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Hip fractures: a deadly and silent epidemic

Jean-Claude Theis

Each year, about 3–4,000 hip fractures occur in New Zealand,[1] and the death rate (over 12 months) worldwide following hip fracture injury has been reported at between 20% and 35%.[2–4]

In New Zealand, very little published data on mortality and morbidity following neck of femur fractures exists to date. In this issue of the *Journal,* the article by William Young et al (*Audit of morbidity and mortality following neck of femur fracture using the POSSUM scoring system*. URL: http://www.nzma.org.nz/journal/119-1234/1986) is very timely as it highlights this life-changing and sometimes life-ending event amongst elderly New Zealanders.

A report by the New Zealand Health Information Service,[1] analysing hospital discharge data for the 1999/2000 period, showed an alarming mortality rate of 27% within 1 year following a neck of femur fracture. With an expected number of deaths of around 10%, the actual hip fracture related mortality was 17%.

With a rapidly ageing New Zealand population, the burden caused by hip fractures on the healthcare system is increasing rapidly. Sixteen percent of the population is currently aged over 60, but by 2050 this will double to just over 30%.[5] The biggest increase will be in the 85-and-over age group. As this group contributes almost exclusively to this fracture type, we can therefore expect an epidemic of hip fractures over the next 50 years in New Zealand.

The incidence of neck of femur fractures has increased in the last decade by 40% in men and 50% in women according to in a study carried out in New South Wales, Australia.[6] This trend is likely to continue in the future.

Young et al look at the value of a clinical severity score (POSSUM)[7] in assessing mortality and morbidity following hip fractures over a period of 6 months. They report a morbidity of 58% in these elderly patients on the basis of age and comorbidities. The mortality was 12% at 30 days and 32% at 1 year (six-fold increase over predicted mortality).

The POSSUM system sorts patients into risk categories which is useful for comparing hip fracture mortality between hospitals. Unfortunately this scoring system cannot be used as a preoperative predictor of postoperative outcomes in individual patients, however.

A medical condition with such high mortality and morbidity (affecting the very frail of our community in a rapidly rising manner) must deserve more attention from our healthcare system. The causes of hip fracture mortality are well known and include age, severity of comorbid conditions, mental status, and delay in time to surgery. The only factor which we can really influence is the time to surgery.

A recent multicentre study in the United Kingdom[8] reported that 40% of procedures were performed more than 24 hours after admission. Delay was associated with an

increase in hospital mortality even after adjustment for comorbidity. The authors recommended that hip fracture patients be operated on within 24 hours of admission if at all possible. Similar delays in access to surgery occur in New Zealand hospitals.

Another issue which needs to be addressed is the perioperative management of these patients which is often left to the most junior members of the clinical teams. Shared care between geriatricians and orthopaedic surgeons has been suggested as a way of improving the outcome in hip fracture patients, and a recent paper from Christchurch[9] reported a significant reduction in inpatient mortality as a result of such a model. However it remains unclear at this stage whether this will translate into a reduced mortality at 1 year.

I believe that it is time now to develop a National Hip Fracture Strategy which will guide the future prevention and treatment of hip fractures in this country. Such a strategy should aim at reducing the incidence of hip fractures by developing a national osteoporosis and falls prevention programme as well as improving postoperative outcomes and long-term quality of life by setting up dedicated multidisciplinary hip fracture teams in our hospitals with strong rehabilitation and community links.

Hip fractures disable and kill: let's act now to control this silent epidemic!

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Older people and after hours care

Ngaire Kerse, Martin Connolly

The population demographic projections ensure that health issues of older people will be a focus for research, health service planning, and provision for at least the rest of this century. Longevity has increased by 10 years over the last half century in New Zealand and it is projected to increase by another 5–6 years by 2050.[1]

In 2002, 39% of the Vote Health budget of New Zealand was spent on 12% of the population—those over age 65 years.[2] By 2021, 18% of the population will be 65 years and over and (considering current per capita expenditure) 50% of the health budget will be needed for them alone.[2]

As the absolute number of those in the oldest age groups will increase by up to 600% over the next half century,[1] it is easy see why there are increasing calls for primary, secondary, and tertiary preventive measures with potential to prolong healthy life expectancy and reduce health expenditure.

As absolute numbers of older people increase, it will be particularly important to have a comprehensive strategy in place to meet the growing needs of the older population. After hours care is part of that need. Consultations with older people make up 23% of all GP consultations, more than expected for 12% of the population.[3] Emergency referrals from GPs also occur at up to three times the rate compared with referrals for those aged 15–54 years,[3] and illness events are not tied to convenient times of the day.

The article by Eastwood and Dowell,[4] in this issue of the *Journal*, shows that…'the *young-old* are particularly under-represented in after hours (primary health care) attendances'…as measured by examination of the two largest after hours practices in the Hutt Valley.

This finding is against the tide of evidence suggesting that consultation rates should be higher in this age group. It did not seem that the *young-old* prefer the emergency department, rather suggesting that they just don't go to the after hours providers available in the Hutt Valley region.

Do older people under-recognise important symptoms that prompt their younger counterparts to seek care after hours, or do they find it difficult to get there? As Eastwood and Dowell acknowledge, it is likely that the discrepancy is not wholly explained by purely medical modelling and that societal problems such as inadequacy of public/private transport and fear of venturing out at night are also implicated. Further qualitative work is suggested to illuminate the reasons for this.

The addition to the analysis of two large practices in the Hutt Valley that were not able to be included in the study would have been interesting. After hours in those practices was provided by the practice GPs themselves, thus potentially allowing an important comparison between two of the ways after hours care is delivered. The Eastwood study was also not longitudinal and there was no examination of outcomes of care (and thus causality cannot be implied).

Simultaneous presentations to the emergency department after hours for older people were recorded as resulting in greater admission rate (not surprising in itself) but also as having greater severity (assessed by triage codes) than those for younger people.

Well documented age-related physiological differences in the appreciation of symptoms such as bronchoconstriction and thirst (dehydration) can surely explain only a minority of the difference observed by Eastwood and Dowell. Thus, potential for more accessible after hours primary care visits to mediate these admissions seems possible.

Since 1988/89, ambulatory sensitive hospitalisations (those that would reasonably be expected to be reduced by appropriate primary care) have increased at a higher rate than unavoidable hospitalisations for those aged 65–74 (4.8% average annual increase compared with 2.8% for unavoidable admissions).[5]

Is there capacity to make after hours care more accessible and acceptable for older people? Gone are the days when a phone call after hours about a health issue was answered by a known voice. Equally remote is the possibility of actually being seen by someone at night who knows you well.

Today's graduates hesitate to commit themselves to a professional lifetime of full time work in one community.[6] Consequently, this increasingly threatens longitudinal continuity and the provision of after hours care to enrolled populations.[7]

The difficulties with negotiating adequate and appropriate after hours care are well documented.[8] Primary care has evolved from high levels of round-the-clock continuity between individual providers and their patients to more moderate levels of continuity with groups of providers, with after hours cover provided by a completely different organisation. Although Eastwood and Dowell did not attempt to consider outcomes, perhaps one consequence of this change is that older people avoid consulting after hours—to the detriment of their health.

New Zealand's *Health of Older People Strategy* calls for a continuum of care that is responsive to older people's diverse and changing needs and that optimises their health and wellbeing.[9] Coupled with the *Primary Health Care Strategy*,[10] which aims to provide integrated and accessible services in the community, implementation has the potential to ensure accessible, acceptable after hours care for older people.

Would the simple provision of dedicated transport to and from after hours surgeries help, and if so, would such a service be cost-effective? And are schemes like the alternative provider medical services currently (and controversially) under trial in the United Kingdom needed,[11] or can the current system rise to the challenge of providing continuous, comprehensive accessible care for older people?

These questions are important and need to be answered.

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After hours healthcare for older patients in New Zealand

Anne Eastwood, Anthony Dowell

Abstract

Aims To explore patterns of general practice after hours service use in different age groups, and to identify possible reasons for any differences between older and younger people in their use of after hours services.

Methods Attendance data from two after hours clinics (AHCs) and the local hospital emergency department (ED) for 2002 were collected and analysed statistically.

Results Older people, especially the "young-old" (aged 65 to 74) used after hours health centres at a lower rate than younger adults. Older people attended the ED at a higher rate than younger adults, except for the "young-old" who attended at a similar rate. European ethnicity, symptoms resulting from an accident, and increasing severity of the illness were positively correlated with ED attendance.

Conclusions Older people presented to after hours clinics less than would be expected, especially given their greater morbidity. Older people attended the Hutt Valley ED after hours at a higher rate than younger people, but at a lower rate than in normal hours. Older people were sicker on arrival at ED (especially after hours) than younger people. These results have implications for service delivery and also equity issues as they affect older people.

Most research and policy documents relating to the health of older people focus on chronic and degenerative conditions, rather than access to, and use of, health services.[1–3] Older people suffer acute health problems and may benefit more from treatment than younger people. Campbell[4] refers to the "threshold effect" in which many older people are close to a point where further small losses of function will seriously affect their independence. Thus it is important to determine how older people use acute care services and whether there are barriers to their access.

Little research into ED and after hours clinic-use exists, and most of it is not specific to older people and is conducted outside New Zealand.[5,6.] In the UK, Foster et al[7] found that a stoical attitude towards health, difficulties with transport, reluctance to go out at night, and a preference for a familiar doctor were factors contributing to a reluctance amongst the elderly to seek after hours medical care.

The absence of accurate New Zealand prevalence data for attendance at after hours services in this older age group indicated a need to explore this issue. . There was also anecdotal evidence from the Hutt Valley area of New Zealand that some older people were deferring seeking healthcare when they became unwell after hours, with resulting adverse consequences for their long-term health.

Methods

The research was conducted in the Hutt Valley where 11% of the 131,000 residents were aged 65 and over (compared with 12.9% of the New Zealand population) and where there is a somewhat higher standard of living than the New Zealand average.[8–10] Existing sources revealed that Lower Hutt was

relatively under-doctored, with Wainuiomata having a particularly low number of general practitioners.[11] The leading causes of hospitalisation and mortality for the Hutt Valley were similar to those nationally.[11] The Hutt Valley District Health Board (HVDHB) had higher avoidable morbidity rates for 65 to 74 year olds than many other DHBs.[3]

Older age was defined as 65 years and over. This is consistent with New Zealand statistical data, the age of eligibility for National Superannuation, and much of the published research. "After Hours" was defined as between 1730 and 0800 hours.

Data was obtained for the year 2002, from two after hours clinics (AHCs). Information was gathered from MedTech 32 software using "Query Builder". All adult attendances were captured and broken down by gender, with the elderly group in 10-year age bands (65 to 74, 75 to 84, and 85 and over).

Information was available from all visits to the Hutt Hospital Emergency Department (ED) in 2002. The data was entered into SPSS version 10 for analysis. Chi-squared tests of association or two-tailed z tests for comparing rates[13] were carried out on selected variables. ED figures include all non-elective, non-obstetric admissions to the hospital. Patients who had been referred by a GP were therefore excluded. Not all patients who saw a GP after hours were captured, since two practices undertook their own after hours care at that time. Overall, these practices, with a combined practice population of 30,000, have a similar combined age/sex profile to the rest of the Hutt Valley.

Results

Attendance rates were reviewed from 38,979 AHC visits (comprising 34,371 visits from 15 to 64 year olds, and 4608 from those aged 65 and older),and 24,065 ED attendances (comprising 18,821 visits from 15 to 64 year olds, and 5244 from those aged 65 and older).

Attendance rates at the after hours clinics were significantly greater for older people (≥65 years) and for women. Meanwhile at after hours EDs, attendance rates for older people were greater and, unlike after hours clinics, rates for men were greater than for women. (Table 1)

The lowest AHC attendances were in the 65 to 74 year age group, at 248 per 1000 for men and 270 per 1000 for women. Modelling the relationship between after hours attendance rates and age group, gender and place of attendance using a Poisson regression showed that (compared to the youngest age group) this decrease was significant ($p<0.001$).

Figure 1 shows the arrival time patterns for older and younger people. Although the shapes of the graphs are similar, there is a significant difference in the pattern of arrival over time, with older people more likely to attend in the middle of the day and less likely to attend at night. ($\chi^2=200.0$, df=11, $p<0.001$).

Table 1. After hours attendance 2002. Rates per 1000 population[1] [2]

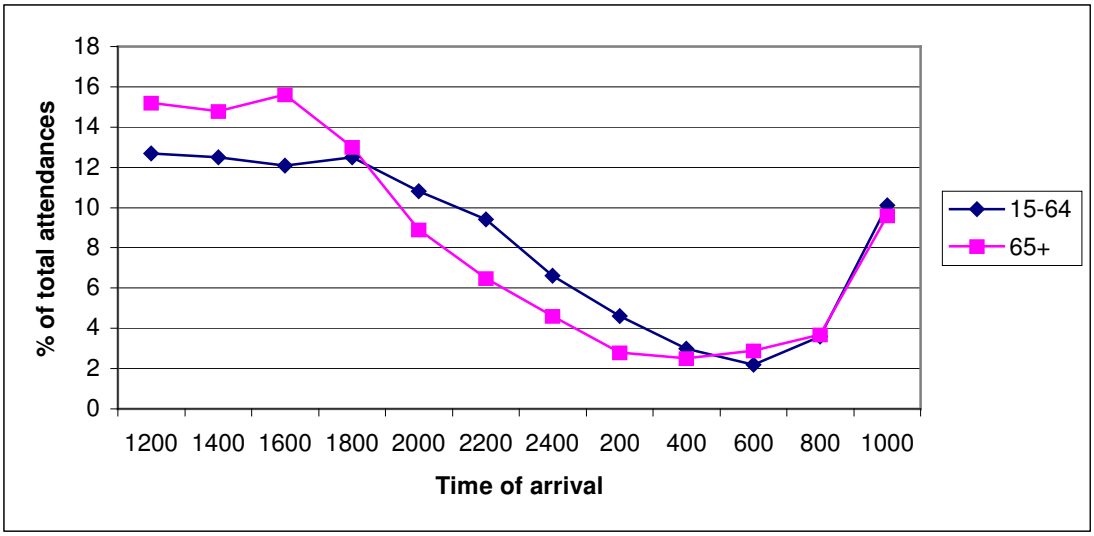
Variable		After Hours Clinics		Comparisons by Age[3]		ED (excl GP referrals)		Comparisons by Age	
		15–64	**65+**	**z**	**p**	**15–64**	**65+**	**z**	**p**
Female		473 *466–480*	331 *319–344*	19.85	<0.001	79 *67–71*	100 *93–107*	6.29	<0.001
Male		314 *309–319*	286 *274–300*	3.72	0.002	91 *88–94*	118 *109–127*	6.21	<0.001
Comparisons by Gender	**z**	37.27	4.71			20.46	3.12		
	p	<0.001	<0.001			<0.001	0.002		

[1] Rates throughout are age and gender specific, based on 2001 Census figures

[2] 95% confidence limits are shown in italics

[3] Two tailed z test for comparing rates (15)

Figure 1. Time of ED arrival by age group



A higher proportion of ED attendances by older people arrived there by ambulance after hours (63.5%) than in normal hours (47.9%) (χ^2=118.4,df=1, p<0.001.). There was a significant increase in the proportion of attendances arriving by ambulance with age, with 36.0%, 50.1%, and 68.0% of older people in the three age groups arriving by ambulance in normal hours—and 51.5%, 69.6%, and 78.1% arriving after hours (χ^2 for linear trend=248.1,df=1, p<0.001). In 2002, 23% of all arrivals at Hutt Hospital ED came by ambulance.

Although the admission rate is an index of the severity of the presenting complaints in an age cohort, it can be influenced by factors such as the availability of beds and social circumstances. The rates of admission from ED are shown in Table 2.

Table 2. Admission rates by age group 2002. Rates per 1000 population[4] (with 95% confidence limits)

Age group (years)	Normal hours (Female)	Normal hours (Male)	After hours (Female)	After hours (Male)
15–64	32 30–33	32 30–34	25 24–26	24 22–25
65–74	81 72–90	92 83–103	52 46–60	62 54–70
75–84	155 142–170	214 194–235	88 78–98	131 115–148
85+	260 232–292	331 282–389	156 134–180	180 145–224

Older people are significantly more likely to be admitted than younger people and the rate of admission increases with increasing age of older people. In all age groups, the proportion of admitted attendances is very similar in normal hours and after hours. Older men have higher admission rates than older women both in normal hours and after hours, but this difference is significant only in the 75 to 84-year-old age group.

On arrival at ED, patients are assigned a triage code indicating the severity of their condition, with code 1 being the most severe. Analysis by triage code showed similar trends to that by admission. For all age groups of elderly, a significantly higher (Chi-squared) proportion of ED attendances had triage codes 1 to 3 after hours than in normal hours (72% compared with 59% for age 65-74 (χ^2=32.6, 1 df, p<0.001) 74% compared to 62% for age 75-84 (χ^2=32.6, 1 df, p<0.001) and 70% compared with 61% for age 85+(χ^2=7.1, 1df, p=0.008)).

Attendance as the result of an accident (when an ACC form was completed) was also analysed for differences between older and younger people, and for differences between after hours and normal hours.

Older men (aged 65 and older) attended ED with accidents at a rate significantly less than that of younger men (15 to 64) both in normal hours (53 per 1000 compared with 92 per 1000 (z=9.55, p<0.001)) and after hours (14 per 1000 compared with 23 per1000 (z=10.69, p<0.001)). Older women presented with injuries at higher rates than younger women, in normal hours (63 per 1000 compared to 42 per 1000 [z=9.96, p<0.001]), but there was no significant difference after hours (22 and 24 per 1000).

The elderly population of the Hutt Valley is predominantly (91%) European, but data from the three largest minority ethnic older populations (Asian 3.7%, Māori 2.8%, and Pacific 2.6%) was also obtained.

[4] Rates throughout are age and gender specific, based on 2001 Census figures

Table 3. ED attendances by older people by ethnicity and gender. Rates per 1000 population[5] (with 95% confidence limits)

Variable	European	Māori	Pacific	Asian
Normal Hours – Female	225 (214–236)	210 (157–280)	180 (134–246)	93 (64–135)
Normal Hours – Male	243 (231–257)	388 (307–490)	213 (149–304)	120 (83–179)
After Hours – Female	123 (116–131)	237 (181–312)	147 (105–206)	50 (30–83)
After Hours – Male	137 (127–147)	224 (165–304)	234 (166–329)	115 (79–168)

Older Europeans had after hours attendance rates which were significantly different from those in normal hours. After hours, Māori, and Pacific older people had significantly higher rates of admission (134 and 122 per 1000 compared with 83 for European, $p<0.05$[(6)]) and were assigned the highest triage codes (191 and 138 per 1000 for codes 1 to 3 respectively) compared to 93 for European ($p<0.05$), but in normal hours there were no significant differences.

Older Asian people presented to ED significantly less often than other ethnic groups both in normal hours and after hours, had the lowest proportion of triage codes 1 to3 (58 per 1000 in normal hours and 59 per 1000 after hours compared with 142 and 93 for European), were admitted less often (60 and 49 per 1000 compared with 140 and 83 for European) and arrived less often by ambulance (24 and 26 per 1000 compared with 114 and 85 for European). There were no significant differences between ethnic groups in their attendance with accidents after hours.

Discussion

This paper demonstrates significant differences between different age groups in their use of after hours services, raising issues for health service planners about service provision and also about what constitutes "appropriate" demand for services at any particular time of the day or night. Given the known increased rates of morbidity with increasing age the relative low presentation by "younger" old people may represent a service gap, or reflect their ability to access services during the day.

These New Zealand findings from AHCs, are consistent with previous research conducted in the U.K by Foster et al.[7] Men and the "young-old" are particularly under-represented in AHC attendances. The 1996/7 NZ Health Survey[14] found that the "young-old" were more likely than younger people to have attended a general practitioner (GP) at least once in the previous year and to have been frequent users of GP services. It also found that older men were only slightly less likely than older women to have visited their GP in the previous year, and were more likely to be frequent attenders. The 2002/3 NZ Health Survey[15] also found high rates of GP attendance in older people. The lower attendance of the "young-old" and men at after hours clinics does not reflect the general trend in GP consultations.

[5] Rates are specific to ethnic group

[6] Significance determined by non- overlapping 95% confidence intervals for all ethnicity data.

Older people (especially men) presented to ED at a higher rate than younger people. This is consistent with findings in Australia[16] and the UK.[17] However rates for the "young-old' are similar to those for younger people. This suggests that the low rate of consultation by the "young-old" at after hours clinics does not just represent a preference for ED. Admission rates and triage codes suggest a higher rate of serious illness in older people, particularly after hours. This was also found by Chu et al[16] in Australia.

Older Europeans attended ED at much lower rates after hours than in normal hours. This trend is not seen in other ethnic groups, except for Māori men who had the highest rate of attendance in normal hours. The 2002/3 NZ Health Survey[15] also found that adult Asians accessed many health services at a comparatively low rate. The tendency to use ED for accidents has been described elsewhere.[18,19]

A particular reluctance of the "young-old" to seek after hours care does not appear to have been described elsewhere in the international literature. The low attendance of recently retired people at after hours services may be due to the relative ease with which they can access day time healthcare. The steady increase in consultation with advancing age beyond 75 should at least partly be explained by increasing morbidity and a greater tendency to live in the care of a relative or institution, which may influence the decision to seek care.

This study did not consider outcomes. It is also not known whether the pattern of attendance of either younger or older people is "appropriate". It may be that the lower use of after hours services by some groups of older people is appropriate, rather than representing a service gap. The definition of appropriate health service use is difficult.

The transferability of the current study's findings to communities outside the Hutt Valley is uncertain. While this elderly population is statistically reasonably representative of the New Zealand elderly, small differences, for example in income levels (indicated by lower than average CSC holding) could be reflected in the study's results.

The free service provided by the Wellington Free Ambulance may have had a significant effect on the use of after hours services by the Hutt Valley elderly.

Information could not be obtained from two practices providing their own after hours services. Total service use and the rates, which are based on the overall population, cannot thus be generalised to other districts in the country.

Possible reasons for the choices made by older people about accessing after hours care may include cost, transport difficulties, difficulty interpreting symptoms, and established healthcare-seeking behaviours. Given the time course of many episodes of acute illness, particularly against a background of chronic morbidity, it is possible that there is an element of stoicism by older people to "wait for normal hours". Older people may need education and encouragement to attend after hours services and GPs and other providers cannot assume that older people will respond to acute illness in the same way as younger people.

Further qualitative information is required to interpret these findings and hence work towards appropriate levels of service provision and patient education. This will be a theme of future work.

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Audit of morbidity and mortality following neck of femur fracture using the POSSUM scoring system

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Abstract

Aims The aims of this study were to compare the morbidity and mortality data for patients undergoing surgical fixation of a fractured neck of femur (during a 6-month period) to the predicted morbidity and mortality rates obtained from the POSSUM (Physiological and Operative Severity Score for the enUmeration of Morbidity and Mortality) scoring system, adapted for orthopaedic patients. The predictive accuracy of the orthopaedic POSSUM system is evaluated for this population. The 1-year mortality for the males and females of the study group (mean ages) is compared to the 1-year mortality of male and female New Zealanders of the same age.

Methods Physiological and operative data was collected from patient notes; patient morbidity and mortality were obtained at 30 days and at 1 year postoperatively. The data were analysed with the orthopaedic POSSUM scoring system.

Results 225 complete datasets were obtained. The mean age of the patients was 83 years; 75% were female. The observed 30-day morbidity and mortality rates were 58% and 12% respectively. The observed 1-year mortality was 38% for males (mean age 79 years) and 29% for females (mean age 84 years). New Zealand census data predicts 7% and 6.4% mortality respectively based on these mean ages.

Conclusions The POSSUM system allocates patients into groups of varying risk. The observed data shows higher numbers of complications, including death, in patients allocated into higher risk groups. The 1-year mortality is much higher than that predicted based on mean patient age from the New Zealand abridged life table.

Patients admitted to hospital following fractured neck of femur have a high postoperative mortality rate of between 20% and 35%[1] after 1 year. The rate in New Zealand has been published at 24%.[2] Walker found that patients from the Christchurch area had a 1-year mortality rate 30% higher than 24% (i.e. 32%). Walker's study incorporated all patients with hip fractures over age 65 years and *included those not receiving surgical fixation*.[2] We excluded conservatively managed patients, but did not exclude patients on the basis of age or mechanism of injury.

There is scant data for morbidity rates following surgery for fractured neck of femur in the literature; most studies document mortality only, or study a specific complication.

The POSSUM system was developed to allow comparative audit of outcome between different populations and subgroups of patients undergoing surgical procedures. Originally described in general surgical patients,[3] it has recently been adapted for use in orthopaedic patients.[4–6] It has also been applied to other surgical specialties,[7] with varying success and adaptations.

The scoring system is based on a set of physiological and operative variables (Table 1).[4]

Table 1. The POSSUM scoring system used for calculating the 30-day mortality and morbidity

Variable	Physiological score			
	1	**2**	**3**	**4**
Age (years)	<60	61-70	>71	
Cardiac signs	Normal	On cardiac drugs or steroid	Oedema or warfarin	Raised JVP
Chest radiograph	Normal		Borderline cardiomegaly	Cardiomegaly
Respiratory signs	Normal	SOB exertion	SOB stairs	SOB rest
Chest radiograph	Normal	Mild COAD	Moderate COAD	Any other change
Systolic BP (mmHg)	110 to 130	131 to 170 100 to 109	>171 90 to 99	<89
Pulse (/min)	50 to 80	81 to 100 40 to 49	101 to 120	>121 <39
Coma score	15	12 to 14	9 to 11	<8
Blood urea (mmol/L)	<7.5	7.6 to 10	10.1 to 15	>15.1
Blood Na (mmol/L)	>136	131 to 135	126 to 130	<125
Blood K (mmol/L)	3.5 to 5	3.2 to 3.4 5.1 to 5.3	2.9 to 3.1 5.4 to 5.9	<2.8 >6
Hb (g/100ml)	13 to 16	11.5 to 12.9 16.1 to 17	10 to 11.4 17.1 to 18	<9.9 >18.1
White cell count ($x10^{[12]}$/L)	4 to 10	10.1 to 20 3.1 to 3.9	>20.1 <3	
ECG	Normal		AF (60 to 90)	Any other change
Variable	**Operative severity score**			
	1	**2**	**3**	**4**
Magnitude	Minor	Intermediate	Major	Major+
Number of operative variables within 30 days	1		2	>2
Blood loss per operation (ml)	<100	101 to 500	501 to 999	>1000
Contamination	None	Incised wound (i.e. stab)	Minor contamination or necrotic tissue	Gross contamination or necrotic tissue
Presence of malignancy	None	Primary only	Node metastases	Distant metastases
Timing of operation	Elective		Emergency Resuscitation possible <48 hours	Emergency Immediate <6 hours

Two equations are employed to convert the individual's scores into predictions of morbidity and mortality for the 30-day postoperative period. For comparison, observed morbidity and mortality should be collected for the first 30 days

postoperatively; morbidity is defined by a standardised list of complications.[3] The predicted morbidity and mortality allows stratification of patients into groups with similar risk probability.

The POSSUM system was designed to provide a 30-day postoperative prediction which could then be compared to observed rates taking into account case mix. The ratio of observed to predicted morbidity and mortality allows comparisons between individual surgeons or surgical units and for comparison of rates over time.

Methods

Data was initially collected prospectively over 6 months, but was incomplete—largely due to the number of variables requiring recording. Therefore a retrospective search for patients having femoral fractures in the orthopaedic procedure database was completed. The notes of patients undergoing surgical fixation within the 6-month period were then reviewed. Only patients undergoing surgery for fractures of the femoral neck were included.

The final 6 month population undergoing surgery was 249 patients. Of these, data was incomplete or absent for 24 patients (in most cases due to unavailability of patient notes), thus resulting in a population of 225 patients. Data was collected from the operating theatre data set; the number of patients receiving conservative management in this period is not known. A separate audit in the hospital (within 1 year of this data collection period) revealed a 2% preoperative mortality rate in this group of patients.

The operative and physiological variables required for the orthopaedic adaptation of POSSUM[3,4] were collected from patient notes. Physiological variables were collected as close to time of surgery as possible.[3] The scores were totalled and the original POSSUM equations were used to produce individual morbidity and mortality scores.

Each of the physiological and operative variables are scored on an exponential scale with three or four bands, with a minimum score of one point and a maximum of eight points, depending on the degree of physiological abnormality or surgical insult. A score of 1 (i.e. normal result) was recorded for a variable if investigations were not performed or the results were unavailable.

The patients' general practitioners and rest homes were individually contacted to collect a 30-day outcome for each patient. Complications described in the Orthopaedic POSSUM scoring system were collected. These morbid events range from minor to severe, and comprise both medical and specific orthopaedic complications. Examples include postoperative haemorrhage, infections at any site, cardiac events (including infarction or heart failure), thromboembolic phenomena, and specific problems such as wound breakdown or prosthetic dislocation.[4] This provides comparative data to test the predictive accuracy of the POSSUM system.

Further analysis was modelled on that detailed in Copeland's initial study,[3] with generation of standard receiver operation characteristic (ROC) curves.

The New Zealand Health Information Service provided 1-year mortality data for our dataset.[8]

Results

Our population thus comprised 225 patients, with a mean age of 83 years and a median age of 87 years. Of these, 75% were female with a mean age of 84 years; the mean male age was 79 years.

Of the 225 patients, 158 (70%) suffered an adverse event, 131 (58%) patients had recorded complications, and there were 27 (12%) deaths within the 30 days of surgery. The 1-year mortality was 71 patients (32%).

Using the POSSUM equations, the predicted morbidity and mortality was calculated for each patient. These figures were allocated into risk bands for analysis, and receiver operation characteristic (ROC) curves were compiled from the sensitivity and

specificity of the comparison between observed and predicted outcome in each risk band. This was modelled on the analysis described in Copeland's original paper.[3]

The predicted life expectancy for our population was derived from data in the New Zealand 2000–2 abridged life tables.[8] The mean age of the female study population is 84 years. This equates to a continued life expectancy of 7 years and a 7.2% chance of dying within 1 year. For the male study population, mean age of 79 years, and the life expectancy is very similar at almost 8 years (with a 6.4% chance of dying during the following year). Our observed 1-year mortality rate was 32% across the whole population; male patients had a 38% mortality rate and female patients had a 29% mortality rate (Tables 2 and 3; Figures 1 and 2)

Table 2. Mortality at 30 days postoperation

Predicted risk of event % (i.e. risk band)	Observed rate % [total number of patients in group]
>30	21.6 [51]
26–30	25.0 [16]
21–25	13.0 [23]
16–20	0.0 [25]
11–15	13.2 [38]
6–10	4.3 [47]
0–5	8.0 [25]

Table 2. Morbidity at 30 days postoperation

Predicted risk of event % (i.e. risk band)	Observed rate % [total number of patients in group]
>79	76.1 [67]
70–9	51.6 [31]
60–69	67.7 [31]
50–59	62.5 [24]
40–49	50.0 [26]
30–39	47.8 [23]

Figure 1. Receiver operation characteristic (ROC) morbidity

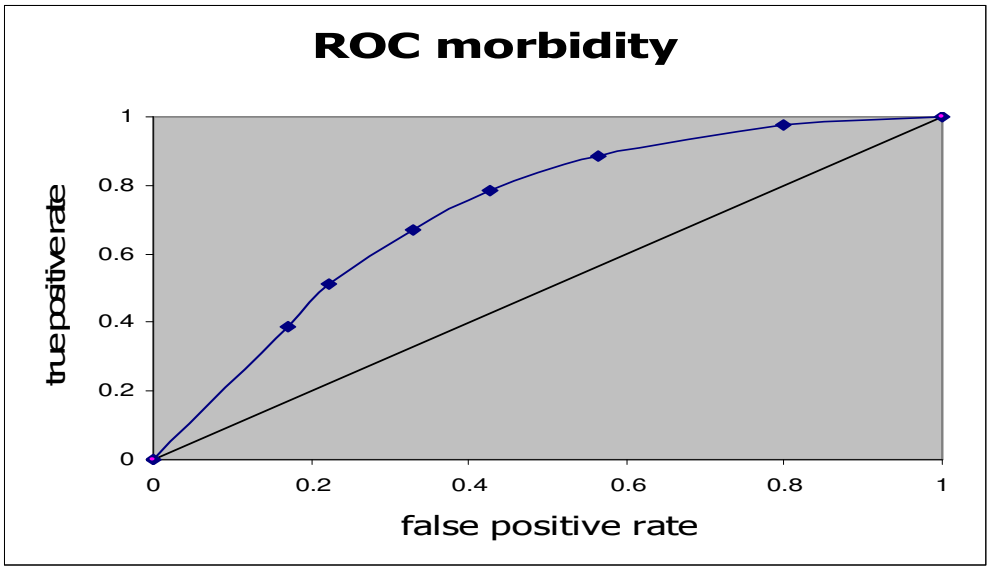
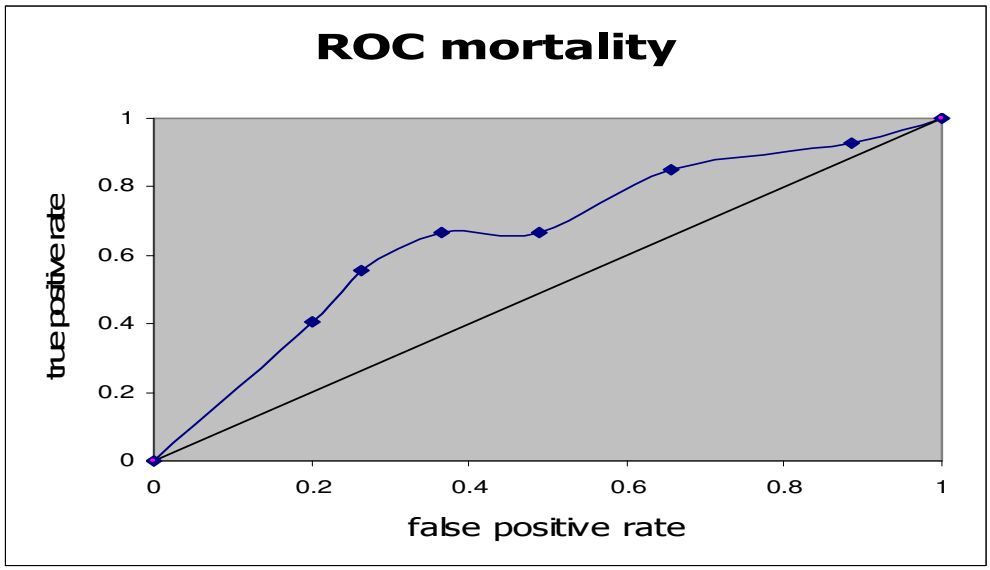


Figure 2. Receiver operation characteristic (ROC) morbidity



Discussion

The POSSUM scoring system provides a means for calculating the 30-day mortality and morbidity for a population of patients. The system was developed through collection of extensive patient data pre- and intraoperatively, observing the morbidity and mortality, and then using logistical regression analysis to develop the POSSUM equations.[3] It was designed as a retrospective audit tool, not as a predictor of morbidity or mortality, and was designed to be applied to groups of patients rather than individuals. The requirement for intraoperative data renders it unsuitable for preoperatively predicting postoperative outcome.

The POSSUM scoring system does allow comparison between cohorts of patients. Individual predictions of outcome following surgery for neck of femur fracture can be made based on ASA status,[9–11] type of fracture,[12,13] confusion status,[10] or site of residence prior to injury.[14]

From our audit, the POSSUM scoring system provides a useful assessment of both the morbidity and mortality, with patients allocated to arbitrary 'risk bands'. There is a degree of over-prediction of both morbidity and mortality with this dataset. This is not unique to our study.[6,7,15] The exponential methods of analysis used in the P-POSSUM equations[16] have produced more accurate predictions of morbidity and mortality[6,7,15] than the linear methods used in POSSUM.[3]

The weighting of POSSUM scoring variables may also be a factor. Most of our patients scored maximum points based on their age (greater than 71 years), points from electrocardiograph (abnormalities other than rate controlled atrial fibrillation score maximally), and the operative magnitude scores all of these patients as a 'major' procedure. It is also apparent that the accuracy of prediction could be greater with

greater numbers of patients within each risk band. The caveat to this is that if our risk bands are widened to increase numbers in a group then predictive accuracy is reduced.

In this group of patients, the sensitivity and specificity of the scoring system is less than that in the original study,[3] and the orthopaedic application of the POSSUM system.[4] However, a more recent study applying the POSSUM system to patients with fractured neck of femur[6] shows results very similar to the present study, with very similar ROC curves. However, this group[6] did not collect physiological data at time of surgery (as originally described[3] and as in the present study), but at time of admission to hospital. Significant changes in some of the physiological markers may occur between the time of admission and operation, which makes direct comparison to similar studies difficult.

The issues arising from sensitivity and specificity are exacerbated by the relatively small numbers of patients followed in the present study. Other studies involving POSSUM have used 1372,[3] 2326,[4] and 1164[6] patients. Those using smaller numbers of patients or higher risk groups have often adjusted the scoring system in various ways in order to improve the correlation between observed and predicted results (e.g. P-POSSUM, V-POSSUM, RAAA-POSSUM).[16–19]

The small numbers involved means that the accuracy of the present study is limited, but highlights the difficulty involved in applying any scoring or prediction system to a relatively small patient group. Unfortunately in New Zealand this may limit the applicability of this scoring system to large or multicentre audits, or require the use of extended durations of study to generate sufficient patient numbers.

Our population appears to be fairly typical of patients suffering from fractures of the femoral neck, with a mean age of 83 years, and 75% female patients. When considering 1-year mortality in comparison with the 1-year mortality based on the mean ages by gender, a marked difference is seen. The male patients' 1-year mortality is predicted at 6.4%;[8] but following this surgery, the 1-year mortality is 38%, an almost six-fold increase.

Female patients fare slightly better, with a 1-year mortality predicted at 7%[8] but observed is still over four times greater at 29%. These observed figures are similar to others from the literature.[20–22] This study confirms that the sequelae from what often begins with a simple fall persist far beyond a single hospital admission and a journey through the operating theatres.

Neck of femur fracture is a life-changing event for elderly patients. In many it becomes a life-ending event.

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Nocturia in adults: draft New Zealand guidelines for its assessment and management in primary care

Mark Weatherall, Ted Arnold

Abstract

Nocturia is a common bothersome condition. An ad hoc group of interested clinicians from a variety of backgrounds has developed draft guidelines for the assessment and management of this condition in primary care in New Zealand. The guidelines propose four steps in the assessment and management: clinical evaluation; simple investigations; assignment of a provisional diagnosis; and management based on the provisional diagnosis.

For nocturnal polyuria-associated nocturia, the draft guidelines recommend that: lifestyle measures should be used as part of the management; if a patient complaining of nocturia has other features of overactive bladder, then bladder retraining and/or anticholinergics can be used; hypnosedatives should not be used to treat nocturia in older adults because of the increased risk of falls; loop diuretics given in the afternoon should be considered for the treatment; and desmopressin can be considered in the management of nocturnal polyuria associated nocturia but that it should be used cautiously in people aged over 65 because of the risk of hyponatraemia. A draft algorithm based on international guidelines is presented.

Nocturia has been defined recently by the International Continence Society (ICS) as a complaint whereby the individual has to wake at night one or more times to void.[1]

The prevalence of nocturia in the community is high and it increases with age in both sexes, although the literature in this area must be considered carefully as rarely does the study definition of nocturia correspond to that of the ICS and different studies use a variety of different methods to ascertain nocturia.

In a study from the Netherlands using the current ICS definition, nocturia was experienced by 17% of men aged 18–34, by 34% of men aged 35–54, by 62% of men aged 55–74, and by 80% of men aged over 75 years. The figures for women similarly increased with age. Nocturia was noted by 36% of women aged 18–34, by 51% of women aged 35–54, by 86% of women aged 55–74, and by 77% in women aged over 75 years.[2] Similar findings, albeit with different definitions of nocturia, have been demonstrated in other studies.[3–7]

Nocturia is a bothersome condition and the impact of nocturia may be substantial. In surveys where the individual symptoms are rated according to degree of 'bother', nocturia is rated almost as highly as incontinence. For those with the problem, around two-thirds rate it as at least a bit of a problem.[8–14] Moreover, questions about nocturia are a common feature of lower urinary tract, condition-specific, quality of life questionnaires.[11,15–17]

Nocturia has been associated with falls,[18] poor sleep patterns,[19,20] and mortality.[21] In addition, evidence shows that nocturia affects quality of life.[22] There is likely to be considerable individual variation in the impact of nocturia however.

The purpose of these guidelines is to propose a framework for the assessment and management of nocturia in adults, together with a clinical algorithm to form the basis for guidelines for management in primary care in New Zealand.

Methods

These New Zealand guidelines have been developed by an ad hoc committee of interested clinicians with backgrounds in general practice, urology, geriatrics, urotherapy and continence advice, nephrology, and clinical pharmacology. Membership details are provided in Appendix 1.

These guidelines and their recommendations are concordant with the international guidelines developed by a group of international interested urologists, gynaecologists, endocrinologists, geriatricians, general practitioners, urotherapists and continence advisors, and experts in sleep disorders and their management, who participated in the *International Consultation on Nocturia* conference in London in 2002, as well as a second one in Malta in 2003.

Definitions and terminology used are as recommended by the International Continence Society and its Standardisation Committees.

Treatments for nocturnal polyuria, to be discussed in the body of the guideline, were assessed using levels of evidence for treatment, graded according to the Oxford classification.[24]

The guidelines

We propose a four-step approach to the assessment and management of nocturia:

- **Clinical evaluation.**
- **Investigations.**
- **Assign a provisional diagnosis.**
- **Specific management.**

Clinical evaluation

The following clinical factors should be assessed in people complaining of nocturia. History-taking may identify these factors. Fear of cancer (particularly of prostate cancer in men) may need an appropriate clinical evaluation.

Ageing is associated with nocturnal polyuria, an overactive bladder, and changes to anti-diuretic hormone (ADH) production, as well as with other sodium ion homeostatic mechanisms.[25–29]

The presence of other lower urinary tract symptoms (LUTS) should prompt consideration of bladder outlet obstruction, chronic urinary retention, overactive bladder, detrusor over-activity with impaired contraction,[30] neurological disorders, and other pathological processes affecting the lower urinary tract.

Haematuria is an important symptom that may require further urological or nephrology investigation. Sleep-disordered breathing can be associated with altered atrial natriuretic peptide (ANP) secretion,[31,32] and nocturia. Pregnancy[33,34] and the menopause are associated with nocturia, although the role of the hormone replacement therapy for the nocturia associated with the menopause is uncertain.[35]

Although urinary tract infections can cause nocturia, symptoms should resolve between infections. Bacteriuria without symptoms is quite common in older women and this may cause diagnostic difficulty.

Other health problems such as congestive heart failure, peripheral oedema, chronic renal disease, and sleep disorders may all be associated with the complaint of nocturia. Pelvic pathology such as pelvic organ prolapse may account for nocturia,[36,37] and pelvic masses or tumours in adjacent organs may be associated with LUTS including nocturia. Some clear-cut causes of excess urine production include diabetes mellitus, diabetes insipidus, and hypercalcaemia. Medication and other ingested substances may also cause nocturia.

Clinical evaluation should then include a physical examination. This should include both a general physical examination relevant to nocturia, and targeted examination to further assess features identified by history-taking.

The clinical examination should specifically include (where appropriate) assessment of the presence of heart failure or peripheral oedema, an abdominal examination for the presence of a distended bladder or other abdominal and pelvic masses, and a focussed neurological examination. The neurological examination must include assessment of the plantar reflexes. A pelvic examination should be performed in women, although it is recognised in primary care that not all practitioners are confident in the full assessment of prolapse as it might reveal atrophic changes in the post-menopausal patient. In men, a digital rectal examination is particularly important in the assessment of the prostate gland.

Investigations

Urinalysis and simple blood tests are recommended in all people complaining of nocturia. A bladder diary is recommended if the clinical evaluation, urinalysis, and simple investigations do not result in a provisional diagnosis. If other disorders are identified by the clinical evaluation then these should be investigated as appropriate.

Urinalysis—An abnormality on urinalysis should be further investigated and managed depending on the pattern of abnormality. Symptomatic urinary tract infections should be treated although as noted the prevalence of asymptomatic bacteriuria is high in older women. It is particularly important to evaluate haematuria as it may have an important urological cause such as malignancy. Haematuria may also indicate a renal abnormality.

Simple blood tests—These should include glucose and calcium levels to identify these substances causing solute (osmotic) diuresis.

Bladder diary—This is a record of the time and volume of all urine passed during 24 hours. Any incontinence episodes should also be recorded. To overcome daily variations, keeping this diary for 3 consecutive days and nights is preferred.

Assign a provisional diagnosis

A provisional diagnosis can often be made based on the results of the clinical evaluation and simple investigations. If these fail to provide a diagnosis, then a bladder diary can distinguish between global polyuria, nocturnal polyuria, or reduced functional bladder capacity, as discussed below.

Global polyuria—The bladder diary may show global polyuria defined as a 24-hour output of more than 2.8 litres.[38] An alternative definition is urine output exceeding 40 ml/kg/day, for example 3.2 litres for an 80 kg adult. Global polyuria can be caused by a water or solute (osmotic) diuresis, which can secondarily increase the thirst and hence the water intake.

The best way to distinguish between water and solute diuresis is the urinary osmolality, which will be greater than 1010 mosmol/kg in solute diuresis and less than 1010 mosmol/kg in water diuresis. It can also be caused by excessive thirst and drinking, dipsogenic polyuria, which is usually psychogenic or behavioural.

Water diuresis—

Primary dabetes insipidus. Failure of pituitary secretion of ADH results in failure of the kidneys to retain water appropriately—with consequent polyuria. It responds to administration of desmopressin, and modest fluid restriction.

Nephrogenic diabetes insipidus. This can result if the renal collecting tubule becomes insensitive to the circulating ADH. Prescribing desmopressin produces no benefit.

Dipsogenic diabetes insipidus. This is caused by excessive thirst, which may be psychogenic or behavioural, and the large urine output is a physiological response to the huge water intake. Prescribing desmopressin is dangerous in this condition as the patient will keep on drinking and the antidiuretic effect prevents the elimination of the excess water that is needed. Water intoxication may follow. Treatment usually requires psychiatric and endocrinology expertise.

Solute diuresis. Osmotically-active substances such as glucose, albumin, and calcium may induce a solute diuresis—the associated water loss tends to produce dehydration, and thirst to correct it. This may need to be quantified in a 24-hour output study, as well as measuring these substances in the blood.

Nocturnal polyuria—The bladder diary may show nocturnal polyuria. Nocturnal urine production is measured as the volume of urine produced excluding the voided volume immediately before retiring, but including the volume of the first void in the morning. There is no widespread agreement as to the definition of nocturnal polyuria. One definition of nocturnal polyuria included a night-time output of more than 0.9 ml/minute,[39] where night is defined as time spent in bed with the intention of sleeping, as recommended by the ICS.

Another definition includes adjustment for body weight, for example as greater than 10 ml/kg of urine produced during the night.[40] This would mean a rather large volume (greater than 800 ml) for an 80 kg person, compared to around 450 ml by the definition of greater than 0.9 ml/minute.

Other definitions are based on relative criteria. For example by dividing the full 24 hour period into one 16-hour period and one 8-hour period: (0600–2200, and 2200–0600). The ICS definition suggests that the nocturnal volume should be approximately 22% of the total 24-hour output in younger patients, but this should be less than 33% in older subjects.[41] The relative definition is appropriate only if the 24-hour volume is within normal limits.[39]

Reduced functional bladder capacity—The bladder diary may show nocturia without polyuria. This suggests a reduced functional bladder capacity (FBC). The

normal range of FBC is 300–450 ml, smaller for older adults and slightly higher for women than men. The causes of reduced FBC include detrusor over-activity, bladder inflammation with or without fibrosis, and other pelvic pathology, such as pelvic masses.

Specific management

Specific management should reflect a specific diagnosis. The ad hoc committee did not rate management based on specific diagnoses, for example global polyuria associated with ADH deficiency due to pituitary disease, or nocturia related to bladder outlet obstruction in men. However the ad hoc committee felt it important to rate some commonly used treatments in primary care for nocturnal polyuria-associated nocturia. These treatments include lifestyle measures, management of the overactive bladder, sleep enhancement strategies, loop diuretics, and desmopressin.

Lifestyle measures—Although the principle of fluid restriction by type (for example tea, coffee, and alcohol) and volume near retiring to bed seems sensible, studies to confirm the effectiveness of this strategy could not be identified.[25,35]

The recommendation of the *International Consultation on Incontinence*[35] was that: conservative management of nocturia, whilst lacking hard data appear nonetheless to be effective or helpful to many patients.

Recommendation 1: Lifestyle measures should be used as part of the management of nocturnal polyuria associated nocturia. (Grade of Recommendation D, Level of evidence 5.)

Management of the overactive bladder—

Bladder retraining. Several studies have found a reduction in nocturic episodes for patients on bladder retraining programs, supplemented at times with anticholinergic drugs.[42,43]

Recommendation 2: If a patient complaining of nocturia has other features of overactive bladder then retraining can be used. (Grade of Recommendation C, Level of Evidence 4.)

Antimuscarinic drugs. These include oxybutynin, and tolterodine (Detrusitol). Tolterodine is not publicly funded in New Zealand. It has an efficacy similar to oxybutynin, but has fewer adverse effects; hence more patients can tolerate the drug in the longer term. Both drugs are effective for nocturia as part of the management of the overactive bladder.[44]

Recommendation 3: If a patient complaining of nocturia has other features of overactive bladder then anticholinergic agents can be used. (Grade of Recommendation A, Level of evidence 1.)

Sleep enhancement—General measures to improve sleep include avoidance of stimulants like coffee or alcohol close to retiring, and treatment of specific mental health conditions such as depression and anxiety. If sleep-disordered breathing is present, it should be treated appropriately.[45]

The use of psychoactive drugs, such as hypnosedatives and tricyclic antidepressants, has been considered;[46] however, these agents are associated with an increased risk of

falls particularly in older adults.[47] Indeed, one randomised controlled trial discovered that withdrawal of psychoactive medication decreased the rate of falls.[48]

Recommendation 4: Hypnosedatives should not be used to treat nocturia in older adults because of the increased risk of falls. (Grade of Recommendation B, Level of evidence 2.)

Loop diuretics—Diuretics in the afternoon, about 6 hours before retiring, might enable excess body water to be eliminated before the person retires.[49,50]

The *International Consultation on Incontinence*[35] recommended that use of loop diuretics given in the afternoon to get rid of any postural oedema should be considered for further therapeutic trial since it is a simple and effective treatment in some patients provided they are screened and monitored for postural hypotension and electrolyte disturbances.

Recommendation 5: Loop diuretics, given in the afternoon, should be considered for the treatment of nocturnal polyuria-associated nocturia. (Grade of recommendation B, Level of Evidence 2.)

Desmopressin—Desmopressin is an analogue of vasopressin with effects like anti-diuretic hormone (ADH) but without any vasopressor effects. Its use has been recommended for persistent primary nocturnal enuresis in children, and for healthy younger adults with nocturnal polyuria, where no treatable cause is found.[51]

Both nasal desmopressin and oral desmopressin (which has poor oral bioavailability) have been used in randomised controlled trials of the treatment of nocturia,[52,53] with reductions in the nocturnal urine volume and the number of nocturnal voids. However there is a risk of hyponatraemia associated with the use of desmopressin particularly in older adults.[54] The manufacturers do not recommend its use in adults aged over 65 years.

Hyponatraemia with the use of desmopressin can occur at any age. Symptoms suggesting the possibility of hyponatraemia include headaches, nausea, vomiting, fatigue, dizziness, weight gain, and ataxia. Caution is required when desmopressin is used in the presence of renal failure or hepatic disease. Desmopressin should not be used in psychogenic polydipsia. Drug-drug interactions can occur with diuretics, anti-depressants (tricyclic anti-depressants and serotonin uptake inhibitors), chlorpromazine, carbamazepine, and non-steroidal anti-inflammatory drugs (NSAIDs).

Recommendation 6: Desmopressin can be considered in the management of nocturnal polyuria associated nocturia. (Grade of recommendation A, Level of evidence 1.)

Recommendation 7: Desmopressin use is associated with hyponatraemia in older adults, and (if used) should be used with extreme caution and close monitoring in adults over age 65 years. (Grade of recommendation A, Level of evidence 1.)

Conclusion

Nocturia in adults is a common bothersome condition, particularly in older adults. The New Zealand ad hoc committee recommends a simple four-step assessment and management strategy for nocturia. Appropriate treatment of identified disorders has the potential to reduce the impact of the symptom for patients.[55]

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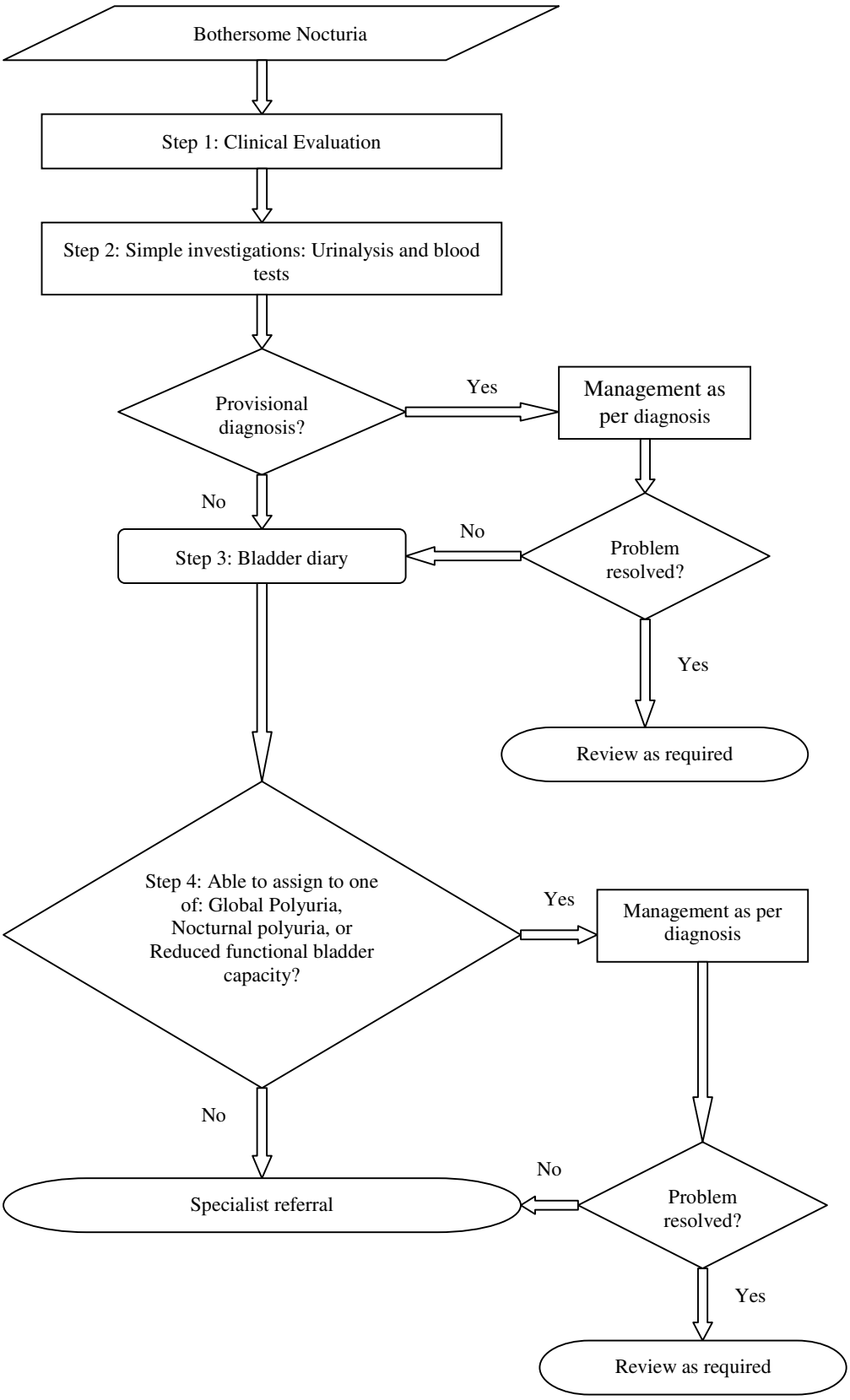
Appendix 1. Membership of the ad hoc New Zealand Nocturia Guideline Committee

- Chair: EP Arnold, Urologist, Christchurch School of Medicine and Health Sciences, Christchurch
- J Boulton, Urologist, Auckland
- J Brown, Urotherapist, Hamilton
- A Catherwood, General Practitioner, Auckland
- T Croker, General Practitioner, Auckland
- R Harris, Geriatrician, Auckland
- SD Mark, Urologist, Christchurch
- R Robson, Renal Physician, Christchurch
- M Weatherall, Geriatrician, Wellington School of Medicine and Health Sciences, Wellington

Appendix 2. Algorithm for assessment and management of nocturia in primary care in New Zealand



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Surgical inclination in senior medical students from the University of Auckland: results of the 2005 Senior Students Survey

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Abstract

Aims To determine the proportion of senior medical students who are surgically inclined and to assess whether gender differences exist in surgical inclination.

Study design Cross-sectional survey. Twenty-five point questionnaire. Likert scale response ranking.

Setting University of Auckland Medical School, New Zealand.

Participants 218 surveys were emailed to functioning addresses of fourth and fifth year students.156 students emailed responses (71.60% response rate).

Results Twenty percent of students were found to be surgically inclined (95% CI 0.15–0.26). The proportion of surgically inclined males was significantly higher than females ($p<0.01$). A greater proportion of surgically inclined students found time spent in the operating theatre educationally valuable than non-surgically inclined students ($p<0.01$). No difference exists in the number of different procedures undertaken by students ($p>0.05$).

Conclusion Males are significantly more likely to be surgically inclined than females at the University of Auckland Medical School.

"Surgically inclined" is a term often used to describe medical students who show a clear preference for surgery over other specialties whilst at medical school.

Interest in surgical training is declining in the United States and elsewhere.[1] It has been suggested that surgical lifestyles, family pressures, indemnity protection costs, and the increasing proportion of female medical students are contributing to this trend. Females are less likely to enter surgical training than males.[3] Females make up more than half of New Zealand medical students.[2–4]

Long hours are necessary for surgical trainees to gain operative experience.[6] Whilst reforms have decreased this time demand, surgical training remains the most time-intensive of all specialties.[7] This is dissuasive, as medical students are more likely to choose specialties less demanding of their time.[8]

Factors shown to be associated with medical graduate's decision to pursue a surgical career have included: a willingness to work long hours; affinity for procedural tasks; the ability to focus for long periods on a task; enjoyment of surgical rotations; and interest in a surgical career whilst at medical school.[9–11]

Students will generally show a preference toward a specialty during medical school.[12] Fifty-three percent of fifth year students at the Dunedin Medical School have been shown to have a strong idea of their career direction.[13] 90% of Malaysian medical

students (a number of which come to New Zealand for their clinical training and subsequent employment) have already decided on their future specialty before graduation.[14] Surgeons may decide their career direction earlier than those working in other specialties.[15]

Method

Creating the definition—A literature review was conducted searching Medline, the Cochrane Library, and BMJ.com. Search terms included: *medical students* AND *career decisions* AND *surgery*; *female medical students* AND *surgery*; *gender* AND *medical students*.

Significant factors which were repeatedly identified in the literature as being strongly predictive of medical graduates pursuing post-graduate surgical training were included in our five point definition for the surgically inclined medical student.[11–13]

Meeting four out of the following five criteria positively identifies a surgically inclined student:

- Explicit interest in a surgical career.
- Preference for surgical attachments over medical attachments.
- Enjoyment of procedural challenges.
- Ability to focus for long periods on a single task.
- Willingness to engage in long working hours.

Development of the survey—Ethical approval was sought from the Multi-regional Ethics Committee. After reviewing a summary of the project's aims and proposed methodology, the Committee's Chair consented to completion of the project without formal ethical review, under the proviso that responses would be made anonymous.

The anonymous survey questionnaire included 25 items. These items were either tick box replies or a five-point Likert scale ranking (1 = strongly agree; 5 = strongly disagree). Demographic information included only gender and year of medical study. Five items targeted the definition directly.

Three pairs of control questions were included to provide a measure of reliability in responses. If answers were reliable, the response to each item per pair clearly correlated and the response was included in the analysis. Responses with no or only one consistent pair were to be excluded from the analysis. Other items examined perception of the role of basic medical sciences, the perceived amount of knowledge of basic sciences, and methods of learning. These questions served to control bias potentially created through a questionnaire which was overtly surgically.

A focus group of four medical students evaluated the survey prior to pre-testing with a pilot survey. Pre-testing was conducted using a sample of 10 fifth-year medical students who were also included in the final sample. These respondents were asked to comment on content, consistency, clarity, appearance and potential for bias in the questionnaire. Potential ambiguities and inconsistencies in scales which were identified were corrected prior to the study sample being completed.

Survey administration—Fourth- and fifth-year class email lists were obtained through class representatives from the University of Auckland Medical School. 284 email addresses were mailed a pilot message; 66 messages were returned to sender by service providers stating permanent failure (thus suggesting those email addresses were no longer valid). Thus, those 66 undeliverable addresses were not sent surveys. The survey form was sent to 218 email addresses; 156 responses were received. These responses were organised with any personally identifiable information removed by a third party.

Statistical analysis—Questionnaire responses were manually entered into an electronic spreadsheet. Responses were divided into two groups for each item (1=strongly disagree/disagree/neutral, 2=strongly agree/agree). Statistical analysis was performed using Microsoft Excel and SPSS software. Confidence intervals for proportions were calculated using a continuity correction for categorical data. Differences were tested for significance using the standard error and a continuity correction for categorical data. P values of less than 0.05 were defined as significant.[16]

Results

Responses—In response to the email, 156 of 218 (71.60%) medical students returned a completed survey (Table 1).

Table 1. Response rate (by study year and gender) of the 218 medical students who received the survey

Medical students	Responses
4th-year males	28
4th-year females	44
5th-year males	34
5th-year females	50
Total	**156**
Response rate	**71.60%**

In all responses, at least two of the pairs of control questions were consistent, thus no responses were excluded from the analysis.

Surgical inclination—As shown in Table 2, the proportion of all respondents meeting the criteria was 0.20 (20%). The proportion of males was significantly greater than the proportion of females meeting the criteria ($p<0.01$).

Table 2. Proportion of students surgically inclined

	Surgically inclined respondents (total)	Male surgically inclined respondents	Female surgically inclined respondents
Proportion*	0.20	0.32	0.12
95% CI	(0.15–0.26)	(0.22–0.45)	(0.07–0.20)

*meeting criteria.

Interest in surgery—Students were asked to rate their interest in a surgical career (1=highly disagree/not at all interested, 5=highly agree/highly interested).

Forty percent of students agreed that they were interested in a surgical career (95% CI 0.32–0.48). Not surprisingly, more students meeting the criteria were interested in a surgical career ($p<0.01$). No statistically significant difference was found between males and females for this item ($p>0.05$) (Table 3).

Table 3. Interest in a surgical career

	Surgically inclined	Non-surgically inclined	All males	All females
Proportion* (95% CI)	0.84 (0.66–0.94)	0.29 (0.21–0.38)	0.53 (0.40–0.66)	0.31 (0.22–0.41)

*meeting criteria.

Lifestyle—Students were asked to rate the importance of lifestyle as a factor in choosing a career within medicine (1=highly disagree/not at all a factor, 5=highly agree/very important factor).

Fifty-six percent of all students agreed that lifestyle was an important factor in choosing a career (95%CI 0.48-0.64). A significantly smaller proportion of surgically inclined students agreed with this item ($p<0.01$). No statistically significant difference was found between males and females for this item ($p>0.05$) (Table 4).

Table 4. Importance of lifestyle as a factor in choosing a career

	Surgically inclined	Non-surgically inclined	All males	All females
Proportion (95% CI)	0.23 (0.1-0.42)	0.94 (0.56-0.73)	0.48 (0.36-0.61)	0.62 (0.51-0.71)

Procedural exposure—Students were asked to report how many procedures they had performed from a list of five procedures commonly performed by medical students (IV cannulation, LMA/ETT intubation, Foley catheter insertion, suturing, minor surgical).

There was no statistically significant difference in the number of procedures performed by surgically inclined medical students and non-surgically inclined medical students ($p>0.05$). No statistically significant difference found in the mean response between males and females for this item ($p>0.05$) (Table 5).

Table 5. Number of procedures performed by students

	Surgically inclined	Non-surgically inclined	Females	Males
Mean number of procedures (95% CI)	3.97 (2.77–5.18)	3.25 (3.07–3.43)	3.39 (3.21–3.62)	3.00 (2.74–3.26)

Educational value of theatre attendance—Students were asked to rate the educational value of time spent in the operating theatre (1=highly disagree/not at all useful, 5=highly agree/ very useful).

Forty-six percent of all students agreed that time spent in the operating theatre was educationally valuable (95%CI 0.38–0.54). A greater proportion of surgically inclined medical students agreed that time spent in the operating theatre was educationally valuable ($p<0.01$). No significant difference was found between males and females for this item ($p>0.05$) (Table 6).

Table 6. Educational value of the operating theatre

	Surgically inclined	Non-surgically inclined	All males	All females
Proportion	0.94	0.34	0.45	0.47
(95% CI)	(0.77–0.99) p<0.01	(0.26–0.43)	(0.33–0.58); p>0.05	(0.37–0.57)

Discussion

Methodological issues—As selection of the sample was not randomised, systematic biases are possible. More females responded to the survey than males, yet this is reflective of medical student demographics in New Zealand.[5] The response rate to this email survey was higher than the mean response to such survey published in medical journals.[17]

Because this survey did not overtly seek surgical respondents, the non-respondents were unlikely to adversely bias the results. Non-respondent bias was thus felt to be well controlled. Socially desired response bias was probably an issue for some items. Still, reliability in student responses was pleasing as tested by responses to control question pairs. Caution should be applied when generalising the results of this survey and proportions should be interpreted as trends rather than absolute values.

The definition—When students were asked if they were interested in a surgical career, 40% of students agreed. As this is considerably higher than the actual proportion of medical graduates who enter surgical training, it may reflect socially desired response bias in this item. The five-point definition of medical student surgical inclination appears to give a more reliable estimate of the true proportion of students who are likely to enter surgical training.

Gender bias in surgical inclination—Females are less likely to enter surgical careers than males.[3] In the United States, the number of females entering medical school has increased, yet the number of females applying for surgical training has remained relatively constant.[18] Thus the proportion of female medical graduates entering surgical careers has actually decreased.

The findings of this investigation suggest these American trends may be generalisable to New Zealand. Thirty-two percent of males surveyed were found to be surgically inclined compared to 12% of females (p<0.01). Kato et al (2004), who investigated the opinions of female surgeons from Japan, commented that the demands of marriage and family on women were probably a major factor in the under-representation of women undertaking a surgical career.[19] Our investigation, like others in the literature, was unable to demonstrate that female medical students are significantly more concerned with lifestyle when choosing a career than males.[3,10]

Encouraging interest in surgery—The busy surgical lifestyle has been shown to be a deterrent for medical graduates.[9] Our analysis suggests that a significant difference between those students who are surgically inclined and those who aren't is the importance they place on lifestyle.[8]

Reforms in the United States have significantly restricted the long hours that trainees are expected to work.[9] While it is hoped that this will increase in surgical careers, there is also concern that shorter hours will lead to inadequate operative experience.[8]

Mentoring for students has been advocated as another way to improve interest in a surgical training.[11] Some medical schools have established surgical interest societies for this purpose.[20] Consultants and trainees who make a concerted effort to teach students on the ward and operating theatre have been shown to motivate students to consider surgical careers.[11]

Our analysis showed that less than half of the students surveyed found operating theatre attendance educationally valuable. Several respondents noted that theatre was useful *when* they could see into the operative field and were being spoken to.

It is the belief of the investigators that identifying and fostering student interest in surgery is important to the future of New Zealand's surgical workforce.

Future study—We propose that future studies look at the experiences of surgically inclined versus non-surgically inclined students as well as experiences of male versus female students during surgical attachments.

Limitations—We encountered difficulty in capturing a higher response rate as unsolicited emails are frequently blocked or put into junk-mail folders by service providers, and treated as spam.

Another limitation was subjectivity in the interpretation of evidence relating to surgical inclination in the formulation of this study's criteria.

Conclusions

Of senior (fourth and fifth year) medical students at University of Auckland Medical School:

- 20% are surgically inclined.
- Males are more likely to be surgically inclined than females.
- Surgically inclined students place less importance on lifestyle in their career choice.
- There is no difference between males and females in the importance placed on lifestyle in career choice.
- Surgically inclined medical students are more likely to agree that time spent in the operating theatre is educationally valuable.

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Current and former smoking increases mortality in patients on peritoneal dialysis

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Abstract

Aims There is limited information on the effects of smoking behaviour on mortality in patients with end-stage renal failure (ESRF).This study aimed to assess the interaction of smoking on death rate in patients with renal failure on dialysis.

Methods All patients (n=1293) commencing peritoneal dialysis between 1985 and 1995 for renal failure in New Zealand were prospectively followed 6 monthly until 1997 and data entered on the National database. Mortality rates were calculated from the national database and rates in patients with diabetes compared with those without diabetes and in those who did or did not smoke.

Results Follow-up data was available on all patients for a range of 20–140 months. 35% of the patients were clinically classified as having diabetic nephropathy as the cause of renal failure (11% type 1, 24% type 2). Seventeen percent of the total cohort were current smokers, 45% former smokers and 38% lifetime non smokers at dialysis commencement. These rates were similar between patients with diabetes (18% current, 51% former, 32% non-smoker) and those without diabetes (17% current, 42% former, 41% non-smoker). At survey end in 1997, 43% of the patients without diabetes had died compared with 59% of patients with type 1 diabetes ($p<0.05$) and 62% of patients with type 2 diabetes ($p<0.05$). The age-adjusted mortality of patients with a history of current or former smoking was higher than non-smokers. Those patients with diabetes and a history of smoking had even higher mortality.

Conclusions Patients with a current or former history of smoking on peritoneal dialysis are at greatly increased risk of death. A strategy of aggressive smoking cessation efforts should be adopted for these patients at the earliest opportunity.

Rates of cardiovascular disease in patients on renal replacement therapy (RRT) for end-stage renal failure (ESRF) are very high. Moreover, the survival of diabetic patients is worse than for non-diabetic patients.[1–4] Patients on RRT who develop an acute myocardial infarction have very high 1 and 5-year mortality rates (60% and 90% respectively), which is even higher in diabetic patients.[5]

Given the high rate of vascular disease in patients with ESRF, aggressive control of modifiable risk factors such as hypertension, raised cholesterol, and strategies to enhance smoking cessation are likely to be especially important. We tested the hypothesis that survival in patients with ESRF may be further adversely affected by smoking and compared survival in patients with or without diabetes as the cause of ESRF who did or did not smoke at peritoneal dialysis commencement.

Methods

Patients—Comprehensive data on all patients commencing peritoneal dialysis in New Zealand has been collected prospectively since November 1985 and entered onto a national database (J. Collins

New Zealand Peritoneal Dialysis Registry, Auckland). Cross-checks with the Australian and New Zealand Dialysis and Transplant Registry was undertaken on patients with missing data on the national dataset. Each patient's dataset was updated 6-monthly by the patient's renal team, and date and cause of death were also recorded from chart review.

All data are collated centrally by a data manager to ensure accuracy of data collection - diabetes status, smoking status at commencement of dialysis and ethnicity was known for 100% of the cohort with only 11 patients lacking detail on vascular disease status. Smoking status at commencement of dialysis was recorded in all centres by patient interview, (prospective smoking status within patient groups was recorded at one centre until 1993) and ethnicity was self-reported.

The cause of ESRF was stated at commencement of dialysis. Patients were classified as having either type 1 or type 2 diabetes and the diagnosis of diabetic nephropathy was made by the patient's nephrologists on clinical grounds. Whilst some patients with nephropathy classified clinically as diabetic in origin may have had additional causes of renal disease, renal biopsies were not routinely performed.

All patients who commenced peritoneal dialysis as initial treatment for ESRF between 15 November 1985 and 15 November 1995 were included in this analysis and followed until survey end (1 July 1997) or death. The primary end-point of the study was death. Relationships between the following secondary end-points and the following independent variables were investigated: diabetes status (no diabetes, type 1 or type 2); smoking behaviour (current, former, non); gender; ethnicity; age at peritoneal dialysis (PD) commencement; subsequent renal replacement treatment (PD, haemodialysis, transplant);and presence/absence of established ischaemic heart disease, cerebrovascular or peripheral vascular disease at commencement of PD.

The complete cohort had updated data entered 6-monthly. At commencement of dialysis, clinical history and examination (including ECG) was used to classify patients as having "confirmed", "suspected", or "no evidence" of established ischaemic heart disease, cerebrovascular disease, or peripheral vascular disease.

Statistical methods—Kaplan Meier survival curves and log rank tests (SAS proc life test) were used to investigate relationships between the independent variables and survival time. Cox proportional hazards regression (SAS proc phreg) was used to investigate the effects of covariates. Contingency tables (SAS proc frequency) were used to investigate relationships between the independent variables and cause of death.

In most analyses, the outcome for patients with type 1 and type 2 diabetes were similar, despite controlling the data for other covariates. Therefore patients with diabetes were grouped together. Similarly, there were no significant differences between the outcomes of current and former smokers (despite correcting for a number of covariates) so current and former smokers were also grouped for most analyses.

It is to be noted that "former smokers" range from those who gave up smoking many years before ESRF to those who gave up immediately prior to dialysis. The registry did not record pack years of smoking, nor years since stopping smoking. However, as we have defined patients who stopped smoking many years ago as "smokers", the group outcomes are extremely conservative.

Classifying patients who gave up smoking more than 5 or 10 years before ESRF as "smokers", was likely to have decreased differences between the two groups. In the one centre that did report smoking status at commencement of dialysis as well as prospectively, analysis showed that smoking status at commencement of therapy for ESRF did not vary over time; very few current smokers at commencement of RRT ceased during the follow-up, and very few former smokers re-commenced smoking.

Inclusion in the study was based on peritoneal dialysis as the initial mode of therapy. However the Australia and New Zealand dataset does have outcome data recorded on all patients regardless of final mode of therapy and thus no censoring of the data was made for patients who transferred to other forms of treatment.

Results

Effects of smoking on mortality—Between November 1985 and November 1995, a total of 1293 patients commenced PD in New Zealand due to ESRF (Table 1). Follow-up data was available on all patients for a range of 20–140 months.

Table 1. Survival and characteristics of patients with end-stage renal failure (ESRF) commencing peritoneal dialysis (PD) in New Zealand between November 1985 and November 1995 (n=1293)

Diabetes status	n (% of total)	Gender	Age* (mean ± SD)	Smoking status (%) *			Ethnicity† (%) *				Treatment group (%)*‡			% dead at 1 July 1997*
				Current	Former	Non	E	M	PI	O	A	B	C	
Non-diabetic	842 (65%)	M : 54% F : 46%	47.6 ± 17.8	17	42	41	62	22	10	6	56	27	17	43
Type 1 diabetes	143 (11%)	M : 51% F : 49%	45.6 ± 10.9	21	41	38	57	32	8	3	61	21	18	59
Type 2 diabetes	308 (24%)	M : 53% F : 47%	55.6 ± 8.4	16	55	29	9	68	19	4	73	4	23	62

*p<0.05 between groups; †E=European, M= Maori, PI= Pacific Island, O=Other ethnic origin; ‡A=PD only; B=PD + subsequent transplant; C=PD + subsequent haemodialysis.

Table 2. Prevalence of clinically established cardiovascular disease at commencement of PD between November 1985 and November 1995 and final survival in patients with ESRF (n=1293)

Diabetes status	n	IHD (%)†*			CVD (%)†*			PVD (%)†*			Status at survey end (01-07-97)*	
	(% of total)	C	S	Nil	C	S	Nil	C	S	Nil	Dead (%)	Alive (%)
Non-diabetic	842 (65%)	13	7	79	6	2	91	6	3	91	43	57
Type 1 diabetes	143 (11%)	22	8	68	20	4	76	6	16	78	59	41
Type 2 diabetes	308 (24%)	23	14	62	13	7	80	5	18	77	62	38

*p<0.05 between patients with and without diabetes; †C=Confirmed, S=Suspected, Nil=No evidence; IHD=Ischaemic heart disease; CVD=Cerebrovascular disease; PVD=Peripheral vascular disease.

Thirty-five percent of the patients had diabetic nephropathy as the cause of ESRF. The patients with type 2 diabetes were older at commencement of dialysis than the patients without diabetes and those with type 1 diabetes. Although current smoking prevalence at commencement of dialysis was similar between patients with diabetes and those without diabetes (and lower than the 1996 New Zealand non-diabetic population),[6] the percentage of patients who were lifetime non-smokers was lower in those with type 2 diabetes. As expected, the patients with diabetes had a higher prevalence of established or suspected macrovascular disease at onset of dialysis than those patients without diabetes (Table 2).

After correction for age, smoking status, ethnicity, and presence or absence of diabetes, mortality was similar in women and men (data not shown). The survival of patients without diabetes was significantly longer than in those with diabetes (Figure 1), even when controlling the data for age, smoking status, and presence or absence of established cardiovascular disease at commencement of dialysis (Table 3).

Table 3. Hazard ratio of different variables on survival time in 1293 patients on PD for ESRF. Data is stratified by patient age at start of PD and adjusted for gender, smoking status, ethnicity, and the presence of macrovascular disease at treatment start

Variable	Risk ratio	Confidence interval
Diabetic / non diabetic	1.68	(1.41–2.01)
Smoker / non smoker	1.22	(1.02–1.46)
Gender	0.99	(0.84–1.17)
Ethnicity	1.00	(0.99–1.01)
Treatment type (PD / PD plus transplant / haemodialysis)	2.52	(2.17–2.93)
IHD	1.17	(1.06–1.31)
CVD	1.18	(1.04–1.35)
PVD	1.17	(1.0–1.36)

IHD=Ischaemic heart disease; CVD=Cerebrovascular disease; PVD=Peripheral vascular disease.

When the data was stratified for patient age at treatment commencement (i.e. when patients of similar age at commencement of dialysis were compared), the difference in survival between patients with diabetes and those without diabetes was even greater (data not shown). There was no significant difference in survival time between patients with type 1 or type 2 diabetes. However, when patients of similar age at commencement of PD were compared, the patients with type 1 diabetes had a shorter survival time than patients with type 2 diabetes (data not shown).

There was a significant inverse relationship between survival time and smoking behaviour—lifetime non smokers survived longer than current or former smokers (Figure 2A), an effect that remained constant after controlling for age, ethnicity, and the presence of diabetes or macrovascular disease at commencement of PD.

Smoking and diabetes both affected survival time (Figure 2B); however those effects were additive rather than multiplicative. This relationship remained constant even after controlling for age, ethnicity, or macrovascular disease at commencement of PD (Table 3).

Figure 1. Kaplan Meier curves showing proportion of patients (n=1293) commencing peritoneal dialysis between 15 November 1985 and 15 November 1995, surviving as at 1 July 1997 with type 1 diabetes (n=143), type 2 diabetes (n=308) or no diabetes (n=842). The survival of patients without diabetes was significantly greater than those patients with diabetes (p<0.001)

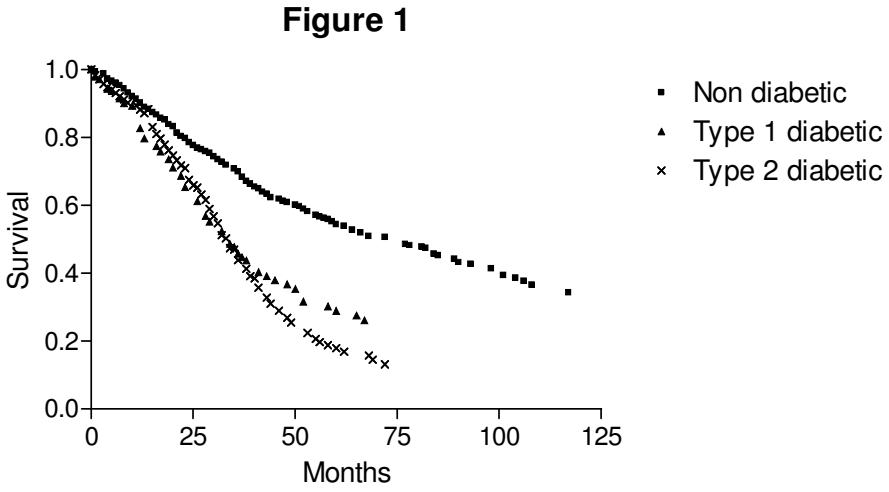


Figure 2A. Kaplan Meier curves showing proportion of patients (n=1293) commencing peritoneal dialysis (PD) between 15 November 1985 and 15 November 1995, surviving as at 1 July 1997 who were lifetime non smokers (n=496), former smokers (n=578) or current smokers (n=219) at commencement of PD. The survival of non-smokers was significantly greater than former or current smokers (p<0.001)

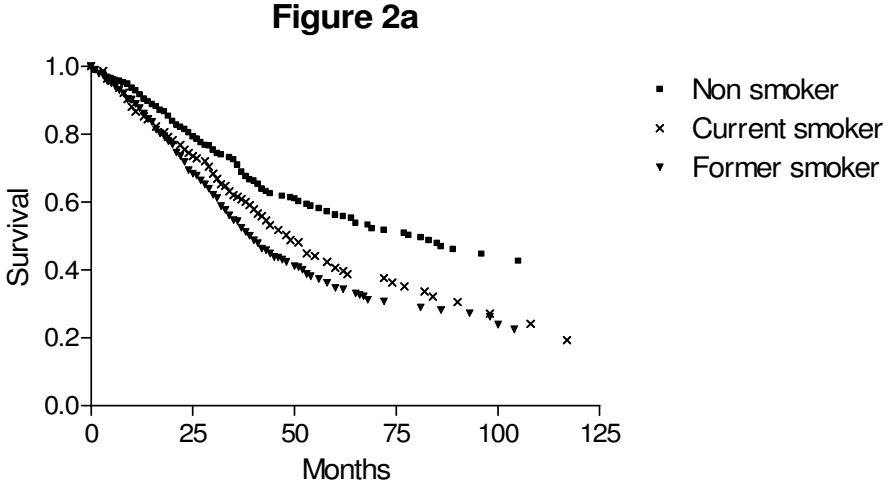
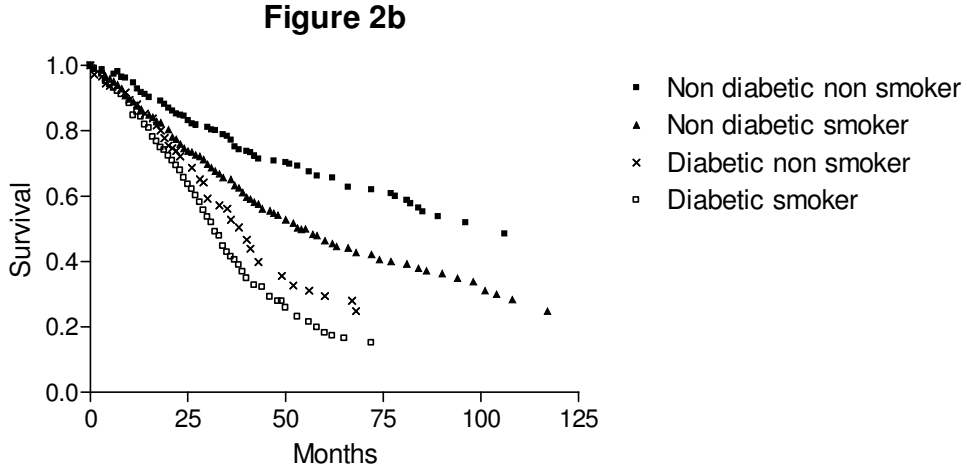


Figure 2B. Kaplan Meier curves showing proportion of patients (n=1293) commencing peritoneal dialysis (PD) between 15 November 1985 and 15 November 1995, surviving as at 1 July 1997, with and without diabetes who were lifetime non smokers or current / former smokers at commencement of peritoneal dialysis. Non-diabetic non-smokers (n=348), non diabetic smokers (n=494), diabetic non smokers (n=145), diabetic smokers (n=306). Each survival curve is significantly different from the others. (p<0.001)



Relationship between diabetes status, smoking, and cause of death—Of the 1293 patients in the cohort, 616 (47.6%) had died and cause of death identified by 1 July 1997. The causes of death were classified as cardiac, vascular, infective, and "other" (includes withdrawal of dialysis). There was no significant relationship between causes of death and smoking behaviour both before and after correction for covariates. However, there was a strong relationship between causes of death and diabetes, with diabetic patients more likely to die of cardiac causes (p<0.001). Of 348 patients without diabetes who died, 46% died of cardiac, 11% vascular, 15% infective, and 28% other causes, whereas of 268 patients with diabetes who died, 59% died of cardiac, 8% vascular, 12% infective, and 20% other causes.

Patients with type 2 diabetes were even more likely to die of cardiac causes than patients with type 1 diabetes and those without diabetes (type 2 61%, type 1 56%, non-diabetic 46%). Maori and Pacific patients had higher rates of cardiac death than Europeans (59%, 57%, 44% respectively; p<0.005). This relationship remained after sequentially correcting the data for diabetes, smoking, and at age PD commencement.

As expected, patients with confirmed or suspected ischaemic heart disease (IHD) and peripheral vascular disease (PVD) at commencement of dialysis had higher rates of subsequent cardiac death than those without those conditions (IHD present 61% versus IHD absent 47%; PVD present 58% versus PVD absent 50%-data not shown).

Discussion

This study has confirmed that patients receiving PD for ESRF due to diabetes had higher mortality than patients with ESRF not due to diabetes.[1–4] Patients with ESRF

who were current (or former smokers) also had higher mortality than non smokers. Patients with diabetes and a history of smoking had the highest mortality of all groups.

The prevalence of smoking in patients with diabetes (and normal renal function) compared to subjects without diabetes in New Zealand is not well established, but is likely to be similar. In 1996, 23.7% of the adult New Zealand population reported that they were regular smokers, with particularly high rates in those of Maori origin (40.5%).[6] Despite a 25% overall population reduction in smoking rates from 1981 through to 1996, the prevalence of smoking in Maori and Pacific Island people in New Zealand remained very high.[6–8]

Diabetes is particularly common in Maori and Pacific Island people, and currently is the leading single cause of ESRF in New Zealand, accounting for about 40% of all new cases over the years 1997–2000.[9] Despite Maori (14.5%) and Pacific Island people (5.6%) making up only 20.1% of the total New Zealand population,[10] 76% of patients with ESRF due to diabetes are Maori or Pacific Island people. Thus, the high rate of smoking in those ethnic groups is particularly concerning.

Patients with diabetes who smoke may develop microvascular complications at a higher rate including an increased risk of developing important proteinuria.[11,12] In the nurses' health study cohort, smoking was associated in a dose-response manner, with an increased mortality among women with type 2 diabetes.[13] The influence of smoking on outcome in patients in ESRF (and especially in patients with diabetes) has, however, received little study to date.

An early report on outcome of RRT in 82 diabetic patients showed that current smoking non-significantly increased the relative risk of death by 2.28 (0.93 to 4.84).[14] Later studies of 196 diabetic patients on haemodialysis (who were followed for 3 years),[4] and 165 non-diabetic patients compared with 118 diabetic patients on peritoneal dialysis (PD)[3] surprisingly showed no adverse effects of smoking on death rate in the diabetic patients when compared with mortality in non-diabetic patients.

In a subsequent study of 52 patients on haemodialysis due to diabetic nephropathy (22 who smoked and 30 who did not), survival at 1 and 5 years was significantly lower in the smoking patients (1- and 5-year survival 68% and 9% in smokers respectively; non-smokers 80% and 37% respectively).[15]

These studies are however either short-term or have very small numbers of patients for follow-up. The largest report on cardiovascular outcome in ESRF patients with and without diabetes (total number 627,983 patients) did not report the smoking status of the patients.[5] A more recent 2-year study of nearly 4000 patients (44% with diabetes) on dialysis showed a 37% increase in mortality rates in patients who were current smokers compared with non-smokers. [16]

Patients in ESRF have high rates of cardiovascular disease.[17] The cause of this high risk is multifactorial and includes the increased risks associated with the underlying cause of the ESRF (such as hypertension and diabetes), but also the added risks caused by ESRF itself.[18–20] Patients on dialysis who suffer an acute myocardial infarction have an especially high mortality.[5]

In the current study, mortality was higher in patients with a history of smoking. Interestingly, there was no significant difference in outcome between current smokers

and former smokers, and both groups fared worse than non-smokers. Former smokers included patients who had very recently quit smoking prior to commencing dialysis, as well as patients with a more distant history of regular smoking.

The fact that former smokers on dialysis had similar adverse outcomes to current smokers suggests that smoking during advancing renal dysfunction accelerates atherosclerosis to a degree that when added together with the independent added burdens of ESRF on progression of atherosclerosis, causes long-term adverse effects not corrected by stopping smoking.

Some centres in New Zealand collected prospective data on each patient's smoking behaviour, not only at commencement of dialysis, but at 6-monthly intervals. These data show that very few patients who were smoking at commencement of dialysis quit during follow-up (14.5 vs 12.8%), and similarly that very few patients who were former smokers at commencement of dialysis recommenced smoking during follow-up (data not shown).

The New Zealand dataset did not prospectively record biochemical variables, and thus the independent contribution of serum lipid concentration, fibrinogen, HbA_{1c} (or other indices of metabolic control in patients with diabetes) on overall outcome is unavailable. It is possible that smokers had more unfavourable lipid profiles than non-smokers, or had more hypertension than non-smokers. However despite earlier reports from the New Zealand dataset showing that patients with diabetes on ESRF had higher blood pressures than patients without diabetes, the patients with diabetes who smoked had far worse outcomes than those patients with diabetes who did not smoke—thus suggesting an independent adverse effect of smoking on mortality.

It is possible that smoking behaviour is a surrogate marker for another factor not examined in this study that does directly impact on mortality (e.g. socioeconomic status, alcohol intake, diet, level of exercise, lung function). The lack of difference on mortality between current and former smokers suggests that in the context of renal dysfunction, smoking causes irreversible effects, presumably on the endothelium with resulting permanent adverse effects on mortality.

A larger (but only 2 year) study[16] of the effects of smoking on cardiovascular morbidity and mortality in patients on dialysis does, however, suggest that patients with a history of having given up smoking within 1 year before commencing dialysis had outcomes comparable to those with a lifetime non-smoking history. This suggests that encouraging patients to quit smoking does have long-term benefits even in the context of advanced renal disease.

In conclusion, this study has confirmed high rates of mortality in patients on peritoneal dialysis, with diabetic patients having higher mortality then non-diabetic patients. In addition, patients with a history of current or former smoking had higher mortality rates then lifetime non-smokers.

Patients with a history of diabetes and smoking had the highest mortality of all groups.

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Māori have a much higher incidence of community-acquired pneumonia and pneumococcal pneumonia than non-Māori: findings from two New Zealand hospitals

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Abstract

To determine the incidence rates of community-acquired pneumonia and pneumococcal pneumonia requiring hospitalisation among Māori and non-Māori, an observational study was conducted in Christchurch and Hamilton. Self-reported data were collected using an interviewer-administered questionnaire. Routine clinical, radiological, and microbiological techniques were used apart from the BinaxNow pneumococcal antigen test for diagnosis of this infection. Census data was used to determine the denominator for statistical analyses. The pneumonia rate overall was 3.03 times higher among Māori than non-Māori ($p<0.001$). Differences were significant for each 10-year age group from age 45–74 years ($p<0.05$). The rate of pneumococcal pneumonia was 3.23 fold higher for Māori than non-Māori ($p<0.001$), but it did not reach statistical significance in the age-related comparisons.

These ethnic disparities are of major concern, and policy planners should consider further interventions to improve the efficacy of current anti-smoking campaigns and to undertake studies of conjugate pneumococcal vaccines for Māori.

Community-acquired pneumonia (CAP) is the most common cause of admission to hospital for adults in New Zealand; it has a reported mortality of between 6.5% and 8%.[1–3] *Streptococcus pneumoniae* is the most frequently identified pathogen in CAP in New Zealand[1,2,4] and worldwide.[3,5,6]

Invasive forms of pneumococcal disease are associated with a high mortality, thus immunisation with the polysaccharide vaccine is recommended for the elderly and those with chronic disease or impaired immunity in New Zealand and elsewhere.[7]

Despite these recommendations, pneumococcal immunisation is very uncommon in New Zealand.[4] Some ethnic groups are also at increased risk from invasive pneumococcal infection. For instance, a population-based survey in Auckland found that Māori and Pacific Island adults in New Zealand had increased rates of invasive pneumococcal disease, and Māori children have a higher rate of invasive pneumococcal disease than Caucasian (New Zealand European) children.[8,9]

High rates of invasive pneumococcal disease have been reported in native Americans, African Americans, and indigenous Australians.[10–14] In response, the Australian guidelines now recommends immunisation of indigenous peoples and Torres Strait Islanders from age of 50 years.[15]

There is no convincing evidence that pneumonia can be prevented by the polysaccharide vaccine in older Western populations,[16] but the spread of penicillin-resistant strains of *S. pneumoniae* has renewed interest in the prevention of

pneumococcal infections in order to reduce antibiotic pressure as well as reduce morbidity, mortality, and hospitalisation.[17,18]

Possible strategies include smoking reduction and the use of the newer conjugate vaccines.[19,20] Because of the potential importance of such strategies for prevention of pneumonia and pneumococcal infection in New Zealand, in this study we determined the age-specific rates of CAP and pneumococcal pneumonia in Māori and non-Māori populations in two major regional centres.

Methods

Participants—All patients over 18 years of age admitted to Christchurch and Waikato Hospitals between 27 July 1999 and 27 July 2000 with a diagnosis of community-acquired pneumonia were screened for inclusion into the study. Christchurch Hospital and Waikato Hospital each have approximately 600 beds.

Both hospitals are the only hospitals in their respective regions that admit patients with CAP, although both act as tertiary referral centres for larger populations. This study is a further evaluation of patients described previously,[4] and the inclusion and exclusion criteria for this study were those used in a previous CAP study.[1]

Pneumonia was defined as an acute illness with radiographic pulmonary shadowing (at least segmental or present in one lobe), which was neither pre-existing or of another known cause. Patients were excluded from the study when pneumonia was not the principle reason for their admission, when they were moribund at presentation (as relevant history microbiological samples and ethnicity could not be obtained), and when the pneumonia was associated with bronchial obstruction or bronchiectasis (as underlying abnormalites alter host susceptibility). Patients with known tuberculosis were also excluded.

Patients with severe immunosuppression—neutropaenia, individuals with AIDS, or those currently receiving cancer chemotherapy were excluded. Patient characteristics and admission clinical and physical findings were recorded on a standardised proforma. Patients identified their own ethnicity by answering the question. " How do you identify ethnically? You may identify more than one—Pakeha/European, New Zealand Māori, Pacific Islander, Asian, European, Other."

Recent antibiotic use and pneumococcal vaccination status were self reported by the patient, and comorbidites were reported by the patient and verified by reference to medical records. At the time of enrolment, blood was drawn for haematological, biochemical, and microbiological analysis. Sputum and urine samples were sought from all patients. All chest radiographs were reviewed by a designated radiologist in each centre to confirm radiological entry criteria. Severity of pneumonia was determined by the method of Fine et al.[21]

Microbiological methods—Blood cultures were incubated aerobically and anaerobically using the BacT/Alert Microbial Detection System (Organon Teknika, Durham, NC, USA). Respiratory samples were cultured on sheep-blood agar, chocolate agar, buffered charcoal yeast extract agar supplemented with (-ketoglutarate, and modified Wadowsky-Yee medium. Urine samples were tested using the NOW™ *Streptococcus pneumoniae* Urinary Antigen Test (Binax, Portland, ME) according to the manufacturer's recommendations.

Criteria for diagnosis as pneumococcal pneumonia—This diagnosis was made if the clinical and radiological criteria for pneumonia were fulfilled and *S. pneumoniae* was isolated from a sterile sample (such as blood, pleural fluid, or lung aspirate sample), or when *S. pneumoniae* antigen was detected in the urine.

Statistical analysis—Subjects were excluded from statistical analysis of the rates of pneumococcal disease if a urine antigen test had not been done, unless a blood culture was positive. Rates were calculated from the 2001 primary self declared ethnicity census data for the catchment areas of the two hospitals. A standardised morbidity ratio (SMR) was calculated for the Māori/non-Māori comparison. The expected values for the Māori group were calculated from the observed rates within each age-sex group for the non-Māori group.

Hypothesis testing and 95% confidence intervals for SMRs were derived from the standard Poisson approximation. All data was entered into a specifically designed Microsoft Access database. The SPSS for Windows 10.0 statistical package was used for the analysis (SPSS Inc., Chicago, USA). The level of significance was set at $p<0.05$.

Results

Patient characteristics—During the 12-month study period, 545 patients were eligible for the study of whom 474 (87%) participants were enrolled. Of these 474 patients, 304 were from Christchurch Hospital and 170 from Waikato Hospital. Of the 71 unenrolled patients, 37 individuals declined study enrollment, 18 were missed for logistic reasons, 10 were unable to give consent and had no available next of kin, and 6 died prior to consent being obtained.

The mean age of those enrolled in the study was 63.7 years (range 18–99 years) and 53% were men. 274 participants (58%) were recorded as having significant comorbidity at time of presentation: 100 (21%) were smokers, 123 (26%) had chronic obstructive pulmonary disease (COPD), 66 (14%) asthma, 52 (11%) diabetes, 95 (20%) heart failure, 28 (6%) renal disease, and 5 (1%) liver disease. Twenty-four patients (5%) were immunosuppressed, 128 (27%) had received an antibiotic prior to admission, 237 (50%) had received influenza vaccine prior to admission, and (19) 4% received pneumococcal vaccine in the previous 5 years. Fifty-seven study participants (12%) identified as being Māori, of whom 41 (72%) were admitted to Waikato Hospital.

Compared with non-Māori, the Māori population were significantly younger (mean age of 50 vs 66 years, $p<0.001$, difference=15 years, 95%CI 10–20 years) and they had a significantly higher rate of smoking (35% vs 19%, $p=0.004$, difference 16%, 95%CI 5%–28%). The mean pneumonia severity index score (PSI)[21] for CAP was similar among Māori and non-Māori (56 vs 49, difference=7.5, CI -6%–21%).

The mean PSI for pneumococcal pneumonia was less among Māori (80 v 95, $p=0.042$, difference = 15, 95% CI 4-25) but this was dependent on the lower age among Māori. There was no statistical difference between the rates of comorbidity other than asthma, antecedent antibiotic use, morbidity, or mortality at 6 weeks follow-up between these two groups (Table 1).

Incidence of community acquired pneumonia—The 2001 Census populations for the Christchurch and Waikato regions for Māori were 27,000 and 39,000, respectively; for non-Māori, they were 327,000 and 198,000 respectively. The population age-specific rates of CAP are shown by ethnicity in Figure 1. The age-specific rates of CAP were statistically significant for each of the three 10-year age groups from 45–54, 55–64, and 65–74 years. The pneumonia rate was 3.03 times higher among Māori than non-Māori in the whole population (Table 2). There was no significant difference in incidence rates by gender or centre in any of the decade groups.

Incidence of pneumococcal community acquired pneumonia—The population age-specific rates of pneumococcal CAP are shown by ethnicity in Figure 2. There was no statistically significant difference in pneumococcal CAP for any of the 10-year age groups, but the rate was higher in the population overall (Table 2). There was no significant difference in incidence rates by gender or centre.

Figure 1. Population age-specific rate of community-acquired pneumonia for Maori and non-Maori (p<0.05)

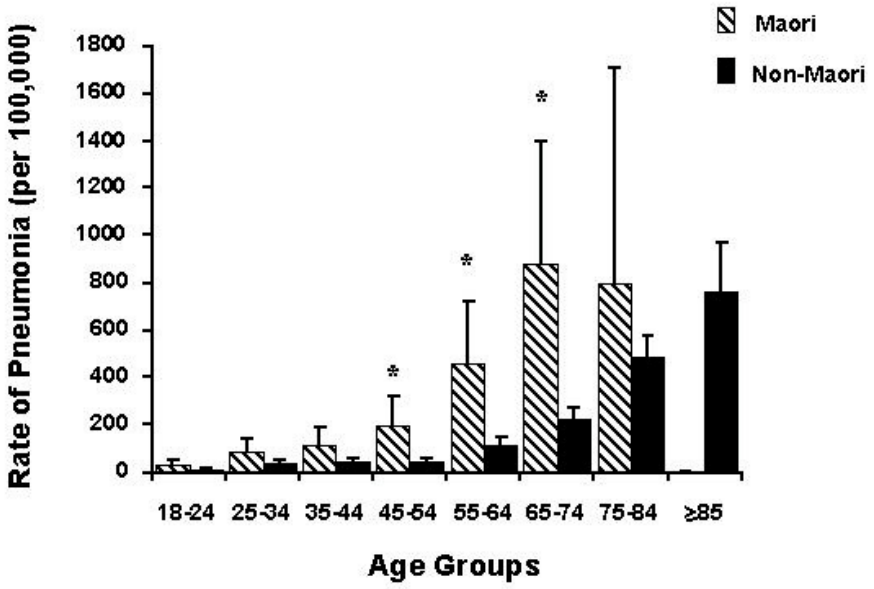

Figure 2. Population age-specific rates of pneumococcal community-acquired pneumonia for Maori and non-Maori

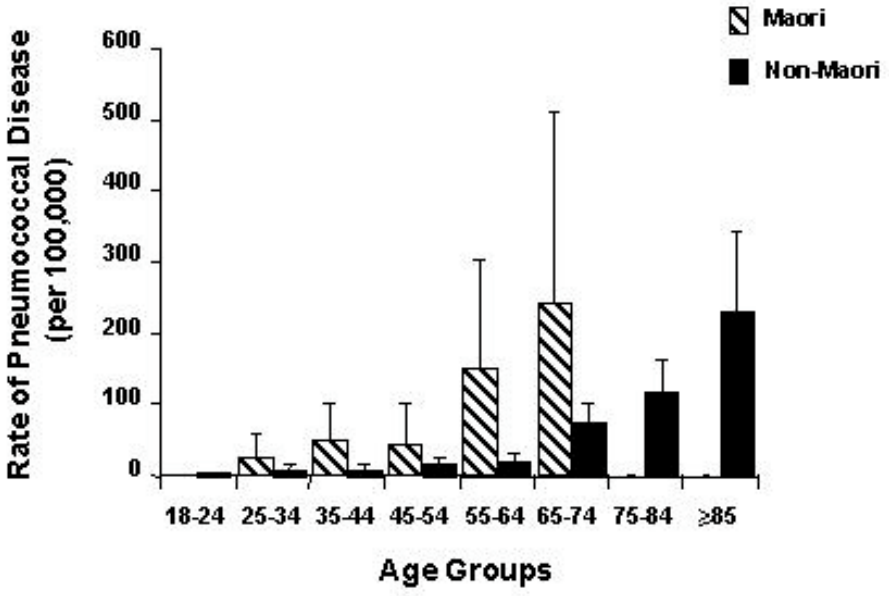

Table 1. Study population patient characteristics and outcome at 6 weeks

Variable	Māori N (%)	Non-Māori N (%)
Community acquired pneumonia	57	417
Pneumococcal community-acquired pneumonia	16 (28)	110 (26)
Prevalence of smoking	20 (35)	76 (19)*
Co-morbidities	36 (63)	238 (57)
Chronic obstructive pulmonary disease (COPD)	12 (21)	109 (26)
Asthma	16 (28)	52 (13)**
Heart failure	15 (26)	81 (19)
Diabetes	8 (14)	46 (11)
Cardiovascular disease	5 (8)	49 (12)
Renal failure	3 (5)	25 (6)
Liver disease	1 (2)	5 (1)
Admission to ICU	1 (2)	15 (4)
Survival at 6 weeks	55 (97)	390 (94)

*p=0.004; **p=0.002.

Table 2. Standardised incidence rates of pneumonia and pneumococcal pneumonia: Māori and non-Māori compared

Variable	Maori	Non-Maori	Standardised morbidity ratio	P value
Pneumonia				
Christchurch	16	8.2	1.94	0.01
Waikato	41	10.6	3.88	0.001
All	57	18.8	3.03	0.001
Pneumococcal pneumonia				
Christchurch	3	1.93	1.55	0.13
Waikato	13	3.01	4.31	0.001
All	16	4.95	3.23	0.001

Discussion

In the catchment areas studied, we have shown that Māori have an increased (3–4 fold) incidence rate of CAP and pneumococcal pneumonia compared with non-Māori. Moreover, the increase in CAP incidence rates seen in non-Māori at aged 65 occurred 20 years earlier among Māori, and pneumococcal pneumonia incidence rates showed a similar pattern.

These incidence rates results cannot be generalised to the general population as the catchment areas of Christchurch and Waikato Hospitals is not representative of the New Zealand population. However, the clear discrepancy in the rates of CAP and pneumococcal pneumonia between Māori and non-Māori (as demonstrated by the disease ratios) probably represents a disease discrepancy present in the general population. These findings are consistent with previous studies that have shown Māori (and other Polynesian) children in South Auckland have increased rates of admission to hospital for pneumonia, and adult Māori have increased rates of invasive pneumococcal disease in the Auckland area compared to Europeans.[8,9,22]

Identification of ethnicity is important for interpretation of the results of this study. To cross-check that the ethnicity data had been collected correctly, we approached 50% of those who identified as Māori at the conclusion of the study, and found complete correlation with the ethnicity as originally recorded. This reassured us that the ethnicity recorded originally in response to the study ethnicity question was correct.

The denominator for calculation incidence rates was derived from the 2001 Census ethnicity data. Although the 2001 Census does not cover the period of the study, we chose data from this Census rather than an interpolation of the ethnicity data between 1996 and 2001 because the question asked was different in those years.

The ethnicity question asked in this study was slightly different from the question used in both the 1996 and the 2001 census. The 2001 census question reads "Which ethnic group do you belong to? Mark the space or spaces which apply to you."

This instruction is followed by a list of ethnicities as follows: New Zealand European, Māori, Samoan, Cook Island Māori, Tongan, Nuiean, Chinese, Indian, Other. In the Census analysis, people who have recorded more than one ethnic group have been counted in each applicable group.

People answering the Census questionnaire may have been more likely to include more than one ethnicity than those answering the study questionnaire. If so, this will have introduced some systematic bias into the results as Māori ethnicity would have been under-reported in the present study compared with the census data. Such an effect is likely to have reduced the difference, however, and thus would strengthen our study conclusions.

Eighty-seven percent of patient eligible for the study participated, but 71 subjects could not be enrolled. Of these, 34 were unlikely to introduce any ethnic bias, as they could not be enrolled for logistic reasons, death, or an inability to obtain consent. The other 37 declined to be enrolled. This could in part be ethnicity related, but we doubt this was sufficiently strong an influence to compromise the results.

There is also a potential bias in that the non-Māori group included non-Māori Polynesians who have increased rates of childhood pneumonia and invasive pneumococcal disease compared with European New Zealanders).[8,22] This would tend to decrease observed differences between the groups and thus increase the robustness of the observations, however.

The determination of incidence rates for pneumococcal pneumonia is difficult, as isolation of *S. pneumoniae* from blood or another sterile fluid is insensitive although highly specific, and isolation for sputum has low specificity because of potential contamination from organisms colonising the upper respiratory tract.

In this study, the diagnosis of pneumococcal infection depends largely on the detection of urinary pneumococcal antigen. The method used differs from previous urinary antigen tests in that it detects a soluble cell wall pneumococcal antigen common to all strains. There have been several studies published on the performance of this test,[23–26]and it has been licensed by the Federal Drug Administration (FDA) in the US. In an adult population, we estimated the sensitivity to be 80% (and specificity 100%) compared with blood culture, and found the test reliable in the presence of previous antimicrobial therapy.[23] It was highly specific in adults as no positive were

found in a large control population, however others have reported positive results in children with nasopharyngeal carriage of *S. pneumoniae.*[26]

Taken together these results suggest the test sufficiently robust to be used to estimate the incidence of pneumococcal disease in adult populations.

The reasons why there is an increased rate of CAP and pneumococcal disease in Māori needs to be examined in further epidemiological studies. Indeed, indigenous peoples worldwide have increased rates of pneumococcal disease compared with others in the same geographic region—including Alaskan and Greenland natives, African Americans, and Australian aborigines.[14–15,26–30]

It is very likely that socioeconomic factors play an important role in this discrepancy. Some of the increase is attributable to smoking, a powerful risk factor for pneumococcal disease, and Māori have higher rates of smoking than the general population.[31]

Other factors such as crowded living conditions, economic status, and access to medical care may contribute to the observed discrepancy but it was not the intention of this study to look for these specific effects and we do not have comprehensive information on the population from which these cases were drawn on which to base any comparisons.

It is possible that some genetic factors exist which contribute to increased susceptibility to pneumonia. Recently Yee et al demonstrated that a homozygous state for FcRIIa-R131 gene is associated with increased mortality for bacteraemic pneumococcal disease, thus suggesting inherited host factors play a role in the pathogenesis of pneumococcal disease,[32] and Roy et al observed homozygotes for mannose-binding lectin codon variants were at increased risk of invasive pneumococcal disease.[33] It is likely that other polymorphisms in host genes influence the outcome of pneumonia.

Increased rates of CAP and pneumococcal disease demonstrated in an ethnic group increases the potential benefit of targeted prevention strategies. Such an intervention could include improved antismoking campaigns,[19] and consideration could be given to improved influenza and pneumococcal immunisation rates for Māori. While doubts remain over the efficacy of the polysaccharide vaccine for the prevention of pneumonia,[16] it is effective against bacteraemic disease (about 90% of which is from pneumonia).

At present, this vaccine is scarcely used in any group, presumably because of cost and access considerations, although it is recommended by the New Zealand Ministry of Health for at-risk populations.[7] There is also evidence that the conjugate vaccine reduces pneumonia in children and has a secondary effect in decreasing pneumococcal disease in adults.[20]

Careful consideration should be given to evaluating the potential value of both pneumococcal polysaccharride vaccine among Māori adults and the conjugate vaccine in children.

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Portal venous thrombophlebitis in a case of perforated appendicitis: lessons from a case

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Abstract

Portal and mesenteric pyelephlebitis is a rarely recognised condition associated with a high morbidity. It usually develops secondary to infection in the drainage area of the portal venous system. We report a case of perforated acute appendicitis complicated by superior mesenteric venous pyelephlebitis and thrombocytopaenia. Appendicectomy and treatment with broad-spectrum antibiotics, anticoagulation, and platelets led to a full recovery. Follow-up imaging revealed complete resolution of the thrombosis. The literature is reviewed and the operative and non-operative approaches for the management of mesenteric and portal venous thrombosis are discussed.

Pyelephlebitis is defined as septic thrombophlebitis of the portal vein or one of its tributaries.[1] It has been well characterised historically[2] but in the modern era is rarely reported. The exact incidence of pylephlebitis is unknown. It may not be recognised at laparotomy and may be missed in autopsy.[3] Greater use of diagnostic radiological imaging may lead to increased recognition. We report a patient with appendicitis who presented with atypical features of appendicitis that was complicated by portal pyelephlebitis and a consumption coagulopathy.

Case report

JT, a 20-year-old male cheese factory worker, presented acutely with abdominal pain, diarrhoea, and vomiting of 72 hours duration. He had previously been well and had no past medical history of note. On admission, his temperature was 37.9ºC, pulse rate 108/min, and blood pressure 117/69 mmHg. His abdomen was generally tender with guarding in the lower abdomen. A provisional diagnosis of gastroenteritis was made.

His haemoglobin was 144 g/l (normal range 130–144 g/l), white cell count 11.8 × $10^{[9]}$/l (normal range 4–11 x $10^{[9]}$/l) and platelets were reduced at 40,000/cu mm (normal range 150–400 x $10^{[9]}$/l). Coagulation profile revealed an INR of 1.2 (normal range 0.8–1.2) and an APTT of 42 sec (normal range 25–40 sec) with increased van Clauss fibrinogen 5.6 g/l. (normal range 1.2-4 g/l).

The X-DP (d-Dimer) was mildly elevated. His liver function tests showed raised serum bilirubin 50 µmol/l (normal range 2–22 µmol/l) as well as elevated alkaline phosphatase 211 U/L (normal range 40–110 U/L) and gammaglutamaryl transferase 162 U/L (normal range 0–60 U/L).

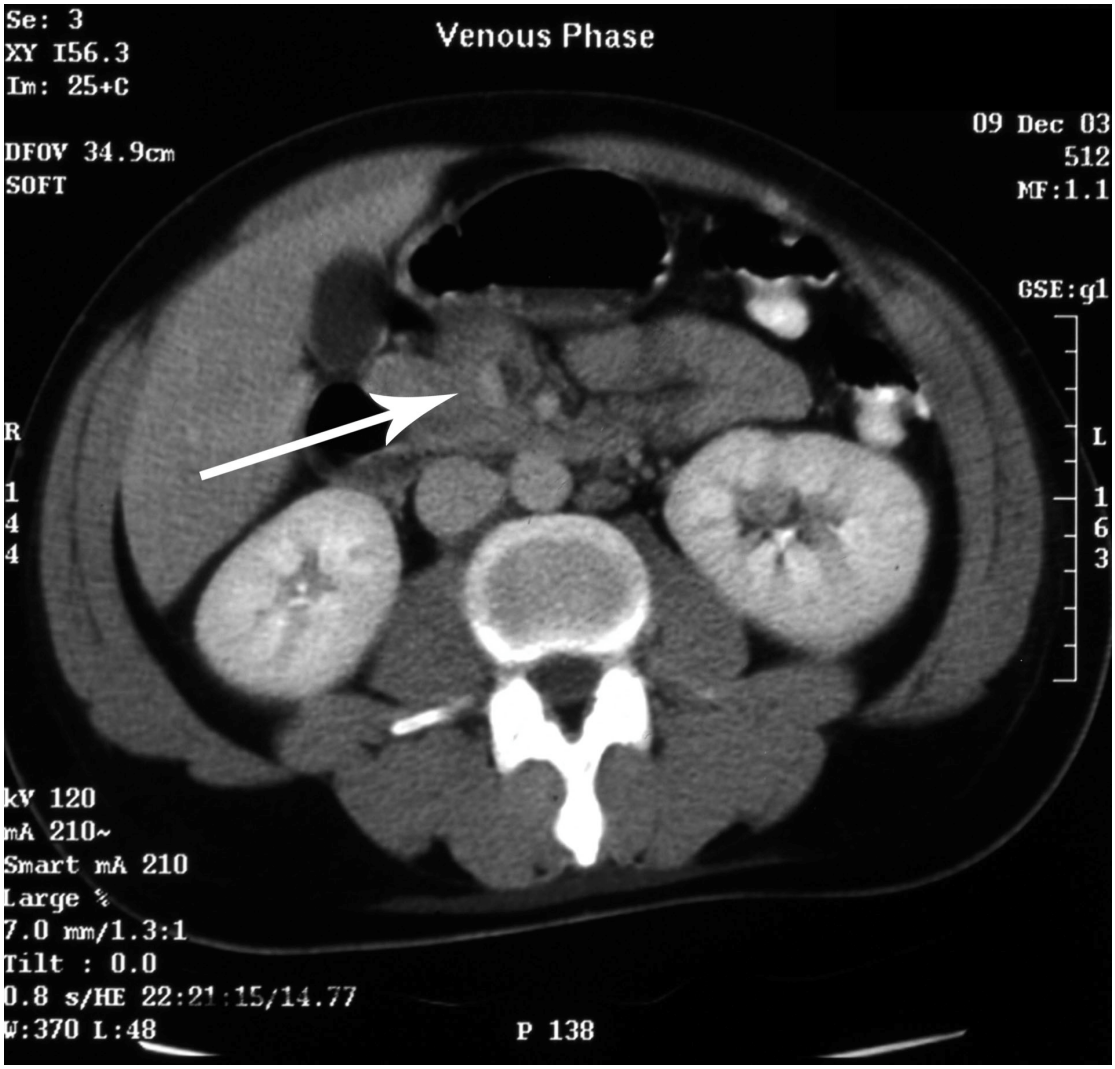
His condition deteriorated over the first 24 hours. His temperature spiked to 39.4ºC with rigors, and he had increasing abdominal pain. Blood cultures grew *Escherichia coli* and *Streptococcus constellatus* in mixed aerobic and anaerobic bottles.

Antibiotics were then started. An abdominal ultrasound (US) scan 18 hours after admission revealed a dilated tubular structure in the right iliac fossa, consistent with

the appendix, with two appendicoliths and surrounding free fluid. There was oedema around the superior mesenteric vein (SMV) and a query was raised about its patency.

A subsequent CT scan showed thrombus partially obliterating the lumen of the SMV and proximal portal vein. (Figure) The spleen was not enlarged.

Figure 1. CT scan with intravenous contrast in our case showing partial occlusion of the superior mesenteric vein by a thrombus (arrowed)



A surgical consult was obtained and a diagnosis of complicated appendicitis and SMV thrombophlebitis was suggested. Intravenous fluids and broad-spectrum antibiotics were continued and he underwent open appendicectomy after a platelet transfusion.

At operation, a perforated appendix with faecoliths was removed. After haematological consultation, he was treated with heparin for 3 days followed by oral anticoagulation with warfarin. He was discharged after 11 days. Warfarin was stopped

after 4 weeks. At 3-month clinic follow-up, he was asymptomatic. An abdominal US revealed complete resolution of the SMV thrombosis.

Discussion

Portal pyelephlebitis is well described as a complication of appendicitis and other infective and inflammatory conditions affecting the intestines, stomach, duodenum, pancreas, and biliary tract.[4] Rarer causes include urogenital lesions, subphrenic abscesses, and malignancies. The true incidence of portal or superior venous pyelephlebitis is unknown. It appears to be uncommon, but the diagnosis may be obscured by the primary disease. Due to advances in management with earlier diagnosis of its underlying cause and the use of antibiotics, it is thought to be less common in modern era.[4] Pyelephlebitis is often not recognised at laparotomy and has been missed at autopsy.[3] Both US and CT are advocated as modalities of diagnostic imaging, but CT is less operator-dependent.[1]

Plemmons et al[1] reviewed 18 cases of pyelephlebitis in the literature and reported one of their own. Bacteraemia was found in 88% of the cases. They suggested the diagnosis of pyelephlebitis should be considered in patients with evidence of intra-abdominal infection and high-grade bacteraemia, especially those due to *Bacteroides fragilis* and/or multiple organisms. Clinically, pyelephlebitis or at least portal bacteraemia should be suspected in any patient with suspected appendicitis who has a rigor.[5]

Pyelephlebitis secondary to infections (e.g. appendicitis) has been distinguished from thrombosis due to other causes by its typically non-occlusive nature, as seen in our case (Figure 1), and a lack of development of portal hypertension.

In appendicitis, spread occurs via the ileocolic vasculature to the superior mesentric vein and eventually to the portal vein.[6] Pyelephlebitis can also give rise to septic emboli that lodge within liver and cause intrahepatic abscesses.[2,7] Deranged liver enzymes were found in our case and could have been indicative of early hepatic involvement.

The suppurative focus will usually need surgical intervention and appropriate antibiotics should also be given. The use of heparin has been advocated,[1] but a benefit of adjunctive heparin therapy has not been clearly demonstrated. Harch et al recommended anticoagulation on the presumption that the process might extend and lead to enteric ischaemia.[11]

Proponents of anticoagulation identify several factors such as documented progression of thrombus while on antibiotics, fever unresponsive to treatment, and the presence of hypercoagulable state to justify therapy.[12] Anticoagulation may also reduce septic embolisation to the liver from infected portal thrombi and prevent liver abscesses.

The optimum duration of anticoagulation is unclear in the literature. If thrombosis is associated with sepsis and not complicated by infarction or embolisation and no underlying thrombophilic factors are identified, then a short duration of therapy seems a reasonable approach, however.

Open thrombectomy and venous ligation[13] appear to have been largely abandoned as therapy for pyelephlebitis. Operative or radiological interventions in the form of

thrombectomy and thrombolysis with direct intravascular infusion of thrombolytics have been advocated.[8–10] for mesenteric and portal vein non-suppurative thrombosis with bowel compromise.

Nishimori et al[14] reported a 16-year-old with septic thrombophlebitis and a liver abscess, who had appendicectomy and thrombus removal from the SMV using a Fogarty catheter. They considered re-canalisation of the portal vein was indicated as an adjunct to surgical removal of the appendix, which was found gangrenous.

The mortality rate reported of up to 32% in cases with SMV thrombosis will in part be due the severity of the associated condition[15] rather than the thrombosis itself but it has been suggested that the complications of untreated portal or SMV thrombosis could be catastrophic.[17]

The high reported mortality rate without anticoagulation and a decreased recurrence rate reported after anticoagulation[16] supports our decision to use it in our patient.

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Neurophysiological findings in a case of cervical anterior spinal artery syndrome: compound muscle action potentials, a marker for prognosis

Ming Lu, Dexuan Kang, Dongsheng Fan

Abstract

We report a case of cervical anterior spinal artery syndrome (ASAS). MRI showed abnormal hypointense on T1-weighted images and hyperintense on T2-weighted images from vertebrae C_2 to T_3. The lesion involved the anterior two-third bilaterally. Spinal angiography showed the superior segmental obstruction of the anterior spinal artery. Regarding nerve conduction studies, no CMAP (the compound muscle action potentials) could be obtained in either median nerves or ulnar nerves, and F-waves were absent. Six months after the onset, there was no any recovery of strength in both arms of the ASAS patient. In our opinion, CMAP could be seen a marker of prognosis for ASAS patients, and absent CMAP might forecast the bad prognosis.

Case report

A 40-year-old Chinese man was admitted to our hospital in November 2004. He was suffered from severe aching of the neck irradiating to his shoulders followed by weakness in both arms. Thirty minutes later, the weakness extended to the legs. Three hours after onset, the weakness was steadily progressing and urinary retention developed. He didn't complain of respiratory distress or difficulty in swallowing. There was no personal or family history of neurological illness, and no history of illicit drug use.

Initial examination showed a complete flaccid tetraplegia. Sensory examination showed dissociated loss of pin-prick and temperature discrimination below C_3, with normal appreciation of light touch, vibration, and joint position. Deep tendon reflexes were absent. Babinski sign was positive bilaterally.

The MRI obtained 5 days after the onset of the illness showed an enlargement of the cord from C_2 to T_3 (Figure 1). Spinal angiography 6 days after the ictus showed the superior segmental obstruction of the anterior spinal artery (Figure 2). CSF was clear and colourless, and the pressure was 160 mmH_2O.

The CSF leucocyte count was 8/μL, and the protein content was 0.72 g/L. Ultrasonic cardiogram showed no abnormal on aortic arch and the lower segment of thoracic aorta. The plasma concentrations of glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and the inflammatory markers (including ESR, HS-CRP, and antinuclear antibody) were all normal. The serum level of homocysteine was 16.4 μmol/L.

Nerve conduction studies were performed 2 weeks after the initial symptoms (Table 1). Sensory nerve conduction velocities on all extremities and motor nerve conduction velocities on the lower extremities were normal, but no CMAP (the compound muscle action potentials) could be obtained on either median nerves or ulnar nerves.

Figure 1. The MRI obtained 5 days after the ictus. The lesion appeared hypointense on T1-weighted image (A), and hyperintense on T2-weighted image (B). On the axial view, the lesion involved the anterior two-third bilaterally (C). There was slightly contrast enhancement after infusion of Gd-DTPA (D).

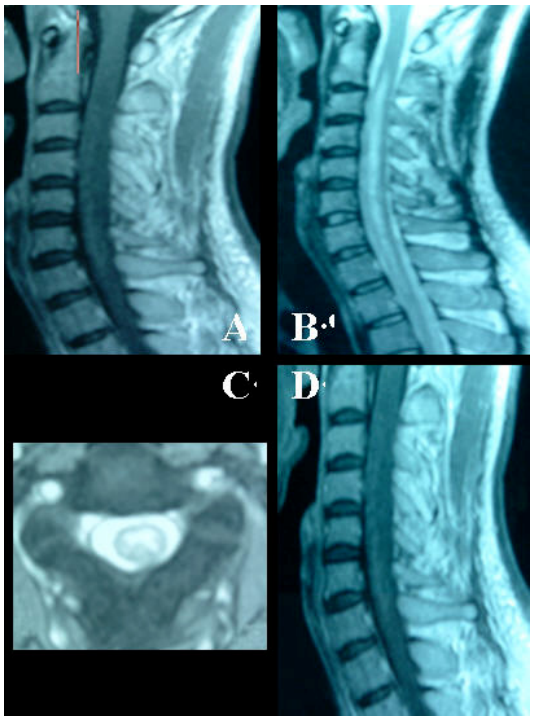
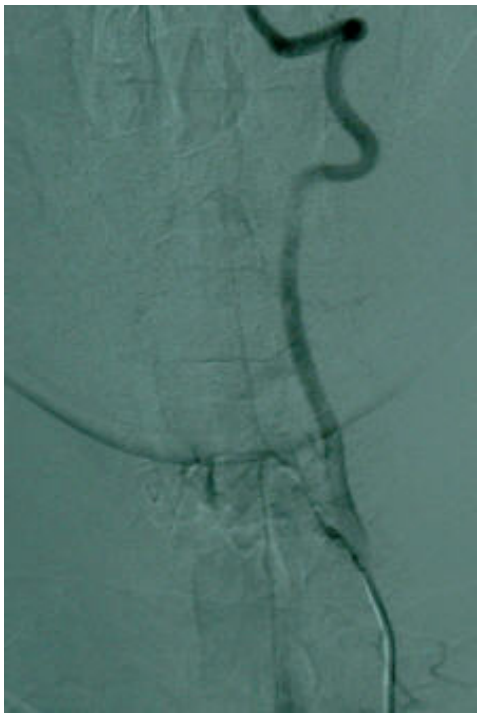


Figure 2. Spinal angiography performed 6 days after the ictus. The anterior spinal artery of the upper cervical spinal cord was opacified, which suggested that the superior segmental obstruction of the artery. This was consistent with the MRI findings of infarction in the anterior spinal artery.



F-waves and the motor evoked potentials on upper limbs were absent bilaterally. However, the somatosensory-evoked potentials showed normal amplitude and latency of the brachial plexus and cortex response on median nerve stimulation at the wrist on both sides, and neither the brainstem auditory evoked potentials nor the visual evoked potentials were abnormal.

The patient was diagnosed as cervical anterior spinal artery syndrome (ASAS), and treated with daily intravenous methylprednisolone 120 mg for 1 week and oral aspirin 200 mg for 6 months. After 2 weeks, he gradually began moving his legs. The recovery of strength of arms was not obviously. Four weeks later, atrophy of the small hand muscles became apparent. Physical examination showed 0/5 strength of both upper limbs and 3/5 on the lower extremities. The ankle jerks were active and the Babinski signs were positive while the biceps brachii and triceps brachii reflexes were absent. The neurological findings did not change during the following 6 months.

Table 1. Nerve conduction studies performed 2 weeks after the initial symptoms

Nerve	NCV (m/s)		Amplitude	
	motor	sensory	motor (mv)	sensory (□v)
N. Medianus				
Right	ND	52.6	ND	14.4
Left	ND	57.1	ND	5.7
N. Ulnaris				
Right	ND	45.2	ND	9.8
Left	ND	62.0	ND	4.4
N. Peroneal				
Right	42.2		5.4	
Left	46.8		5.4	
N. Tibial				
Right	41.3		9.2	
Left	45.2		7.0	
N. Sural				
Right		46.7		6.0
Left		52.4		7.8

NCV=nerve conduction velocity; ND=not detected.

Discussion

In the present study, we reported a case of cervical ASAS, and found that no CMAP could be obtained in either median nerves or ulnar nerves. Six months after the onset, there was no any recovery of strength in both arms of the cervical ASAS patient.

Spinal arteries follow nerve roots to the cord and then bifurcate into anterior and posterior radicular arteries. The anterior radicular arteries supply the anterior spinal arteries, and the posterior radicular arteries feed the posterior spinal arteries.[1] There is no anastomotic network between the single anterior spinal artery and the paired posterior spinal arteries. The cervical and upper thoracic cord is supplied by the vertebral artery and radicular arteries of the ascending cervical arteries.[2] The ventral two-thirds of the spinal cord are absolutely dependent upon the patency of the anterior spinal artery and receive no collateral blood supply from the paired posterior spinal arteries. Occlusion of the anterior spinal artery will result in dysfunction of the ventral two-thirds of the cord, including anterior horns, spinothalamic tracts, and pyramidal tracts.[2]

ASAS was first described in 1904 by Preobranshenski and characterised in 1909 by Spiller. It occurs when the territory of the anterior spinal artery, supplying the ventral two-thirds of the spinal cord, is involved.[3] In acute ASAS, the initial symptom is a local or radicular pain at the level of the vascular occlusion rapidly followed by complete motor paralysis.

Initially, a flaccid paralysis with loss of tendon reflexes occurs. As the spinal cord shock resolves, flaccidity is replaced by spasticity of all muscle groups below the level of occlusion.[1] Muscles at the level of infarction remain flaccid and become atrophic from the necrosis of the anterior horn cells. Bowel and bladder dysfunction is common.[4] There is loss of pain and temperature sense because of the interruption of the spinothalamic tracts, and paring of position, vibration, and motion sense owing to the reservation of posterior columns.[5]

Nowadays, MRI has been established to be the method in detecting cervical spinal cord ischaemic lesions including those in the territory of the anterior spinal artery. But the clinical contribution of angiography to diagnosis of ASAS may be limited because of its lower specificity.[3,6,7] Since the ischaemic process involves neither the spinal ganglion nor the dorsal column, abnormal sensory nerve conduction studies and somatosensory evoked potential findings were absent in our cervical ASAS patient.

Regarding motor nerve conduction studies, however, Amoiridis et al had reported a considerable reduction of CMAP in an ASAS patient.[8] But the fully absent CMAP in our patient has not been observed previously. F-waves represent a simple electroneurophysiological measures for assessing the proximal segment of a nerve.[8]

The absent F-waves in our patient were assumed that the state of inexcitability of the anterior horn cells. It is tempting to speculate that Wallerian degeneration of peripheral nerves resulting from necrosis of cervical anterior horn cells may take responsible for the absent CMAP in median and ulnar nerves. Six months after the onset, there was no any recovery of strength in his both arms. In our opinions, CMAP could be seen a marker of prognosis for ASAS patients, and absent CMAP in motor nerve conduction studies usually forecasts the bad prognosis.

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New Zealand cancer patients should have access to erythropoietin treatment

John Carter, Jennifer Clay

Abstract

Erythropoietin was the first haematopoietic growth factor to be cloned and put to clinical use in patients with anaemia. In New Zealand, the agent is approved and funded for patients with anaemia secondary to renal failure. Although there is Medsafe approval for its use in various other conditions, including cancer patients, it is not funded by PHARMAC for these conditions.

There is good evidence that erythropoietin will induce meaningful increases in haemoglobin levels in approximately 60% of cancer patients. Non-responders can be identified within 2-4 weeks of starting therapy and the drug discontinued, thus improving the cost-effectiveness of the programme. Responders have a significant reduction in blood transfusions, have an improved quality of life, and possibly have a better tumour response to chemo-radiotherapy, thus resulting in longer survival. British and American guidelines advocate a significantly greater use of erythropoietin than the very restrictive New Zealand use.

PHARMAC should review the current evidence as to the benefits of increased erythropoietin usage in New Zealand, and endorse increased access to this agent.

Medication	Recombinant human erythropoietin is available in New Zealand as epoetin alpha (Eprex. Janssen-Cilag) and epoetin beta (Recormin. Roche)
Indication	Medsafe registers both preparations, and usage indications include: • Treatment of anaemia associated with chronic renal failure with or without dialysis; • Treatment of anaemia associated with non-myeloid malignancies (including multiple myeloma, chronic lymphocytic leukaemia, non-Hodgkin's lymphoma); and • Adult patients with mild-to-moderate anaemia scheduled for elective surgery with an expected moderate blood loss. • The prevention of the anaemia of prematurity. • Increasing the yield of autologous blood from patients in a pre-donation programme.
Administration	Various dosages, intravenous (iv) or subcutaneous (sc) × 3/week
Regulation	PHARMAC funding only for patients with the anaemia of chronic renal failure (with or without dialysis)

Background

Erythropoietin is a 166 amino acid glycosolated polypeptide produced by the kidneys and liver. There is a good understanding of the biochemistry and physiology of this natural hormone.[1] While the cause of anaemia in cancer patients is often multifactorial, a significant factor is a relative decrease in erythropoietin production in these patients [2].

The encoding gene for erythropoietin is on the long arm of chromosome 7 (7q21). It was the first haematopoietic growth factor to be cloned (1985) and, 20years ago, the efficacy of erythropoietin in correcting the anaemia in renal dialysis patients was documented.[3] Soon afterwards its use in solid tumours and haematological malignancies was being reported.[4,5] Subsequent to these early studies, much literature has confirmed both the efficacy and safety of erythropoietin in treating the anaemia found in cancer patients.

Anaemia is common in patients with malignancy. A large prospective study in 24 European countries studied 15,000 cancer patients and found 67% had anaemia either at diagnosis or during treatment. Of these patients, only 40% ever received treatment for the anaemia (at a mean Hb level of 97g/L). A strong correlation between quality of life (QOL) and anaemia was found in that study.[6] Indeed, the relationship between QOL and anaemia is significant.[7] Patients place great importance on QOL issues, and of these issues, fatigue (which correlates well with the degree of anaemia) is given the highest rating.[8]

A large (2370 patients) prospective study showed a strong correlation between an erythropoietin-induced rise in haemoglobin and QOL in community-treated cancer patients.[9] Functional improvement is seen up to an haemoglobin level of 120g/L; subcutaneous injections are acceptable to patients with cancer if they perceive the treatment as effective [10].

The ability of erythropoietin to improve the anaemia of malignancy has been studied in many randomised trials, and a meta-analysis of 19 trials conducted between 1993 and 2001 showed the effect of erythropoietin in reducing transfusion requirements with an OR = 0.41; 95%CI: 0.33–0.5 ($p<0.00001$). By using a cumulative meta-analysis methodology, these authors demonstrated that a statistically significant effect of erythropoietin had been demonstrated by 1995.[11]

There is a significant literature documenting the relationship between anaemia, tumour hypoxia, response to chemotherapy/radiotherapy, and survival in both haematological and solid tumours in man and experimental animals.[12] From these studies, it can be concluded that the use of erythropoietin to raise haemoglobin levels (and reduce tissue hypoxia) may improve patient outcomes to treatment.

Cost-effectiveness studies are difficult for this treatment. A full evaluation of the societal costs of transfusion therapy has not been done in New Zealand, and dollar measurements of QOL gain are debated.[13] Despite these problems, a US study demonstrated a 20% improvement in cost-effectiveness for erythropoietin use over 4 months in cancer patients.[14]

While approximately 60% of patients will respond to erythropoietin with a rise of haemoglobin >20g/L, it would be cost-effective to be able to recognise non-responders early. An accurate prediction of response is possible within a few weeks of

starting therapy by using assays for erythropoietin, transferrin receptor and reticulocyte and haemoglobin response. Such monitoring should be incorporated into treatment protocols and costing studies.[15]

As a result of data confirming the efficacy and safety of erythropoietin in treating anaemia in cancer patients, evidence-based clinical guidelines have been produced by British/European and American Professional groups.[16,17] New Zealand clinicians are unable to provide care to cancer patients at the levels recommended in these standards due to funding constraints.

Comment

Anaemia is common in patients with cancer and results in significant morbidity. It is under-treated, and reliance on blood transfusions as therapy is associated with significant problems.

Erythropoietin is a safe and effective agent for increasing haemoglobin levels in the majority of patients with cancer. In those patients that respond, prospective, randomised, controlled trials show a significant improvement in formal quality of life scores, reduced use of blood transfusions, and possibly improved tumour response to chemotherapy and radiotherapy, thus leading to longer survival. Patients place a high utility on treatment that improves quality of life, and are increasingly asking clinicians for access to this treatment.

The reduced need for blood transfusions that would result from the funding of erythropoietin therapy is important. One of the guiding principles of the New Zealand Blood Service is to minimise waste of the blood donor's gift. Similarly, when synthetic medications can substitute for donor blood they should (in principle) be used.

As erythropoietin is not funded for use in cancer patients in New Zealand, very few patients receive this agent. It is possible to apply to the Hospital Exceptional Circumstances Panel for approval for use in a specific patient (with payment coming from the hospital budget). This process is time-consuming and frustrating for clinicians who therefore seldom proceed down this pathway. The outcomes of such applications are inconsistent (records on file). The combination of a limited number of applications and variable outcomes means there is not uniform access of patients to this treatment. This is inconsistent with Government policy for healthcare in New Zealand that places great emphasis on equity of care across the Public Health System.

Evidence-based Best Practice Guidelines from several countries, including Great Britain, recommend the use of erythropoietin in the management of cancer patients. As a result of a failure to fund this agent, New Zealand is failing to deliver patient care to the standard being delivered by countries our Ministry of Health usually choses to benchmark against.

We consider it is appropriate for PHARMAC to consider expanding access to erythropoietin to patients with cancer.

Disclosures: None.

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Odds and ends of a year's surgery. An unusual cause of death after the operation for the radical cure of inguinal hernia

This case report was written by Philip James, F.R.C.S., Wellington and published in the New Zealand Medical Journal 1906, Volume 5 (19), p39–47

A young man, aged 22, who suffered pain and inconvenience from an inguinal hernia of six years' standing, was admitted into the Hospital for operation, which was done according to Lockwood's method, which is a modification of Bassini's and the one I have adopted for many years.

There was nothing unusual about the operation, but the patient was violently sick after the anaesthetic (A.C.E. mixture). This lasted, with intervals of ease, for three days. He then complained of severe abdominal pain, and the upper part of the abdomen became somewhat distended. During the day the vomiting continued, but never became faecal.

On the following morning the distention had increased, so Dr. Ewart washed out the stomach, which contained a small amount of brown-coloured liquid, and ordered a turpentine enema, which acted, but without reducing the distension. I saw him the same morning, and finding that the distension had much increased since the previous day, I decided to open the abdomen, and did so as soon as he could be prepared for operation.

Speculating as to the probable cause of trouble, I favoured the diagnosis of a perforated gastric or duodenal ulcer, as he had a history of long-standing dyspepsia. It seemed also just possible that a small knuckle of intestine might have got nipped between the two ligatures carrying the stump of the sac, which are passed through the abdominal wall; but I did not think this likely, as the symptoms did not indicate intestinal obstruction, Moreover, the distension seemed to be peculiarly limited to the upper zone of the abdomen.

I first made a small incision in the median line just above the pubes, through which I explored the site of the hernia and found all right there. I then opened above the umbilicus, as for gastric or duodenal ulcer. Some free fluid escaped, but no gas. I explored the duodenum and both surfaces of the stomach, but there was no perforation. The jejunum was much distended and deeply congested, a small portion of it almost black. I noticed near the pylorus a small quantity of effused blood between the layers of the transverse meso-colon where they ate reflected over the surfaces of the stomach and colon. On making a close examination of the jejunum, I found that about 2 ft. of the gut had passed through a rent in the meso-colon, and become partially strangulated. The right side of the abdomen was filled with a large clot of blood which had come from a vein in the meso-colon.

I discovered afterwards that the patient's mother several years ago died of internal haemorrhage after an operation. There was nothing at the operation to indicate that he was a bleeder. The cause of death was hernia of the jejunum through a laceration in the meso-colon, with subsequent bleeding from a torn vein. No haemorrhage was

going on at the time of the second operation, nor did it recur, but he died about eighteen hours later from shock.

If any major operation in surgery can be said to be without risk, it is that for the radical cure of hernia, and yet here a death occurs in the most unexpected manner, and one may say from a cause totally apart from the operation. The same thing might happen after any other operation involving the prolonged administration of an anaesthetic.

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Proceedings of the 182nd meeting of the Otago Medical School Research Society, Thursday 18 May 2006

The effect of secreted-amyloid precursor protein on NMDA receptors in cultured rat hippocampal slices. I Ballagh[1], D Ireland[1], B Mockett[1], K Bourne[2], W Tate[2], J Williams[3], W Abraham[1]. [1]Department of Psychology, [2]Department of Biochemistry, [3]Department of Anatomy and Structural Biology, University of Otago, Dunedin.

Alzheimer's disease has been linked to decreased levels of a neuroprotective protein, secreted amyloid precursor protein-α (sAPPα). sAPPα regulates memory-related synaptic plasticity in the hippocampus, a process dependent on the N-methyl-D-aspartate glutamate receptor (NMDAR). The present study investigates the effect of sAPPα exposure on NMDAR function in the rat hippocampus using an *in vitro* slice culture method.

Hippocampal slices from 7- to 12-day old rat pups were maintained in culture for 7-12 days. Recordings of isolated NMDAR-mediated excitatory postsynaptic currents (EPSCs) from the cell bodies of individual CA1 pyramidal neurons were obtained using standard patch clamping methods. Cells exposed to 1 nM sAPPα showed a significant reduction in the mean time course of the $EPSC_{[NMDA]}$ evoked by a single stimulus (91.5 ± 9.3 ms, mean ± SD, n = 8,) compared to untreated cells (123.0 ± 42.1 ms, n = 11, $P < 0.05$; unpaired *t*-test). Longer exposure to sAPPα led to greater depression of the time course ($P < 0.05$; linear regression). Exposure to 1 nM sAPPα increased the time course of the $EPSC_{[NMDA]}$ evoked by a train of ten pulses (132.6 ± 25.6 ms, n = 5) compared to untreated cells (90.4 ± 8.0 ms, n = 5, $P < 0.02$; unpaired *t*-test).

Slice cultures obtained from 3 animals were grown in media containing 1 nM sAPPα for periods of 1, 6 and 24 h and processed to obtain postsynaptic density-enriched membrane fractions. Preliminary Western blot densitometric analysis showed increases in the concentration of the NR1 NMDAR subunit in the postsynaptic density at 6 h relative to untreated slice cultures in all 3 animals.

These results suggest that sAPPα can alter the functional characteristics of the NMDAR, perhaps through a change in the subunit concentration and/or composition. This could be a mechanism by which sAPPα affects synaptic plasticity.

Bioinformatically informed analysis of the gene transcription cascade following induction of long-term potentiation in the rat dentate gyrus. S Bisky[1], S Mason-Parker[2], W Abraham[2], J Williams[1]. [1]- Department of Anatomy and Structural Biology, Otago School of Medical Sciences, [2]-Department of Psychology, University of Otago, Dunedin.

This project aimed to use bioinformatics and quantitative realtime PCR (qPCR) to analyze a part of the genetic network responsible for maintaining long-term potentiation (LTP) in the rat dentate gyrus (DG). LTP is a well-established model for

memory, the persistence of which is dependent on activation of specific transcription factors (TFs) and their downstream response genes. Using bioinformatics, we aimed to find possible targets of some of these TFs based on binding sites in their promoter regions.

Known rat gene promoters obtained from databases were scanned for binding sites of four TFs involved in LTP (NFκB, CREB, AP1 and EGR-1). Of these, 198 promoters contained sites for one or more of these factors, suggesting that these genes may be involved in LTP maintenance. To test the biological relevance of these results, two genes (coding for tissue plasminogen activator [tPA] and lipoprotein-receptor related protein [LRP]), whose promoters showed possible EGR-1 binding sites, was quantified following LTP.

Five rats were bilaterally implanted with electrodes to stimulate their perforant path and record excitatory postsynaptic potentials from granule cells of their DG. One hemisphere remained unstimulated as a within-animal control. After monitoring potentiation for 5h, the rats were killed and their DG removed, in order to isolate total RNA and perform reverse transcription. A SYBR-green based qPCR assay using gene-specific primers showed significant upregulation for LRP (average fold expression change: 1.84 ± 0.2 SEM, $P < 0.01$), as well as a smaller but significant change for tPA (1.5 ± 0.28 SEM, $P < 0.05$).

These results identify two possible downstream targets of EGR-1, and indicate that knowledge from database mining can be used to inform the search for parts of the LTP-related transcriptome puzzle.

Leptin does not act directly on gonadotrophin releasing hormone neurons to regulate fertility in rats. R Geddes, D Grattan, G Anderson. Centre for Neuroendocrinology and Department of Anatomy and Structural Biology, University of Otago, Dunedin.

The hormone leptin is produced by adipose tissue and has a central permissive role in regulating fertility. It provides the communication link between nutritional state and the fertility-controlling centres of the brain, such that low levels caused by undernutrition lead to infertility. The study aimed to determine, using immunohistochemistry, if this action of leptin is mediated directly through gonadotrophin releasing hormone (GnRH) neurons, the central drivers of fertility. As leptin receptors are difficult to detect, a downstream leptin-activated cell-signalling factor, phosphorylated signal transducer and activator of transcription 3 (pSTAT3) was used to identify leptin-activated cells.

Female Sprague-Dawley rats (n = 16) were food-restricted (60% of *ad libitum* intake) for 12 days to up-regulate leptin receptors and enhance leptin sensitivity. This feeding regime caused a 17% reduction in body weight compared to *ad libitum* fed rats. Recombinant mouse leptin (4µg) or vehicle was given to the animals intracerebroventricularly, 30 minutes prior to fixing the brain with 2% paraformaldehyde by cardiac perfusion. Coronal 35µm sections through the preoptic area of the hypothalamus were cut. Double-label immunohistochemistry was used to identify pSTAT3 immunoreactivity in GnRH neurons. GnRH neurons were identified using unenhanced diaminobenzidine tetrahydrochloride (DAB) and pSTAT3 identified using nickel-enhanced DAB, staining GnRH neurons brown and pSTAT3

black. Three sections evenly spaced throughout the medial septum and preoptic area were examined per rat, and all the GnRH neurons in these sections counted. Relatively little pSTAT3 staining was observed in vehicle-treated rats. In the leptin-treated group, pSTAT3 staining was present on numerous unidentified cells in the vicinity of the GnRH neurons, however none of the 246 neurons counted were co-localized with pSTAT3 staining.

These results provide compelling evidence that leptin does not act directly on GnRH neurons, but instead is likely to act through an indirect neuronal pathway to support fertility.

Discovery of Inhibitors of Fungal Plasma Membrane Proton Pump ATPase. R Keng, K. Niimi and B. Monk. Department of Oral Sciences, University of Otago, Dunedin.

Opportunistic fungal infections caused by *Candida* species have increased in recent years, particularly in immunocompromised individuals, and emergence of antifungal drug resistance has become a clinical problem. There are, however, only four classes of antifungal drugs available for treatment of systemic infections. The discovery of new classes of antifungal drugs is therefore urgent. The aim of this study was to discover broad-spectrum inhibitors of fungal plasma membrane proton pump ATPase (Pma1p), an essential enzyme for cell survival.

Thirty selected compounds, which have been identified as potent inhibitors of *C. albicans* Pma1p ATPase *in vitro* were obtained from Pfizer Inc. Each compound was tested against major pathogenic *Candida* species, *Cryptococcus neoformans* and a model yeast *Saccharomyces cerevisiae*.

One of the compounds (compound 10) gave broad-spectrum inhibition of the growth of pathogenic yeast species and *S. cerevisiae* (minimum inhibitory concentration [MIC] 6.25 - 12.5 µM). Compound 10 inhibited the Pma1p ATPase activity of plasma membranes isolated from these species (IC50 0.2 - 9.4 µM). It also acted as a pH sensitive chemosensitizer that made cells sensitive to a sub-MIC concentration of fluconazole (FLC), a widely used antifungal drug. It did not affect cell growth in the absence of FLC, indicating that compound 10 may also inhibit fungal ATP-binding-cassette (ABC) transporters.

Compound 10 was identified as a potent Pma1p inhibitor for all the fungal species tested. Further chemical modification will be required to improve its antifungal and chemosensitisation activities.

T-lymphocyte contribution in a model of cerebral ischaemia. K McKelvey, R Rahman, S Nair, J Ashton, I Appleton. Department of Pharmacology & Toxicology, Otago School of Medical Sciences, University of Otago, Dunedin.

Stroke is the third-leading cause of mortality and the leading cause of disability worldwide. Recent reviews have implicated inflammation as a major cause of the delayed progression of neural injury following stroke. Post stroke, a portion of the inflammatory response is induced and propagated by cytokines secreted by activated T-lymphocytes. Depending on the T-lymphocyte involved, the cytokines may enhance or dampen the inflammation, identifying them as a potential avenue for

therapeutic intervention. This study sought to quantify the contribution of T-lymphocytes in post-ischaemic neurodegeneration and delineate the immune cell response.

Male Sprague-Dawley rats (265 - 295 g) were utilised in a middle cerebral artery occlusion model of transient focal cerebral ischaemia. Animals (n = 4) were sacrificed at days 0 (non-intervention control), 3, 7 and 14 post-stroke induction. Acetone fixed cryostat sections were used in the immunohistochemical (IHC) labelling. Primary antibodies against CD3, CD4, CD8, interferon-gamma (IFN-γ and interleukin (IL)-4 were visualised using horse-radish peroxidase (HRP) with chromagen 3'3' Diaminobenzidine tetrahydrochloride (DAB) or fluorochrome conjugated secondary antibodies. CD3 labelling, which identifies all T-lymphocytes, confirmed that there was a significant and sustained up-regulation in T-lymphocyte infiltration to the ischaemic area up to at least 14 days following stroke. CD4 and CD8 IHC labelling revealed that CD4 T-helper cells were the predominant infiltrate, as opposed to CD8 T-cytotoxic cells, in the ischaemic area.

Double immunofluorescence was used to differentiate between the two T-helper (Th) cell subsets, Th_1 and Th_2. Th_1 cells secrete the pro-inflammatory cytokine, IFN-γ leading to a cell-mediated response. Conversely, Th_2 cells secrete the anti-inflammatory cytokine, IL-4, producing a humoral response. Temporal profiling of the T-lymphocyte response illustrated that CD4/IFN-γ Th_1 cells were the major T-helper cell present in the infarct.

In conclusion these results demonstrate that the immune component of the prolonged neurodegeneration following stroke is a CD4 Th_1 cell-mediated response.

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Colon obstruction

Chi-Lun Tsai, Khee-Siang Chan, Che-Kim Tan

A 95-year-old male presented with a 3-day history of diffuse abdominal pain and distension. He had chronic constipation and Parkinson's disease. Abdominal radiographies were taken at supine (Figure 1) and left decubitus positions (Figure 2).

Figure 1

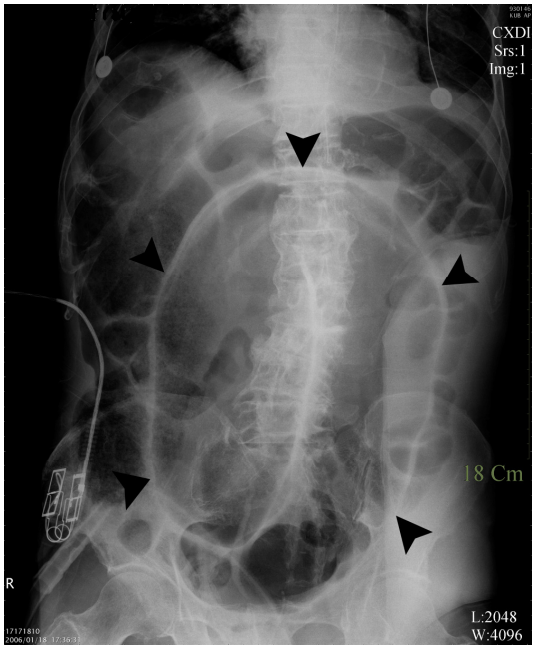
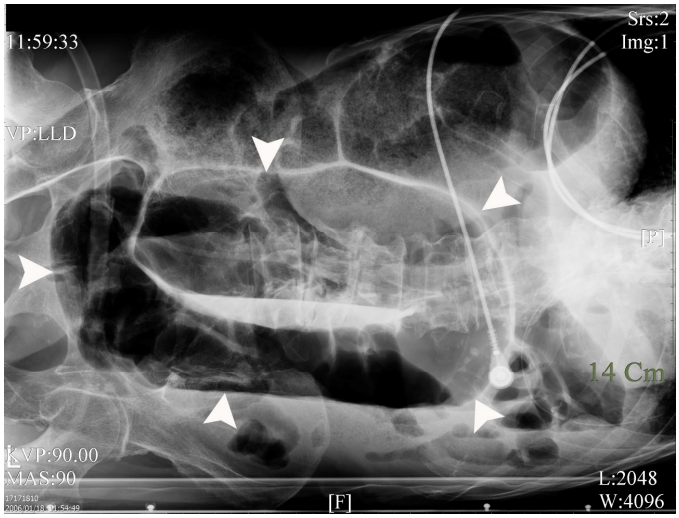


Figure 2



Questions—*What is the diagnosis and what is the management?*

Diagnosis: sigmoid volvulus

The pictures show a significantly dilated sigmoid colon with unremarkable haustra. The loop bends superiorly, and the two limbs of the loop converge inferiorly, forming the “coffee-bean” appearance (arrowhead).

In the absence of features of peritonitis or bowel necrosis, colonoscopic volvulus derotation is recommended, followed by semi-elective single-stage colonic resection.

If a skilled hand in colonoscopy is unavailable, emergent resection with or without anastomosis also provides an effective outcome.

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Statins against sepsis in patients with cardiovascular disease?

Now and again an old drug is given a new role—aspirin being the most notable: analgesic and then antiplatelet action. So it is not a great surprise that it may happen to the statins. In a recent obervational study of 141,487 patients with cardiovascular disease and statin usage, the authors conclude that statin therapy is associated with a considerably decreased rate of sepsis, severe sepsis, and fatal sepsis.

An accompanying commentary speculates that the pleiotropic effects of statins—e.g. anti-inflammatory and antioxidative properties, modulation of cellular immunity, improvement of endothelial function, or increased bioavailability of nitric oxide—might contribute to the putative antisepsis effect, and most of these effects are independent of lipid lowering.

Lancet 2006;367:413–18 and 372–3

Screening mammography for breast cancer—the pros and cons

Two recent papers, one from the Nordic Cochrane Centre and the other an editorial discuss (?debate) this issue. It has been estimated that for every 400 women screened over a 10 year period, one less women dies from breast cancer than would have died had they not been screened. This equates to one in eight fewer breast cancer deaths in the target age group.

That is the good news. The down side is the rate of recall of women for assessment who do not have cancer. Approximately 1 in 8 of all women who are screened three times over a 10 year period will be recalled at least once. This seems high and the frequency of these “false positives” is certainly alarming for the women concerned.

The Nordic group believe the benefits and harms of screening for breast cancer are delicately balanced and women should decide for themselves, on an informed basis. Furthermore they believe that they are not adequately informed. The editorial view is that despite limitations, it does save lives.

BMJ 2006;332:499–500 and 538–41

Cystic fibrosis and inhaled hypertonic saline

Impaired lung function and predisposition to infection are the hallmarks of cystic fibrosis—presumably both due to tenacious thickened mucus in the bronchi and associated impairment of ciliary action. Inhaled hypertonic saline increases mucociliary clearance and, in short-term trials, improves lung function in people with cystic fibrosis. But is it feasible and useful in the long term? A recently reported trial compares the effects of inhalation of 4 ml of either 7% hypertonic saline or 0.9% (control) saline twice daily for 48 weeks. A bronchodilator was given before each dose, and other standard therapies were continued during the trial.

Lung function tests and clinical well-being were significantly better in the hypertonic group. An accompanying editorial notes the benefits but wonders whether patients will be able to tolerate the taste of the saline and spend the 30 minutes (×2) required for the treatments.

N Engl J Med 2006;354:229–40 and 291–3

White coats or not—again

University hospitals in North America are awash with seas of white coats. Doctors are readily identifiable, their name and clinical service clearly embroidered on their breast pockets. Students are also part of this white brigade, albeit in shorter coats.

It used to be like that here—a few would prefer it to so now. However, the white coat persists in the USA. Why? Surveys mention pockets being useful for stethoscopes, reflex hammers, penlights, work notes, "to do" lists, and pocket clinical manuals. Then there are traditional reasons—instant recognition by patient and public alike and the white coat's value as an integral part of the tradition and practice of medicine.

All seem valid reasons to your scribe.

Med J Aust 2006;184:257

Brave new (electronic) world

Speaking in the House of Lords recently, neurobiologist Susan Greenfield asked a question that affects all of us: is technology changing our brains?

A recent British survey of 8 to 18-year-olds suggests they are spending 6.5 hours a day using electronic media. Such a method of learning is completely different to the process of traditional book-reading, which involves following an author through a series of interconnected steps in a logical fashion. Traditionally, book learning enabled us to "build a conceptual framework that enables us to evaluate further journeys…One might argue that this is the basis of education…"

She fears that the flashing icons may alter the way children think. Yes think about that.

Guardian Weekly, 28 April–4 May 2006, p14

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Regarding New Zealand Medical Association's position on the minimum purchase age for alcohol

The New Zealand Medical Association (NZMA) opposed the lowering of the drinking age in 1999 and until recently supported returning it to 20 years of age. In their recent written submission to the Select Committee they concluded:

> Although the NZMA opposed the original decision to lower the purchase age, we are not convinced that the problems associated with excessive alcohol use by young people can be curbed simply by re-raising the age to 20 years. Therefore, we do not support that proposal within the Bill.

This stance simply ignores the research evidence. Four studies conducted in New Zealand, by independent groups of researchers, using a variety of methods, showed deleterious health effects of lowering the minimum purchase age in 1999.[1–4] Furthermore, in a meta-analysis of 23 published studies on the effects of increasing the drinking/purchase age in the USA, median reductions in the incidence of various traffic crash outcomes were 12%–16%.[5]

In their submission, the NZMA only refer to one of numerous published papers on this subject. Could the NZMA explain to readers why their submission was not based on an adequate review of the public health evidence?

Dr Boswell in his oral submission to the Select Committee is reported (*Otago Daily Times [ODT] 4 May 2006*) as saying "*There is no clinical evidence to suggest alcohol was more harmful to an 18-year-old than a 20-year-old.*" Could Dr Boswell advise readers whether this is an accurate quote and if so: (a) what is meant by 'clinical evidence?' and (b) the lengths that NZMA went to verify this statement.

Dr Boswell is reported (*ODT 4 May 2006*) as advising the Select Committee that there had *"…been vigorous debate among NZMA members—many of them medical students."*

The written submission also states:

"…membership includes significant numbers of medical students and young doctors." Readers could be forgiven for thinking that factors other than a considered review of the evidence were bought to bear on their deliberations. Could NZMA advise the relevance of these statements in undertaking an evidence-based approach to the evidence?

John Langley
Director

Kypros Kypri
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Response

Drs Langley and Kypri are obviously disappointed that the NZMA does not support their view that New Zealand, having lowered the legal age for alcohol purchase from 20 to 18 in 1999, should raise it again to 20 in 2006.

NZMA policy is determined by the NZMA Board, on the advice of elected representatives from committees and views expressed by individual NZMA members. This issue was debated vigorously and the Board determined by consensus that as a matter of policy we do not support the raising of the legal purchase age.

Factors taken into account include the following:

- New Zealand has serious problems with alcohol misuse at all ages, including ages much younger than the current legal purchase age.
- Current advertising in New Zealand promotes alcohol to young people and associates it with heroic figures such as sportspeople.
- New Zealand regards 18 as the age of maturity for other purposes such as marriage, voting, and service in the armed forces.
- Countries with which we identify such as Australia and the UK also have 18 as their legal purchase age.
- We can find no clinical evidence (I expect readers will understand this term) that alcohol does harm to an 18-year-old that it does not do to a 20-year-old.
- There is evidence that the current law is not being enforced effectively (such as recent public health officer and police operations which revealed bars and bottle stores selling alcohol to minors without checking their identification).

Langley and Kypri quote four studies conducted in New Zealand by independent groups of researchers, using a variety of methods which, they say *"showed deleterious health effects of lowering the minimum purchase age in 1999."* I do not doubt their sincerity or their accuracy, but I dispute the relevance of these studies. Evidence that lowering the purchase age was associated with increase in harm is not evidence that raising it again will decrease harm. Even if it were, we are aware of other evidence conflicting with their view of the effect of the reduction in the drinking age: drivers aged 15–19 accounted for 14% of fatal crashes in 1996—3 years prior to the law change and only 9.1% in 2002, 3 years after it.[1]

Harm reduction should be the target of any new legislation in this field, but published evidence that we can find is that where the legal purchase age has been raised from 18 to 20 reduction in harm was minimal.[2–4] While it is possible, even likely, that raising the legal purchase age to 20 might have some effect in preventing injury and ill-health, we have no doubt that raising it to 30, or 40, or 50 would be considerably more effective. The choice of 20 as a proposed age is entirely arbitrary.

In our view, the proposal to raise the age to 20 is not well justified, and it falls far short of dealing effectively with the problems that New Zealanders, and especially young New Zealanders, have with alcohol. For that reason we do not support it. We have called instead for a comprehensive package of measures including public education, enforcement of the existing laws, and controls on advertising.

Ross Boswell
Chairman, NZMA

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In defence of Ayurvedic medicine

Dr van Schalkwyk and his colleagues are right to alert the profession to contaminated preparations (*Ayurvedic medicine: patients in peril from plumbism*; http://www.nzma.org.nz/journal/119-1233/1958) in the 5 May 2006 issue of the NZMJ, but they overstep the mark when they cast aspersions upon one of the World's major medical traditions.

When they state…

> We wish to alert the medical community to a substantial threat to wellbeing posed by a particular form of herbal remedy, namely Ayurvedic medicine

…they appear to be unaware that Ayurvedic medicine consists of a great deal more than "a particular form of herbal remedy."

Herbal remedies form a part of Ayurveda, but to taint Ayurvedic medicine and, by implication, its practitioners as a "threat to wellbeing" based on their findings in eight isolated cases is unfair. The preparations in the cases cited appear to have come from unaccredited facilities and should not be taken as representative of all Ayurvedic herbal preparations, nor of Ayurvedic medicine in general.

For example I have visited the Maharishi Ayurveda Products Laboratory (MAPL) run by Maharishi Mahesh Yogi's organisation in Delhi. I was impressed by the management's systematic approach. MAPL holds Certification of Compliance ISO/IEC 17025: 1999. This relates to product standardisation and the exclusion of heavy metals and residual pesticides. MAPL also holds ISO-9001-2000, HACCP, WHO-GMP, and the National GMP certificates. As holder of these certificates, MAPL is regularly audited by independent authorities. The only metals used in MAPL products are iron and zinc.

Ayurvedic medicine is a vast compendium of medical knowledge representing a tradition of some 4000 years found in India, Sri Lanka, and Thailand. Within the classical treatise, the *Charaka Samhita*, are detailed techniques of diagnosis, a knowledge of anatomy, instructions on dietetics, a system of aetiology and pathogenesis from which we could learn much, a classification of diseases, therapeutics including lifestyle interventions, and a clear definition of health. Ayurvedic medical therapy takes into account individual body type, time of life, and seasonal variations in its treatments.

The *Charaka* includes ethical considerations and regulations for the dispensing of preparations derived from detailed knowledge of the actions and uses of the 10,000 or so herbs contained in the Ayurvedic pharmacopoeia. Ayurvedic medicine suffered greatly during Indian occupation, tending to become scattered with a loss of standardisation. During the last 20 years, a number of organisations, including the World Health Organization have been involved in its revival. In particular, the Indian sage and scholar Maharishi Mahesh Yogi has thrown new light on Ayurveda and made an invaluable contribution to its proper and widespread understanding.[1]

I suggest, in keeping with the trend towards cultural awareness, we remain mindful of the well-known advice concerning motes and planks when evaluating another medical tradition. After all, there is also a common belief among the public that use of 'Western medicine' is harmless.

With iatrogenesis now ranked as a major cause of death in the United States,[2] this assumption is far from the truth—further indeed than any such assertion about Ayurvedic medicine. The roster of adverse effects from Western preparations is long and sometimes disastrous—as we saw recently in the case of TGN1412 when it was trialed in the UK.

Properly practised, and its preparations correctly prepared and dispensed, the long-established tradition of Ayurvedic medicine is benign when compared to the unedifying mortality and morbidity that has accrued under the fledgling Western tradition.

Hugh David Lovell-Smith
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Response

Dr Lovell-Smith refers to the preparations we described in our paper as *contaminated*, but he fails to address the issue (stated in our paper) that traditional Ayurvedic medicine appears to attribute beneficial therapeutic effects to administration of carefully prepared heavy metals. It would seem that according to Ayurvedic tradition, heavy metals are *deliberately introduced* for therapeutic effect. The presence of lead in the amount of 20% by weight (Case 1) can hardly be seen as 'contamination'.

We are pleased that the organisation he commends appears to have broken with Ayurvedic tradition in excluding lead from their preparations. Until all practitioners of Ayurvedic medicine similarly exclude heavy metals from their products, it would seem wise to exercise caution with such products.

The quality controls Dr Lovell-Smith mentions are also important. Even a generally well-informed consumer of Ayurvedic medicine may well not be aware of the importance of accredited testing in laboratories implementing ISO/IEC 17025—one of the cases we described was a pharmacist (Case 8)! It is worth mentioning that ISO/IEC 17025 (General Requirements for the Competence of Calibration and Testing Laboratories) is largely a product of Western science, not Ayurvedic tradition.

It should be clear from our paper that we are not commenting on other aspects of Ayurvedic medicine (diagnoses, anatomy, dietetics, disease classification and pathophysiology, therapeutics, and health). Each of these should wisely be taken on its own merits. Nor are we acting as apologists for Western medical iatrogenesis! We are simply alerting medical practitioners to the consequences of an age-old tradition which here turns out to be incorrect and harmful.

Eight cases of lead poisoning in the Auckland region can neither be considered 'isolated' nor be disregarded in deference to 'cultural awareness'. There are doubtless many 'traditional' aspects of Medicine (Western and alternative) which similarly need to be examined under the spotlight of reasonable science.

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Buteyko breathing technique and asthma in children: a case series

Asthma is a common disorder in New Zealand, with estimates of prevalence as high as one in six of the population affected.[1] The annual cost of asthma drugs is high—in 2005, approximately NZ$34 million was spent on inhaled corticosteroids and β_2-agonists.[2]

The use of β_2-agonist in chronic asthma is itself contentious, with a recent meta-analysis concluding that regular use of β_2-agonist resulted in tolerance within 1–3 weeks as well as being pro-inflammatory to the airways.[3] Interventions that have the potential to reduce β_2-agonist insult to the airways of people with chronic asthma are deserving of further investigation.

The Buteyko breathing technique (BBT) is an intervention for asthma that is associated with significant reductions in medication use as well as improvements in other indices such as symptom scores and quality of life in adults.[4–7]

Previous work demonstrates the effectiveness of BBT in adults.[4,6] To date, there has been no published work looking at the impact in children.

We report a case series that considers the place of BBT in children.

Methods

To find suitable participants (Table 1), we approached local general practices and advertised in the local (Gisborne) newspaper. Twenty-six children were identified of whom 8 (aged 7–16 years) were eligible for inclusion; being previously diagnosed with asthma by their GP and using medication for asthma for at least 6 months with significant use of medication for asthma in the 2 weeks prior; no prior instruction in BBT; and no significant unstable medical condition.

Intervention

Participants underwent training in BBT (by a representative of the Buteyko Institute of Breathing and Health) over five sessions of 60–90 minutes held over 5 consecutive days. BBT consists of a series of exercises promoting nasal breathing and periods of hypoventilation.[8]

Outcome measures

Prior to tuition, and at 3 months following instruction in BBT, participants (along with their parent/guardian) self completed a questionnaire ascertaining:

- Medication use over the previous 2 weeks;
- Symptom scores over the previous 2 weeks;
- Courses of oral steroids over the previous 3 months; and

- Absences from school due to asthma over the previous 3 months and admissions to hospital over the previous 3 months.

At 3 months, participants were also asked whether BBT had been helpful or not in the management of their asthma. Any changes in medication after instruction were to be in association with their own general practitioner.

Results

Table 1. Characteristics of participants at end of run-in

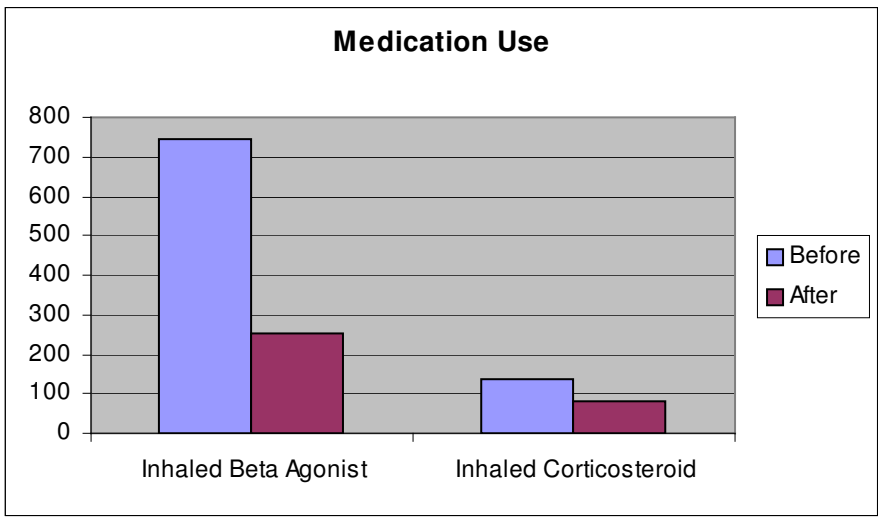
Variable	BBT Group (n=8)
Gender (male : females)	4 : 4
Mean age (range) in years	11.1 (8–14)
Ethnicity (European : Maori)	4 : 4
Mean years with asthma (range)	7.5 (4–12)
Mean daily adjusted β_2-agonist dose in mcg equiv salbutamol (standard deviation)	742 (624)
Mean daily adjusted inhaled steroid dose in mcg equiv fluticasone (standard deviation)	137 (119)

BBT=Buteyko breathing technique.

Changes in medication use

Average β_2-agonist use reduced from 743 mEq of salbutamol per day to 254 mEq/day, a drop of 66%. Inhaled steroid use reduced from 138 mEq of fluticasone per day to 81 mEq/day, a drop of 41% (Figure 1).

Figure 1. Medication use (mEq) by participants before and after training in Buteyko breathing technique



Qualitative measures

There were no admissions to hospital in the 3 months before or after instruction in BBT for any of the participants. In the 3 months prior to instruction in BBT, 8 days of school were missed by three participants. There were 4 days missed by two participants in the 3 months after BBT tuition. The post-instruction period of 3 months did, however, include 6 weeks of school holidays.

In the 3 months prior to tuition in BBT, three participants had 11 courses of oral steroids, and in the 3 months post-tuition, one participant had one course of oral steroids. Average symptom scores in the 3 months before tuition in BBT went from 1.5 to 0.875 in the 3 months post-tuition (where 0=no symptoms, 1=mild, 2=moderate, and 3=severe).

Of the eight participants, one reported "no change" in his/her asthma, six reported "slightly improved", and one reported "markedly improved". There were no reports of "slightly deteriorated" or "marked deteriorated".

Discussion

There have been several published randomised controlled trials involving the use of BBT in adults with asthma.[4,6,7] These trials have all shown positive results with marked reductions in inhaled β_2.agonist along with reductions in inhaled corticosteroids without negative impact on measures of lung function and with no apparent adverse effect. There is, however, no data for BBT in a paediatric setting.

In this study we used accepted diagnostic criteria for asthma.[9] We recognise that this has the potential to include a broad group, including dysfunctional breathing.[10]

In this series, we have identified that BBT is associated with change in medication in children that mirrors results found in adults (Table 2).

Table 2. Comparison of medication reductions in BBT trials to date

	Brisbane[3]	Gisborne[5]	Nottingham[6]	This series
Beta-agonist reduction	95% *	85%	100% *	66%
Inhaled steroid reduction	49%	50%	41.5% **	41%

BBT=Buteyko breathing technique; *Results are reported as mean unless marked with * in which case are median; **Nottingham did not attempt reductions in inhaled steroid use until assessment of airways hyper-reactivity was finished.

In addition to reduction in medication there were improvements in measures of quality of life scores, symptom scores, and also a reduced number of courses of oral steroids.

The small size and self-selection of the patient group in this case series limits any more meaningful commentary on the results.

However given the association between BBT and medication reduction in this group of children, and the similarity with adults, we suggest that BBT would merit exploration by a randomised controlled trial in children. In addition, we agree with a

recent review of BBT which states that further research is necessary to establish whether BBT is effective, and if so, how it may work.[11]

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