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Parallel infusion of hydrocortisone ± chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites

Simon G A Brown
Emergency Physician, Fremantle Hospital & Health Service, and Clinical Senior Lecturer in Emergency Medicine, University of Western Australia, Department of Emergency Medicine, Fremantle Hospital, Alma Street, Fremantle, WA 6160.
simon.brown@health.wa.gov.au

TO THE EDITOR: Gawarammana et al present an interesting study of premedication to prevent adverse reactions to snake antivenom,[1] but I have concerns with the data presentation and analysis. The 95% confidence intervals presented in Box 3 of their article are impossibly narrow. For example, recalculation of the first cell (hypotension rate for treatment A) by the binomial method gives a 95% confidence interval of 12%–62%, not 30%–36% as presented. Also, my analysis of the aggregate endpoint differs. Using the Fisher exact test to compare reaction rates in the hydrocortisone + antihistamine group (11/21) with placebo (13/16), for the difference in proportions of 0.29 I obtain a 95% confidence interval of −0.04 to 0.58. This has a *P* value of 0.14 using a 2-tailed test, according to the program Analyse-it.[2]

This comes as no surprise given that steroids take hours to work, and that histamine is just one of many mediators released during anaphylaxis, rising early and only transiently during severe and protracted anaphylactic reactions.[3] Although antihistamines reverse the effects of histamine infusions which mimic anaphylaxis, animal studies indicate that they are ineffective for treating anaphylaxis mediated by mast-cell degranulation.[4,5]

Human studies have shown that H_1 blockade is useful in preventing mild reactions to immunotherapy that are confined to the skin, but do *not* appear to prevent severe reactions.[6,7] One human study has compared H_1 + H_2 blockade with H_1-only blockade for the management of mild allergic reactions, finding a small benefit of combined H_1 + H_2 blockade.[8] However, a confounder was that adrenaline was administered more frequently in the combined H_1 + H_2 antihistamine treatment group. A study of reactions to immunotherapy has failed to show any benefit from H_1 + H_2 blockade.[7]

I suspect that, instead of proceeding to study combination prophylaxis with antihistamines, steroids and adrenaline, it might be better to examine the preparation for and management of allergic reactions to antivenom. Many doctors fear intravenous adrenaline infusions, but in our experience this approach to managing anaphylaxis is safe, well tolerated and immediately effective, without the unpredictable, unpleasant, and (in the setting of venom-induced coagulopathy) potentially dangerous side effects sometimes seen with intramuscular, subcutaneous and intravenous bolus injections.[9] Perhaps it is time for a trial of premedication with subcutaneous adrenaline versus an "as required" approach using a carefully titrated intravenous infusion.

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S Abeysingha M Kularatne,*
Indika B Gawarammana†
* Senior Lecturer, † Lecturer, Department of Medicine, Peradeniya University, Sri Lanka. samkul@sitnet.lk

IN REPLY: Brown has pointed out some interesting observations about antihistamines and mediators such as

histamine, released during anaphylactic reactions.

First, we must address the statistical issues. We are grateful to Brown for detecting an important error in Box 3 of our article.[1] When we were asked to calculate confidence intervals for the percentages, we used a formula recommended by Spiegel.[2] As this formula was not available in our software packages, we programmed it ourselves. We made an error in our programming and we apologise for this. (See *Correction*, page 428.)

For the difference in reaction rates for the treatment regimens, we used the following calculation.

Treatment	No.	Reactions	Probability
A	21 (N_1)	11	0.5238 (P_1)
B	16 (N_2)	13	0.8125 (P_2)

The difference $P_1 - P_2 = -0.2887$

To calculate the confidence interval, we calculated the standard error (SE) of the difference by the following formula.

$$SE = \sqrt{\frac{P_1(1-P_1)}{N_1} + \frac{P_2(1-P_2)}{N_2}}$$

$$= 0.1463$$

$$95\%\ \text{CI} = -0.2887 \pm 1.96 \times 0.1463$$

$$= -0.002 \text{ to } -0.5754$$

This interval does not include 0, so Brown's P value of 0.14 is not reasonable. We do accept that the statistical significance is marginal.

We agree that antihistamine is ineffective as a prophylactic agent in anaphylaxis. This was observed in studies in Sri Lanka and Brazil, where chlorpheniramine and promethazine, respectively, were used to prevent reactions to antivenom.[3,4] However, we defended the observed reduction of mild to moderate acute reactions to antivenom in our study by highlighting the counter-effect of antihistamine on released histamine after mast-cell degranulation.[1]

Our study was to test the usefulness of an established practice in Sri Lanka, where steroid infusion is used to counter reactions to antivenom. The crux of the problem is the highly antigenic antivenom preparations used in Sri Lanka, despite ever-increasing reaction rates, because of the lack of facilities for developing purified antivenom.

The proposal of using intravenous adrenaline infusion to reduce allergic reactions is novel and exciting. This should be tested by randomised controlled trials.

1. Gawarammana IB, Kularatne SAM, Dissanayake WP, et al. Parallel infusion of hydrocortisone ± chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites. *Med J Aust* 2003; 180: 20-23.
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Val J Gebski

Principal Research Fellow, NHMRC Clinical Trials Centre, Level 5, Building MO5, Mallett Street Campus, University of Sydney, NSW 2006. val@ctc.usyd.edu.au

COMMENT: Kularatne and Gawarammana compared the proportion of side-effects given in their table above using the well-known (and easily understood) test of the difference between two proportions using the normal distribution. However, as each of these proportions follows a binomial distribution (13 "successes" out of 16 trials and 11 "successes" out of 21 trials), the normal approximation is only useful if the number of trials is greater than 30.

Because of the small sample sizes, "exact" methods better reflect the true difference (in terms of P values and confidence intervals) between the two proportions. The more complicated methods (different formulations of the exact test) and the resulting confidence intervals provide a clearer indication of whether the proportions are indeed different (statistically). In this instance, the evidence is not sufficient to declare the two proportions statistically different. ❑

Multidisciplinary care for women with early breast cancer in the Australian context

Michael A Quinn

Director, Oncology and Dysplasia Unit, Royal Women's Hospital, 5th Floor, 132 Grattan Street, Carlton, VIC 3053. michael.quinn@maynegroup.com

TO THE EDITOR: A recent article by Zorbas et al[1] highlights some of the many difficulties experienced by Australian women in accessing multidisciplinary care after they have been diagnosed with breast cancer. A multidisciplinary approach to women with gynaecological cancer has been the cornerstone of care since the establishment of gynaecologic oncology units in Australia in the early 1980s. Over 20 years' experience has reinforced the value of this approach.

By and large, however, the success of this model has very much depended not only on the skills of the multidisciplinary team but also on the readiness of referring doctors — in this case, specialist gynaecologists — to refer patients for management that is often surgical and could easily be done by themselves. Reinforcing the concept that care of the patient is holistic and that surgery plays an important (but not definitive) role in overall care has led to increased referrals, but there are still many to convince. For instance, a survey published in the Journal in 2002[2] showed that in the late 1990s more than half the women with ovarian cancer in Victoria were still being operated on outside established gynaecologic oncology units or by a non-gynaecological oncologist.

It is to be hoped that new National Health and Medical Research Council guidelines on the management of ovarian cancer (soon to be released) will reduce this deficit and thereby improve outcomes for women with ovarian cancer. Much of the development of this benchmark care has come from patients, who, thankfully, are becoming increasingly articulate in their expectations of optimal clinical outcomes.

The question of rural patients is an extremely important one. In Victoria, over a period of more than 10 years, the three major metropolitan gynaecologic oncology centres have established satellite clinics in country towns to facilitate patient follow-up, often involving local specialists and family doctors. This system seems to have worked well and is worthy of assessment as a model that might be transferable to other specialties.

In conclusion, it is all very well setting up multidisciplinary teams, but the key to their success has to be the recognition of professional equality. If teams are based on a hierarchical setup they are likely to fail in their major aim, which is to provide the best care available based

on input from a broad range of professionals and from patients themselves.

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2. Grossi M, Quinn MA, Thursfield VJ, et al. Ovarian cancer: patterns of care in Victoria during 1993–1995. *Med J Aust* 2002; 177: 11-16. ❑

Susan C Pendlebury,* Katherine J Clark,† Martin H N Tattersall‡

* Radiation Oncologist, † Palliative Care Physician, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050; ‡ Professor of Cancer Medicine, University of Sydney, Sydney, NSW.
spendleb@email.cs.nsw.gov.au

TO THE EDITOR: Zorbas et al[1] have highlighted both the complexities and resource intensiveness of multidisciplinary care for women with early-stage breast cancer. The same arguments exist in advanced disease, where input from many disciplines is the norm. However, there is no evidence that such a process improves outcomes in the Australian setting. The references the authors draw upon relate to regions in which breast cancer outcomes have historically been poor. Evidence from Australian studies suggests higher standards of care and appropriate changes over time.[2,3,4]

The National Health and Medical Research Council (NHMRC) *Clinical practice guidelines for the management of early breast cancer*[5] provide an evidence-based strategy for managing the disease. Enshrined within them is the concept that many different treatment approaches are equivalent and that patient preferences are important. Patient input into multidisciplinary case conferences is frequently minimal. Case conferences can be confusing for patients, and it may not be clear to them who is their doctor. Many clinics include a breast nurse, who commonly acts as a patient advocate. Zorbas and colleagues note the different models of multidisciplinary care, but the minimum approach required to achieve good outcomes has not been established.

It is not surprising that 34% of rural surgeons find it difficult to implement a service in which all women have access to a full range of treatment options in a multidisciplinary setting. There is no evidence, however, that their patients are more unhappy or that management outcomes are inferior. Similarly, the guidelines correctly promote the importance of psychosocial support for patients, but the suggestion that this can be better achieved by a psychologist via teleconferencing rather than by the patient's general practitioner is purely speculative.

None of the multidisciplinary models suggested by Zorbas et al addresses the management of patients at relapse, and yet data and clinical experience indicate this is the time of greatest stress for patients,[6] a time when input from a number of specialties — medical care, radiation oncology, palliative care — is the norm.

Multidisciplinary care appears to be beneficial regardless of the stage of disease. However, the execution of some of the models is resource-intensive. We need to evaluate not only whether the objectives of the NHMRC guidelines are met, but whether patient satisfaction and participation are enhanced, survival outcomes are improved and care through all stages of the disease is optimal. Currently, by such measures, multidisciplinary care has not been shown to be superior to a small number of well-directed, evidence-based selective consultations.

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Helen M Zorbas,* Bruce H Barraclough,† Katherine J Rainbird,‡ Karen A Luxford,§ Sally Redman¶

* Clinical Director, ‡ Manager, Treatment Program, § Program Director, National Breast Cancer Centre, Locked Bag 16, Camperdown, NSW 1450; † Director of Cancer Services, Department of Surgery, Royal North Shore Hospital, St Leonards, NSW; ¶ Director, Institute for Health Research, Sydney, NSW.
karenl@nbcc.org.au

IN REPLY: We agree with the comments by Pendlebury et al that knowledge about outcomes for patients receiving multidisciplinary care in Australia is limited. Hence, the National Breast Cancer Centre has investigated the application of multidisciplinary care and outcomes for women with breast cancer. Our article focused on the "Principles of multidisciplinary care" developed as a basis for a subsequent project (outcomes yet to be published). It was necessary to define such principles at the outset, as there is not yet an agreed view about what constitutes "multidisciplinary care" within the Australian healthcare context.

We also agree that the standard of clinical care in Australia is generally good. However, delivery of care is often fragmented and inconsistent.[1] In other countries with high quality services, multidisciplinary meetings have been found to result in care that is more in accord with the evidence than non-multidisciplinary care.[2] The Principles emphasise the role of the general practitioner, while recognising that some patients will require appropriate specialist referral.[3] They also state that living in a rural area should be no impediment to accessing care.

We agree that multidisciplinary care is as important in advanced breast cancer as it is in early disease. The Principles were developed before the release of the guidelines for advanced breast cancer and it would be useful to extend them in the future.

The importance of one main contact for women is acknowledged. The purpose of a multidisciplinary case conference is to identify treatment options and their relative merits. This ought to assist communication with women and enable them to make a more informed choice.

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Australian rural high school students' interest in health careers: implications for our future workforce?

John Fraser,* Christian Alexander,† Berniece Simpkins‡

* Director, † Senior Research Fellow, ‡ Health Career Promotion Project Officer, New England Area Rural Training Unit, New England Area Health Service, PO Box 83, Tamworth, NSW 2340

jdfraser@doh.health.nsw.gov.au

TO THE EDITOR: We read with interest the recent article concerning Australian medical workforce issues.[1] Brooks et al comment on feminisation, lifestyle changes, increased community demand and globalisation as major issues for the future medical workforce.

Here, we present data from recent rural high school health career promotion activities, describing student interest in health careers. These data further support this trend in feminisation. Promotion of health careers in high schools is a core long-term rural workforce strategy in Australia.[2] It is justified, as rural origin is an important predictor of medical graduates pursuing a rural health career.[3]

The New England Area Rural Training Unit (NEARTU) promotes rural health careers to school students, undergraduates and postgraduates in northwest New South Wales. Multidisciplinary regional health career expos were offered to all high school students in Years 9 to 12 from 2000 onwards in the regional centres of Armidale, Tamworth and Moree.

Medical, nursing and allied health professionals and undergraduates (of both sexes) staffed the expos. Inquiries were recorded by sex, year at school and health career. Students could enquire about multiple careers.

In 2000, 453 high school students (394 female; 59 male) expressed an interest in health careers at expos. The Box displays that, for both female and male Year 9 to Year 11 students, interest in a nursing career far exceeds interest in either allied health or medicine, and, for Year 12 students, an interest in allied health far exceeds interest in either nursing or medicine.

Enquiries were more frequent from females than from males, ranging from just over four times (medicine) to eight times more frequent (nursing). In 2000, 60% of these students' enquiries (270 enquiries) referred to nursing, 33% (151 enquiries) referred to allied health and 7% (32 enquiries) referred to medicine. Compared with the Australian Bureau of Statistics 2001 data, which showed a 50.4 to 49.6 ratio of females to males in the region's high schools, our increased interest by females is statistically significant ($P < 0.01$). In other careers projects by NEARTU in 2000–2002 (eg, work experience placements, and health career promotion at local agricultural field days), similar sex differences were observed (female-to-male ratio range, 10:1 to 3.5:1).

Increased interest by female high school students is consistent with other reports of high school students' health career preferences in the United States.[4,5] Registering interest is only the first step in considering a health career. The higher proportion of females expressing this interest in rural high schools is important for rural workforce planning.

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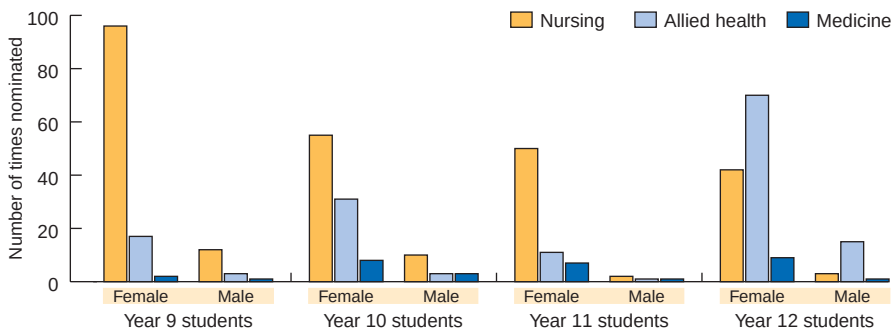
Interest in health careers by high school students in 2000



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Nodular melanomas and older men: a major challenge for community surveillance programs

Alex J Chamberlain,* John W Kelly†
*Registrar, †Head, Victorian Melanoma Service, The Alfred, Prahran, VIC. alex_chamberlain@hotmail.com

TO THE EDITOR: Janda and colleagues' survey of skin screening by general practitioners in regional Queensland[1] demonstrated that only 20% of participants had undergone a total-body skin examination in the previous 3 years and that examination rates were slightly lower for patients 50 years of age and older. They conclude that those at greatest risk (older people, especially men) will need to be targeted if screening programs are to reduce melanoma mortality.

In the same issue of the Journal, a study by English and colleagues of excisional biopsies of pigmented lesions by Perth GPs showed that the excision rate for patients under the age of 50 years (62%) is nearly twice that for patients over 50 years (38%), and that in the younger cohort this is primarily harvesting benign naevi.[2] They conclude by encouraging GPs to increase their suspicion and lower their biopsy threshold in older patients in order to detect more melanomas.

These studies serve to remind us that it is predominantly older people (and especially men) who are at greatest risk of thick (and potentially lethal) melanoma.[3] The evidence provided by these studies of mismatch between skin cancer risk and resource allocation to surveillance and excisional surgery might help explain why recent advances in early detection seem to have bypassed elderly men. It is of continuing concern that despite the fact that melanomas are currently diagnosed at an earlier stage when compared with 20 or 30 years ago, the background incidence of thick melanoma has remained stable, both in Australia and around the world.

In a recent study conducted in Victoria,[4] we found that thick melanomas (≥3 mm) were predominantly nodular melanomas, primarily affecting people over 50 years of age and especially men. This elusive subtype frequently fails to fulfil the "ABCD" (asymmetry, border, colour, diameter) diagnostic criteria in that they are more often uniform in colour, symmetric in shape and predominantly amelanotic.[5] A possible *aide-mémoire* that we have suggested elsewhere for identifying nodular melanoma is the addition of "EFG" ("elevated, firm, growing for more than 1 month") criteria.[6]

The observation that nodular melanomas grow quickly, leading to deep invasion within a few months, poses a significant obstacle to the potential success of community-based screening programs.[1] It is likely that many nodular melanomas will escape early detection by such programs, as they will evolve significantly in the interval between screening examinations.[4,5] It is important that all clinicians recognise this subtype if we hope to reduce melanoma mortality in Australia.

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