970s, revealing confusion in clinical assessments and differential diagnoses in these patients. In this country, leprosy in its clinical manifestations is seen infrequently, and by many clinicians not at all, so that the diagnosis is often simply not considered.

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References

Not only monoclonal antibodies . . .

The recent case report by Commons et al.1 suggests that monoclonal antibody therapy was the triggering factor for the development of melioidosis in a patient with psoriatic arthritis.

As the physician caring for this patient at the time, I feel the authors have jumped to a conclusion regarding the possible connection with anti-tumour necrosis factor and anti-IL12/23 treatment in this case. While this patient’s spondylitis responded well to biologic therapy, he also suffered from severe, extensive plaque psoriasis that was largely unresponsive to treatment (aside from a short lived initial improvement after etanercept therapy).

Given the fact that there is a considerable (>100) number of patients maintained on biologic therapy in Darwin in the last 5–10 years and the fact that this is the first case of melioidosis observed in this group, I remain unconvinced that treatment was a triggering factor in this case. Working in the garden during the wet season with extensive psoriatic skin lesions and without the use of protective gear seems to have been the most likely route of inoculation. Therefore, in my opinion, it would have been more appropriate to add active psoriasis to the author’s list of risk factors for acquiring melioidosis in endemic areas.

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Reference

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Author reply

We thank Nossent for his response to our article on melioidosis in a patient on monoclonal antibody therapy. Nossent raises the important point that skin exposure is a common method of inoculation and patients with psoriatic skin disease are at heightened risk for inoculation. The patient we reported sustained a recent cut while gardening after heavy rainfall, which was felt to be the likely time of inoculation. As described in the Darwin Prospective Melioidosis Study, 20% of patients who contract melioidosis do not have recognised risk factors, and we acknowledge that any association with adalimumab in this patient remains speculative.

However, there are several features that heighten our suspicion that monoclonal antibody therapy may have predisposed our patient to melioidosis. First, the rapid onset presentation with bacteraemia is very similar to patients who are immunosuppressed or receiving high-dose corticosteroids and is rarely seen in otherwise well patients.

In addition, we have now had a second patient diagnosed with melioidosis who presented in a very similar fashion while on adalimumab for ankylosing spondylitis. This 68-year-old man presented early this year with 24 h of headache, lethargy, nausea and high fevers, with onset several days after exposure to wet season rains in the Top End of the Northern Territory. He had chronic lung disease but no other risk factors for melioidosis. Blood cultures grew *Burkholderia pseudomallei* and he responded well to standard therapy, initially with intravenous cefazidime.

Finally, animal data have demonstrated that neutralisation of interleukin-12 and tumour necrosis factor (TNF)-α led to increased susceptibility to melioidosis, and adalimumab acts as a TNF-α inhibitor. It is apparent that specific risks for individual monoclonal antibody therapies may only be identified through post-marketing surveillance. In particular, the links between natalizumab and progressive multifocal leukoencephalopathy and TNF-α inhibitors and listeria have now been well documented.

As noted by Nossent, melioidosis had not been documented in >100 patients on biological therapy in Darwin until our report. However, it is possible that adalimumab has a particular ability to interfere specifically with critical immune pathways in the host defence against *B. pseudomallei*. While we cannot claim that adalimumab was definitively a causative risk factor for melioidosis in these two cases, we feel it is important to highlight the potential link. Further surveillance for melioidosis is warranted in patients being treated with adalimumab and other monoclonal antibody therapies who live in or travel to melioidosis-endemic locations.

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References

Redesign versus resources: continuity lost

I read with interest the results of the redesign of General Medical Units at Auckland Hospital in your journal.1 The reduction seen in length of stay and bed days saved actually occurred when two simultaneous interventions occurred, namely service redesign but in addition the service attained increased staffing. So in this pre/post-trial design, it is difficult to ascertain which of these interventions had the most effect. Clearly before 2011, the Auckland Hospital General Medical Service was overwhelmed with patient numbers and therefore increasing both senior and junior medical staffing 24 h/7 days a week would no doubt assist with looking after the patients in a more timely manner, improve educational opportunities for junior medical staff, and there is no medical department in the world that does not want extra resourcing to improve morale.

All general medical units around the world are reviewing their model of care to improve patient care and efficiency and external drivers like the 4-h rule in Australia and similar rules in New Zealand are key influences. However, there are aspects of the new model of care described in Auckland that trouble me greatly.

First, the authors should be congratulated in improving senior consultant supervision during admitting days by rostering physicians in the evening. This can only improve patient care, junior medical staff supervision and efficiency. The real concern I have is with the loss of continuity of care that occurs with the introduction of separate admitting and receiving teams as well as the lack of single point accountability in decision making when multiple consultants care for a particular patient. There are many methods of load sharing without having to break these two key tenets of good physician care.

Our acute inpatients are becoming more complex with many comorbidities, polypharmacy, complex social and functional issues, and thus it takes significant time and effort to understand the nuances of each particular patient. There are higher expectations in quality of care from patients and relatives. We are entering the era of personalised therapies. So good care is very difficult to achieve when medical staff are changing during a very short admission and there are multiple handovers.

There is another important factor. With good continuity of care one receives constant feedback on all of the decisions made during the patient’s journey; not only the big decisions but also the tiny small ones as well. We all make hundreds of decisions every day. The outcomes of your decision making may not be apparent by the next day; it may take till discharge or review in the clinic or with the readmission! This constant feedback over years refines our consultant skills and I believe makes physicians a superior clinician compared with disciplines that do not have this opportunity. It would be a great loss to lose this intrinsic advantage.

Space precludes me from commenting on the ducking and weaving that can occur when single point accountability is lost; or the hindrance to mentorship and role modelling when junior staff have to deal with multiple consultants with differences in opinions on the same case; or the flawed claim of no change in case mix by referencing a US study; or commenting on a 30-day mortality without any methodology or results presented in the paper.

In conclusion, there is no evidence in this paper that the model of care was the key driver in improving the process indicator of length of stay. The patient you know best is the one that you have admitted, and I want my admitting registrar to be my discharging registrar.

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Reference

Author reply

We are very pleased that Denaro took an interest in carefully reading our paper.1

We agree that it is difficult to conclude which specific components of our new work model contributed most to the benefits we observed. If another department was interested in reproducing these improvements to their own length of stay (LOS), the simple solution would be to adopt all of the components from our bundle of interventions. As such, we were careful in our conclusions to list all of the component changes as being responsible for the improvement in LOS.2 Having said this, we are confident that the reorganisation of our work model, rather than our increase in staffing, was the major contributor.

Many studies have already shown that reconfiguration, rather than addition, of hospital resources has significant effects on efficiency. It has been demonstrated that the on-call schedules of medical personnel have strong effects on the variation in daily discharges,3 and removing such variation improves patient flow.4 Additionally, smoothing (not increasing) patient discharges over the course of the week increases capacity in the emergency department.5 Finally, spreading the load of daily admissions over the whole service reduces median LOS.6 Therefore, our expectation of decreased LOS from ‘line-averaging’, and stratification of the patient journeys, was well founded.

Although the increase in Senior Medical Officer (SMO) staffing was a requirement of the new model, the number of SMO on clinical duties at any one time is unchanged; we had 12 working SMO teams in the old model, and 12 in the new one. The addition of the SMO evening shift actually occurred 6 months prior to the implementation of the new work model, and was not associated with any change in median LOS. Conversely, there was an immediate step change in median LOS with the introduction of the new model. These observations suggest that the re-configured inpatient team structure was largely responsible for the benefits in LOS.

Denaro cherishes patient continuity with good reason. It makes sense for the patient as well as for the continuing education and development of the training doctors. However, the first problem is that true continuity is an illusion. An audit in our own hospital in the old model showed that 62% of patients were discharged by a different team than the one who did the admission. There are many forces that disrupt continuity that we have learned to manage, not least of which is SMO going off service for annual leave. Geographic, unit-based teams are another such force, one that is accompanied by many benefits including better coordinated multidisciplinary care. Finally, the change of ownership of a patient’s care is an opportunity for better diagnostic performance, a built-in system to provide a second opinion.

Notwithstanding this defence of our findings and our work model, we are continuously searching for changes that optimise the many positive principles at play that make for better patient care, including doctor–patient and physician–trainee continuity.

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1 Denaro CP. Redesign versus resources; continuity lost. Intern Med J 2015; 45: 592.
The true prevalence of diabetes in hospital patients and its implications

We read with interest the article by Cromarty et al. on the effect of diabetes on hospital-acquired conditions and length of stay. They should be commended for addressing issues of crucial and increasing importance to the modern Australian health system. However, this paper raises methodological issues that require careful consideration if we are to interpret and apply its findings. The authors acknowledge that their coding-based strategy (using a pre-2012 coding standard that restricted recording diagnoses to ‘those conditions actively monitored or treated in the episode’) could potentially underestimate diabetes prevalence. However, the likely scale and importance of this effect were not made explicit. In particular, their reported 4.5% diabetes prevalence contrasts with rates of 15–35% in a recent cross-sectional diabetes prevalence survey that used active case detection in inpatients at 11 Melbourne metropolitan hospitals. Our institution Western Health (Footscray and Sunshine Hospitals), which has similar catchment population demographics to Northern Hospital (i.e. a rapidly expanding metropolitan population with high proportions from non-English-speaking backgrounds and lower socioeconomic strata), had the highest prevalence (35.1% at Western Health). We have also found similar rates (33%) in General Medical patients, using retrospective methods employing a post-2012 coding strategy to an administrative dataset. Assuming prevalence at Northern to be similar to our own, we estimate that their study may in fact have wrongly defined as many as six out of seven patients with diabetes as being ‘non-diabetic’. Therefore, the potential for their study results to be subject to differential misclassification bias is large. In particular, we wonder whether this effect may have diluted observed differences in study end-points between ‘diabetic’ and ‘non-diabetic’ groups. Notably, the ranking of the top six hospital-acquired diagnoses was the same in the ‘diabetes with end-organ sequelae’ and ‘non-diabetes (Charlson Comorbidity score ≥1)’ groups. Conversely, their allocation strategy could also have selected patients with more advanced or complicated diabetes and therefore exaggerated between-group differences (such as the overall much higher rate of hospital-acquired diagnoses in the diabetic group). As the authors also acknowledge, their pre-2012 coding definition for diabetes creates significant issues of generalisability. How are we to identify prospectively and then apply future interventions only to inpatients whose diabetes is ‘actively monitored or treated in the episode’? A simple, broad and inclusive definition (i.e. ‘patients with known diabetes’) is much easier to apply. We also question the appropriateness of analysis of variance and linear regression to analyse length of stay data (which usually has a highly skewed distribution). The authors do not comment on whether necessary assumptions (linearity, normality, independence and homoscedasticity) were met.

Unfortunately, the sorts of research questions that arise in this area are generally poorly amenable to conventional prospective research designs. By contrast, retrospective studies utilising administrative datasets are logistically feasible but throw up a host of methodological challenges. It is important that studies such as this are published so that we can address these challenges and work to improve study designs and analytical methods.

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References


Author reply

We agree with Somarajah et al.1 that our study2 should not be used to estimate the prevalence of diabetes in the inpatient population; however, this was not our aim. We sought instead to estimate the rates and types of hospital-acquired diagnoses and their effects on length of stay for patients identified with the most severe diabetes in routine hospital data. Our study is clearly not a basis for estimating prevalence of diabetes, which the contemporaneous paper by Bach et al.3 does very well.

As their letter points out, and as we acknowledge at several points in our research report, the cases we identified were those where diabetes required active treatment or monitoring. As such, we did not include in our sample those cases of diabetic patients controlled with diet or oral medications. We do not consider this to be a ‘mis-classification’ of diabetes patients, but rather an issue in generalising our findings to the broader diabetes population in hospital.

However, we have every confidence that patients in our sample with end-organ sequelae of diabetes or other symptoms that require active in-hospital treatment are clinically identifiable and were in fact correctly classified. This, we believe, is the most valuable group to identify and assess, as these patients attract the largest proportion of health funding and hence are the group that has the greatest potential for improvement. Interventions focused on changing care of all diabetes patients may not be useful or cost-effective. As the authors of the letter note, the effect of any ‘under-identification’ of the broader diabetes population would be a conservative one, that is, to ‘dilute’ the differences between our sample patients and the general inpatient population. We regret terming the latter the ‘non-diabetes group’ but found it difficult to come up with a concise alternative.

This is a foundation study assessing the inpatient complications among the diabetic population, which aimed to provide a basis for future in-depth analysis of these patients. The next stage of our research is to collaborate with clinicians on interventions to identify and reduce occurrences of inpatient complications, and to introduce hospital-based auditing systems to better identify patients most at risk.

We did not extend the manuscript with a defence of our statistical approach to the analysis. We rely on Lumley et al.’s evidence from simulations4 that parametric assumptions can be relaxed for large public health data sets such as ours, allowing use of analysis of variance and linear regression on skewed data.

We wholeheartedly endorse the authors’ observation that ‘studies such as this’ should be published to improve study designs and analytical methods for research that is not amenable to conventional prospective research designs. We stand by our design and methods in finding that patients with end organ sequelae of diabetes suffer common hospital-acquired complications at 7–10 times the rate of similarly comorbid patients and have lengths of stay significantly extended both by their diabetes and by their hospital-acquired complications.

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References


Systemic lupus erythematosus patients and tertiary specialist care – simple considerations dropping through the cracks: osteoporosis monitoring as an example

We read with interest the paper by Nikpour et al.1 noting the lack of Australian epidemiological data for lupus treatment.

As lupus and its treatments directly impact on osteoporosis, we expect that tertiary lupus specialists be actively aware of this common comorbidity and their patients’ routine bone monitoring investigations followed, whether these are conducted in hospital or externally by general practitioners. We recently reviewed rates of osteoporosis monitoring in a tertiary hospital cohort of well-defined systemic lupus erythematosus patients under non-endocrinological specialist care, identifying significant gaps in practice in this at-risk group.

The monitoring aspects were presence of documented bone densitometry (DXA) and biochemical markers of bone turnover to determine the level of active awareness of this co-morbidity in our patient cohort.

Between 2002 and 2010, 2325 positive anti-dsDNA antibody tests were performed by the state public pathology provider in Western Australia. Removing serial results on the same patient, and patients not seen in the tertiary hospital system, we identified 271 potential subjects, for whom 190 medical records were available for review. This confirmed 103 subjects had systemic lupus erythematosus and ongoing tertiary hospital care. Paediatric patients, patients not seen at least four times in the tertiary clinics and patients with discoid lupus, drug-induced lupus, rheumatoid arthritis, overlap syndrome or inflammatory bowel disease were excluded.

Our population was mostly female (87.4%) with a median age of 44 years (interquartile range 34.5–55.5 years) and rheumatological (82%), cutaneous (79%), bone marrow (56%), renal (51%) or serosal (29%) disease manifestations. This cohort was cared for by immunology and/or rheumatology (87%), with renal medicine (33%) or other specialities (dermatology, haematology, neurology) in 12% of patients overall. Overall, 30% of patients were under the care of more than one treating team.

A single DXA was performed in 27% of subjects, and more than once in 37% with no difference in frequency between males and females. A comparison of the percentage of patients with multiple serum measures, as opposed to a single measurement, of calcium (71% vs 88%), vitamin D (47% vs 63%), parathyroid hormone (18% vs 37%) and fasting metabolic bone studies (14% vs 23%) suggests that monitoring over time for these indices may also be lacking. The relative frequency of serial DXA scans correlated positively with the duration of prednisolone treatment (normalised to time under observation since 2002) (Spearman’s R = 0.51, P < 0.0001) indicating that awareness of glucocorticoid-induced osteoporosis may at least be present. If traditional risk factors for osteoporosis were documented, then we noted a correlation with ordering of all monitoring tests at least once (R = 0.23, P = 0.03) or serially (R = 0.32, P = 0.003); however, patients were not more regularly monitored if under shared care compared with being under a single non-endocrinological speciality (P = 0.9).

As the purpose of this audit was evaluation of tertiary hospital care, there is potential bias in patient selection, which may not reflect care provided outside of the hospital setting; however, as an indicator of non-endocrinological specialist awareness and management of a co-morbidity associated with active lupus, it indicates management we can improve on in Western Australia.

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