

EDITORIAL

Bandolier leads this month with a report of an alternative medicine intervention in depression. This sound systematic review shows that St John's wort was more effective than placebo, performing as well as (low) doses of antidepressants.

Time and effort

There is a problem here. Much time and effort goes into writing a systematic review of this calibre, and the number of people who can do it is finite. But choosing this topic means that another topic will not be reviewed. Limited resources mean that if something is done something else will not be. We need to be clear about our priorities. For which topics should money be provided? Should we put our limited resources into investigating alternative medicine remedies, knowing that that choice necessarily excludes other work?

Alternative medicine

Bandolier is puzzled about the origin of the pressure to receive alternative medicine into the church of conventional medicine. Is it due to the (sensible) realisation that much of shop-floor medicine is about coping with self-limited disease, and that alternative medicine remedies can help at least as well in this setting? Or is it due to a wider consumer pressure, a desire to wrest control from the professionals? The reality is that people choose to spend vast sums of money on these remedies, and systematic reviews like that on St John's wort help us to advise on which may be effective. We also have 9 systematic reviews of acupuncture on file, at least one of which is helpful.

Returning, like your tongue to a hole in your tooth, to our quandary about priorities, where do you think that the spotlight should shine? Has alternative medicine too high or too low a profile? Those of you who also read the *Lancet* will know that *Bandolier* welcomes your letters.

HERBAL REMEDY FOR DEPRESSION

Systematic reviews which tell us something we didn't know not only qualitatively but quantitatively as well, are few and far between. A first class review on the use of the herb St John's wort (*Hypericum perforatum*) for depression is a superb example [1].

Depression is a major public health issue, affecting many people, many of whom do not wish to use powerful synthetic antidepressants which can have significant adverse effects. Some herbal remedies can be effective, as *Bandolier* pointed out for Ginkgo biloba in peripheral vascular disorders in *Bandolier* 18.

St John's wort

Extracts of this herb have long been used in folk medicine. In Germany it is licensed for use in anxiety, depression and sleep disorders. The extracts contain many different chemical classes, so the "active agent" is a matter of uncertainty.

Quantitative systematic review

The review sought studies which were randomised comparisons of *Hypericum* extracts against placebo or other antidepressants. They found 23. When judged against a validated quality scoring system, almost half scored 80% or more of the possible points available.

The judgement of success was set by the reviewers as treatment responders. To be a responder, patients had to have a Hamilton depression score of less than 10, a reduction in Hamilton depression score of at least 50%, or be much improved or very much improved on a clinical global impressions index. Treatment or observation periods were usually four to eight weeks.

Seven different preparations had been tested. Daily doses of extract varied considerably in the trials, and dose was not a criterion used to judge efficacy.

Hypericum against placebo

Thirteen trials had extractable data. The overall response rate with placebo was 22% compared with 55% with *Hypericum*. Results of these trials are shown here in two plots.

The L'Abbé plot shows that 11 of the trials were in the upper left half of the graph, demonstrating effectiveness. A ladder plot of the risk ratio shows that nine of the 13 trials, and the combined estimate, all showed *Hypericum* to be significantly better than placebo (combined risk ratio 2.7, 95% CI 1.8 - 4.0).

The pooled NNT calculated from these numbers was 3.0 (95%CI 2.6 - 3.8). This means that for every three patients with depression treated with Hypericum, one more will have been relieved of depression whose depression would not have resolved on placebo.

Hypericum against conventional anti-depressants

Three studies compared Hypericum alone against rather low doses of maprotiline, imipramine or amitryptiline in trials involving 300 patients. There was no statistical difference in the trials singly or combined.

Adverse events

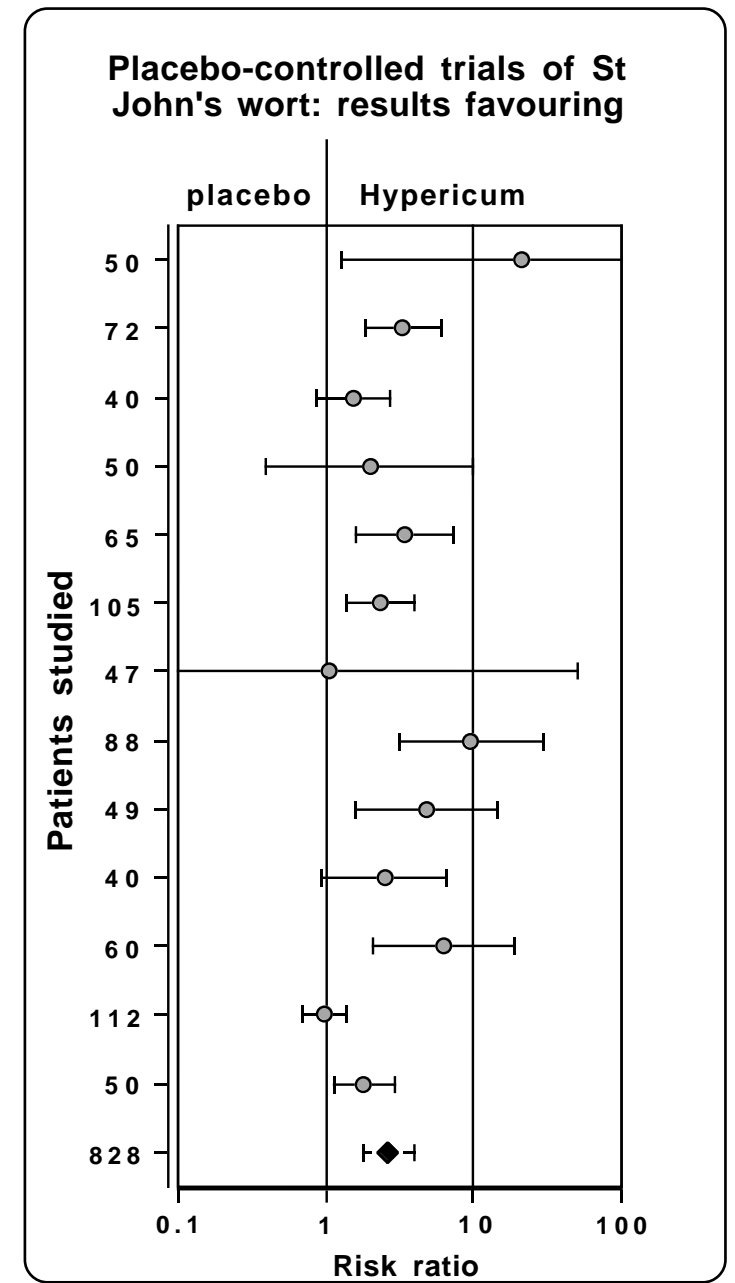
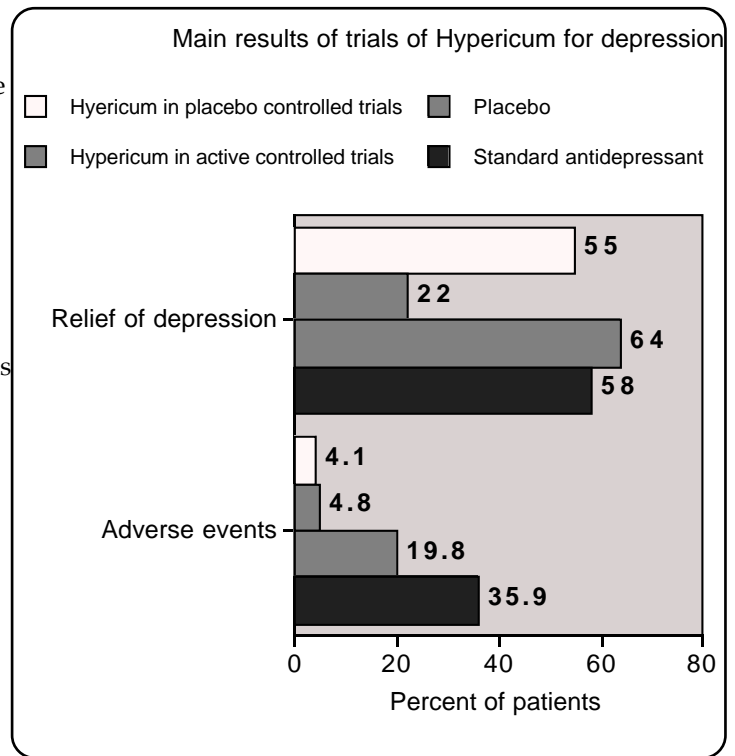
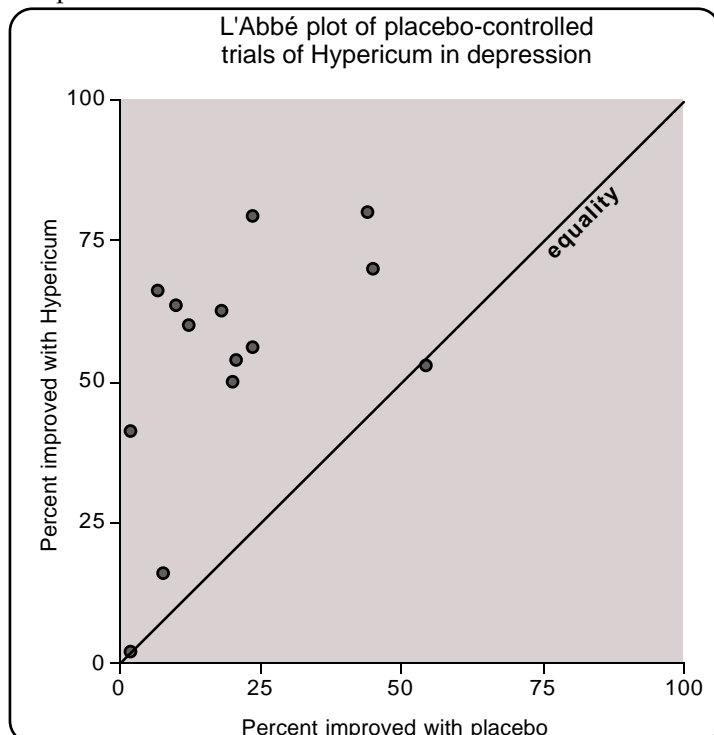
In placebo-controlled trials, 4.1% of patients reported adverse events with Hypericum compared with 4.8% on placebo. Major adverse events (withdrawals) were 0.4% and 1.6%.

In active controlled trials, 20% of patients receiving Hypericum reported adverse events compared with 36% with standard antidepressants (but remember the low doses). This yields a number need to harm for standard antidepressant (NNH) of 6 (95% CI 4 - 12); this means that for every six patients with depression treated with standard antidepressant, one fewer will have an adverse event who would not have had one if treated with Hypericum. Adverse event withdrawals were 0.8% and 3% for Hypericum and standard antidepressants respectively.

Comment

The authors make several points.

- That none of the articles would have been found if searches had been restricted to the English language.
- That multiple publication is a problem. One trial was published five times with two different first authors.



- That pooling studies of herbal preparations is problematic, because you really don't know what's in them.
- That despite these promising results, we need trials to evaluate the effectiveness of Hypericum against other antidepressants, and the trials need better defined classification of disease.

Reference:

1 K Linde, G Ramirez, CD Mulrow et al. St John's wort for depression - an overview and meta-analysis of randomised clinical trials. British Medical Journal 1996 313:253-8.

VERRUCAS AND GAMES

Bandolier's GP callers do ask some hard questions. One, faced with the problem of a schoolgirl patient not being allowed to take swimming in school because she had a verruca, challenged *Bandolier* to find any evidence that there was risk of infection.

Well, there is some. *Bandolier* could only find one paper which seemed to address this question, published in the US GP journal Family Practice in 1995 [1].

Plantar warts

Plantar warts (verrucae plantaris) are usually caused by type 1 human papillomavirus (HPV). The route of infection is thought to be through an abrasion or cut, and the virus attacks the granulosum and keratin layers of the skin.

Prevalence of plantar warts in a 1955 study of 13,000 East Anglian schoolchildren was 6.5 per 1,000, with a peak incidence at 13 for girls and 14 and 15 for boys. A US prevalence study in 1953, with 2,300 children studied in Illinois, was higher at 45 per 1,000.

Study of verruca infection

146 adolescents in Nashville, Tennessee, aged 10 to 18 years, were recruited from a local school (on the day of the study 80 of 150 children asked to participate agreed) and all the 66 members of a swimming club under 19 years. The two groups used different public changing rooms, but only the swimming club members used a public shower.

A standard protocol was used by physicians to collect information on use of public showers, use of shower sandals when bathing, sport participation, and history of verruca. Diagnosis of plantar wart was made on physical examination using the criteria of a well circumscribed cauliflower appearance and texture on palpation. All positive cases were examined by one doctor.

Results

Nineteen cases of plantar warts were found in the 146 adolescents studied - an incidence of 13%. Only 1 of 80 school-

children had a verruca (1%). By contrast, 18 of 66 swimming club members of the same age who used communal showers had a verruca (27%).

Previous infection with verruca was higher among those with a current infection (67%), compared with 27% of those not currently infected reporting previous infection. Half of shower room users reported previous infection, compared with 16% in those who did not use a communal shower

Comment

In terms of levels of evidence, this study comes fairly low on the scale. The main problems are that the numbers are small and from two distinct populations. The two groups used different public changing rooms, but only the swimmers used public showers.

Is it right to ascribe the huge difference in verruca infection (27% versus 1%) to the public showers? To be fair, the author criticises these aspects of the study, but balances this against a literature search which (though limited in yield) shows at least one study which excludes swimming pools themselves as sources of infection. This does not alter the fact that there could be some other extraordinary factor in this swimming club which has led to the high rate of verruca infection.

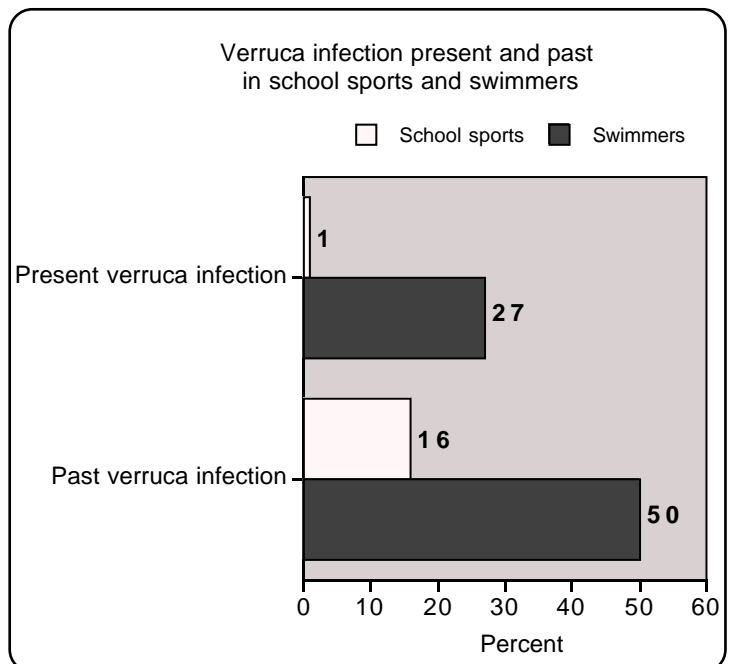
On balance, with a large pinch of salt, this is a believable result until proven wrong. Perhaps the surprising thing is that there appears to be so little literature for so common a problem, and one which causes parents and GPs so much trouble.

The truth is out there

Is there anyone out there who knows of more or better information, is doing a study or is keen to do one? The truth is out there, but it needs to be gathered in. Should this be the first *Bandolier* epidemiological survey?

Reference:

1 LW Johnson. Communal showers and the risk of plantar warts. Journal of family Practice 1995 40:136-8.



FREEZING WARTS

The other issue concerning warts is their treatment, which occupies a great deal of time for patients, GPs and dermatologists. Two papers from the department of Dermatology at Leicester Royal Infirmary have addressed the effectiveness of different treatment cryotherapy strategies in randomised controlled trials.

In patients who do not respond to conservative therapy like use of keratolytic compounds, cryotherapy with liquid nitrogen is often used. It is also offered by many GPs. The two issues addressed in these papers are the value of a second freeze-thaw cycle, and the interval between cryotherapy treatments. Can cure rates be affected by different cryotherapy regimens?

Value of a second freeze-thaw cycle

The first study examined this point [1]. It was a randomised, open study of 300 patients of all ages newly referred for treatment of warts of hands or feet. Daily wart paint use by patients was part of the treatment.

Study

Patients were seen at 3-weekly intervals. Plantar warts were pared with a scalpel until capillary bleeding. Patients were randomised to receive single or double freezing. Cryotherapy involved applying liquid nitrogen using cotton wool buds until a halo of ice was seen around each wart. For those receiving the double freezing technique, all signs of freezing were allowed to resolve before repeating the procedure.

At 3 months, cure rates were assessed. A cure was defined as no visible evidence of warts at review, or those who had returned a postal questionnaire saying their warts were cured.

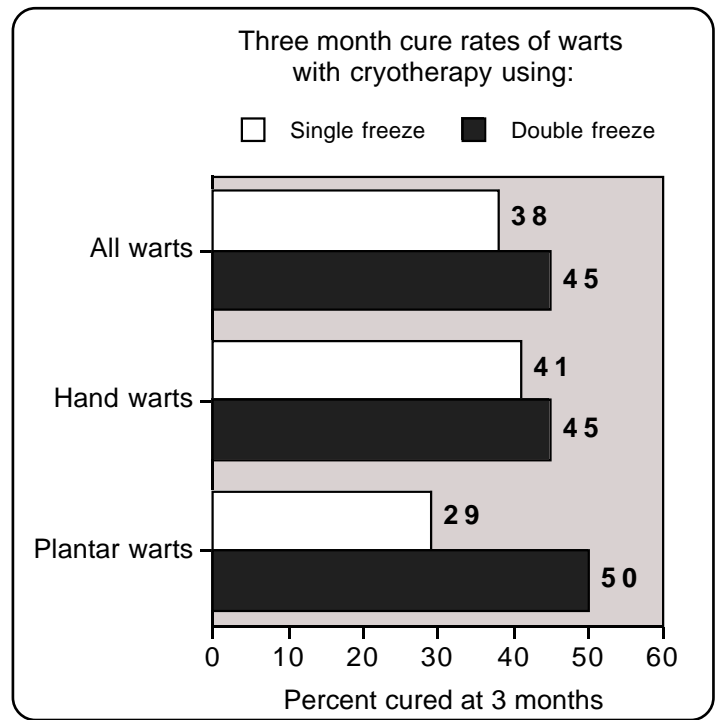
Results

Results were available on all but 35 of the 300 patients. On an intention to treat basis, reporting results as a percentage of all patients randomised, single freeze produced a three month cure rate of 38% (56/149) and double freeze 45% (68/151; no significant difference).

When hand warts and plantar warts were analysed separately, a slightly different picture emerged. Cure rates for hand warts was not improved by double freezing (45% cure compared with 41% cure for single freeze). Plantar warts had a 50% cure with double freezing, compared with only 29% using the single freeze technique. This was statistically significant (relative risk 1.7, 95% CI 1.1 - 2.8).

NNT

The NNT was 4.8 (95% CI 2.6 - 26); this means that for every five patients with plantar warts treated with double freezing, one more will have a three month cure who would not have been cured if treated with a single freezing technique.



Frequency of freezing

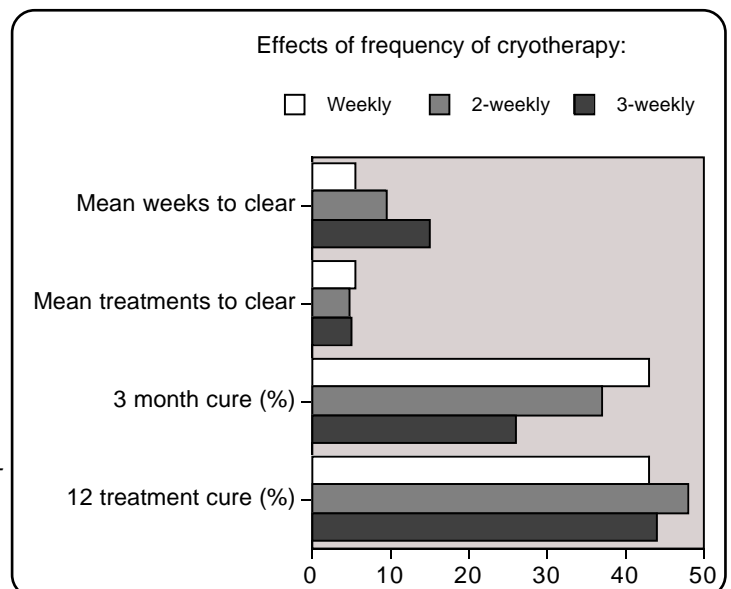
The traditional frequency of cryotherapy when treating warts is 3 weeks. The second Leicester study investigated whether increasing the frequency of cryotherapy to 2 weeks or 1 week had any influence on the cure rate.

Study

Newly referred patients were asked if they were prepared to attend clinic weekly if necessary. Those who agreed were randomised to receive cryotherapy at 1, 2 or 3 weeks. Wart paint was to be used daily during the duration of the study.

Cryotherapy and plantar wart preparation were the same as the first study. Blistering or soreness was noted at each visit, and blistered warts were not re-treated. Inflamed or painful warts were treated, subject to patient tolerance.

Cure rate was assessed after 3 months of treatment, and after receiving 12 treatments (3 months for weekly group, 6 months for 2-weekly group and 9 months for the 3-weekly group).



Results

Warts cleared faster with more frequent treatment. The mean time to clearance was 6 weeks for weekly, 10 weeks for 2-weekly and 15 weeks for 3-weekly treatment. The mean number of treatments to achieve clearance was the same - 5.

The cure rate was the same (about 45%) after 12 treatments, but after three months higher cure rates were seen with more frequent treatments.

NNT

Weekly, rather than 3-weekly, treatment produced significantly higher cure rates (relative risk 1.7, 95%CI 1.1 - 2.7).

The NNT was 5.8 (95% CI 3.1 - 41); this means that for every six patients with warts treated with cryotherapy weekly, one more will have a three month cure who would not have been cured if treated every three weeks.

Adverse events

Adverse events are given in the table. Blistering was significantly more common in those treated weekly. The number needed to harm (NNH) was 3.5 (2.5 - 5.4); this means that for every four patients with warts treated with cryotherapy weekly, one more would have a blister who would not have had one if treated every three weeks.

Adverse events with cryotherapy for warts

Event	weekly	2-weekly	3-weekly
soreness	7%	5%	3%
blistering	29%	7%	0%
withdrawn with pain	1	2	0

Workload

More frequent treatment means more work. The mean number of treatments given for weekly treatment was 9 (range 1 - 29). It was greater than that for those treated 2-weekly (6, range 1 - 21) and 3-weekly (6; range 1 - 20).

Comment

These were well conducted studies on large numbers. They probably represent the truth for cryotherapy treatments of warts. *Bandolier* has chosen to present the results as intention to treat, as did they. This is the most conservative way of presenting the data.

So what we can say is that double-freezing of plantar warts is effective, and that more frequent freezing of all warts leads to a quicker cure, but not a greater rate of cure.

References:

- 1 J Berth-Jones, J Bourke, H Eglitis et al. Value of a second freeze-thaw cycle in cryotherapy of common warts. *British Journal of Dermatology* 1994 131:883-6.
- 2 J Bourke, J Berth-Jones, PE Hutchinson. Cryotherapy of common viral warts at intervals of 1, 2 and 3 weeks. *British Journal of Dermatology* 1995 132:433-6.

AUTOLOGOUS BLOOD TRANSFUSION

Correspondence

Bandolier was delighted to receive the following letter from one of its Internet readers about a piece we carried in July 1995. That described a cost effectiveness analysis of autologous blood transfusion in the *New England Journal of Medicine* with results that suggested that it was not cost effective.

Neil Blumberg disagrees. We reproduce his e-mail below, and then analyse the paper that Dr Blumberg and colleagues published this year which came to the opposite conclusion, that autologous blood transfusion is cost effective.

To the editor:

In *Bandolier* 17 you quote a study from the *New England Journal of Medicine* (332:719, 1995) purporting to demonstrate that autologous transfusion is not cost-effective. The authors of that study chose not to consider extensive data that patients receiving only autologous transfusions have much reduced morbidity and costs of hospitalisation.

More recent analysis by our group based upon actual hospital data suggests that not only is autologous transfusion cost effective, it has the potential to dramatically reduce the cost of providing some surgical services (*American Journal of Surgery* 171: 324-330, 1996). Not to put too fine a point on it, the latter work is based upon actual "evidence," whereas the *New England Journal of Medicine* report is based purely upon a theoretical analysis with no actual patient data.

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The issue

Because of the (real or imaginary) dangers of viral infection (hepatitis, HIV) from normal donated blood transfused during an operation (allogenic transfusion), some people deposit their own blood to be used, collected before the operation (autologous transfusion). This takes time and money. The cost effectiveness argument has concentrated on the costs of collecting an individual's blood compared with the possible benefits from avoiding an infection, and the costs associated with that. Blumberg and colleagues were unable to perform a randomised trial because the practice of autologous transfusion was routine, so used survey data.

Cost analysis of autologous and allogenic transfusion in hip-replacement surgery

Hip replacement was chosen because it is the most common indication for autologous transfusion. The two randomised trials comparing autologous with allogenic transfusion were done in colorectal surgery, so Blumberg and colleagues [1] based their analyses on case-control studies in their own hospital setting, in which autologous blood collection is common.

Costs of collecting autologous blood were conservative. They did not include any costs of discarding autologous blood, but neither did they include savings from not having to test the blood for viral diseases. Data were collected for 140 patients in 1992, as well as an historical cohort from 1986 to 1988 (with costs adjusted for inflation).

Results

1992 Cohort

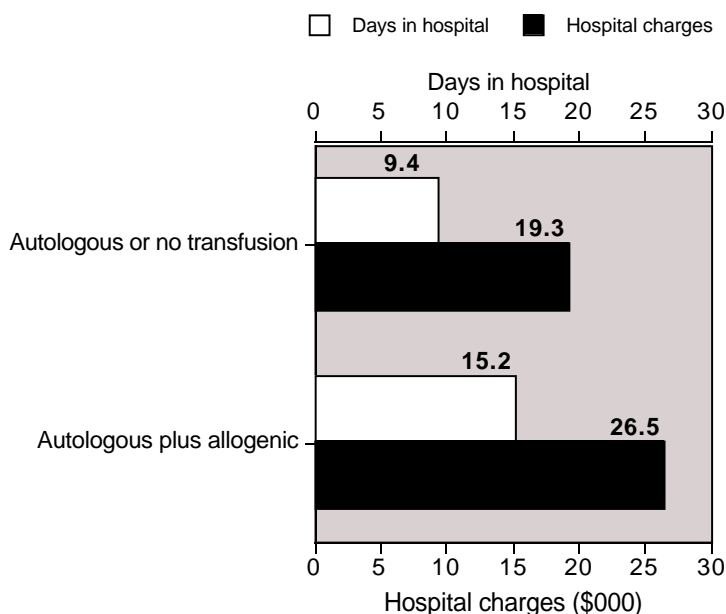
Patients receiving autologous plus allogenic transfusions (n = 30) spent significantly longer in hospital (mean 15 days) than those receiving only autologous or no transfusion (mean 9 days). Each incremental unit of allogenic blood transfused increased the length of hospital stay. Autologous transfusion of up to 5 units did not increase hospital stay.

Total mean charges for autologous plus allogenic recipients were \$26,000, significantly greater than for those receiving only autologous or no transfusion (\$19,000).

Extra costs arose from haematology, chemistry and blood gas tests, and extra charges from blood banking and pharmacy.

On average each allogenic transfusion was associated with additional actual costs of about \$1,500, compared with a maximum of \$50 for each autologous unit collected.

Transfusion type, hospital stay and costs (1992 cohorts)



1986/8 Cohort

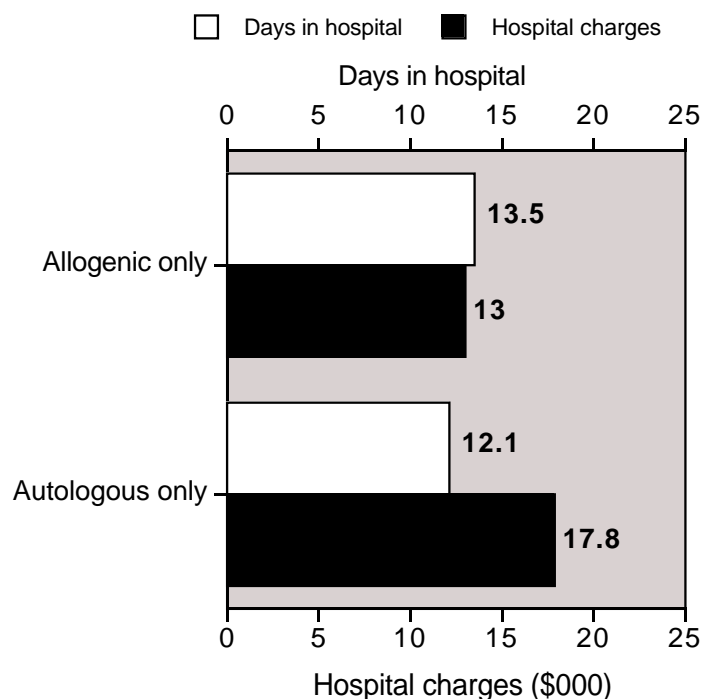
Because present practice of autologous transfusion did not allow a direct comparison of allogenic with autologous transfusion, records from a previous study were examined for a comparison of 33 patients having 2 or 3 units of autologous blood only and 49 patients having 2 or 3 units of allogenic blood only. The patients were well matched for age, sex, duration of surgery, blood loss and days of wound drainage. The rate of infection was 32% in those receiving allogenic transfusions, but only 3% in those receiving autologous blood.

Recipients of autologous transfusion had reduced hospital stay (12.1 versus 13.5 days for allogenic transfusions), and reduced hospital cost of \$4,800.

Extra costs arose from microbiology, haematology and blood gas tests, and extra charges from blood banking and pharmacy.

On average each allogenic transfusion was associated with additional actual costs of about \$1,050.

Transfusion type, hospital stay, and costs (1986/8 cohorts)



Comment

These analyses are based on real data, albeit on a small number of patients. Cost is an issue, but not the most important. The consistent finding that autologous transfusions result in lower short term morbidity is important. Blumberg and colleagues highlight other studies, retrospective and randomised, that come to similar conclusions.

Avoiding low risks of very unpleasant diseases may be one driving force for autologous transfusions. Producing lower postoperative morbidity generally has much wider implications. Any cost savings would be a useful spin off.

Bandolier originally thought this to be an interesting, but

somewhat recherché topic. Reading Blumberg's paper suggests that it would repay a more thorough review with particular implications for purchasers.

Reference:

- 1 N Blumberg, SA Kirkley JM Heal. A cost analysis of autologous and allogenic transfusions in hip-replacement surgery. *American Journal of Surgery* 1996 171:324-30.

ONCE-DAILY AMINOGLYCOSIDES?

Severe bacterial infections where gram negative bacteria are present are usually treated with aminoglycosides. Broader spectrum antibiotic therapy is generally started before specific bacteriologic culture reports are available, so aminoglycosides typically would be given as well as other antibacterials.

Peak concentrations in serum inhibit bacterial growth, but minimal trough concentrations may be required to avoid risks of damage to ears and kidneys. Randomised trials of once-daily against standard dosing have yielded conflicting results, and many had insufficient numbers of patients to answer the question. Meta-analysis may give the answer.

Meta-analysis

A group from Hamilton, Ontario, sought studies that were randomised and compared an intravenous once-daily aminoglycoside regimen against a standard regimen in immunocompetent adults [1]. They looked for evidence of bacteriologic or clinical cure, mortality nephrotoxicity (an increase in serum creatinine of at least 35 to 45 $\mu\text{mol/L}$) and ototoxicity (a 15 dB reduction in hearing at any frequency).

Results

They analysed 13 studies. Once-daily dosing made no difference to bacteriologic cure. They did not pool data for clinical cure, although 11 of 12 studies appear from their figures to have a risk ratio that included 1 (i.e., not significantly different).

Mortality nephrotoxicity and ototoxicity were all lower with the once daily regimen, though without

the difference from standard dosing being statistically significant. Point estimate numbers needed to treat to prevent one event with once-daily compared with more frequent dosing were 111 for mortality 77 for nephrotoxicity and 61 for ototoxicity

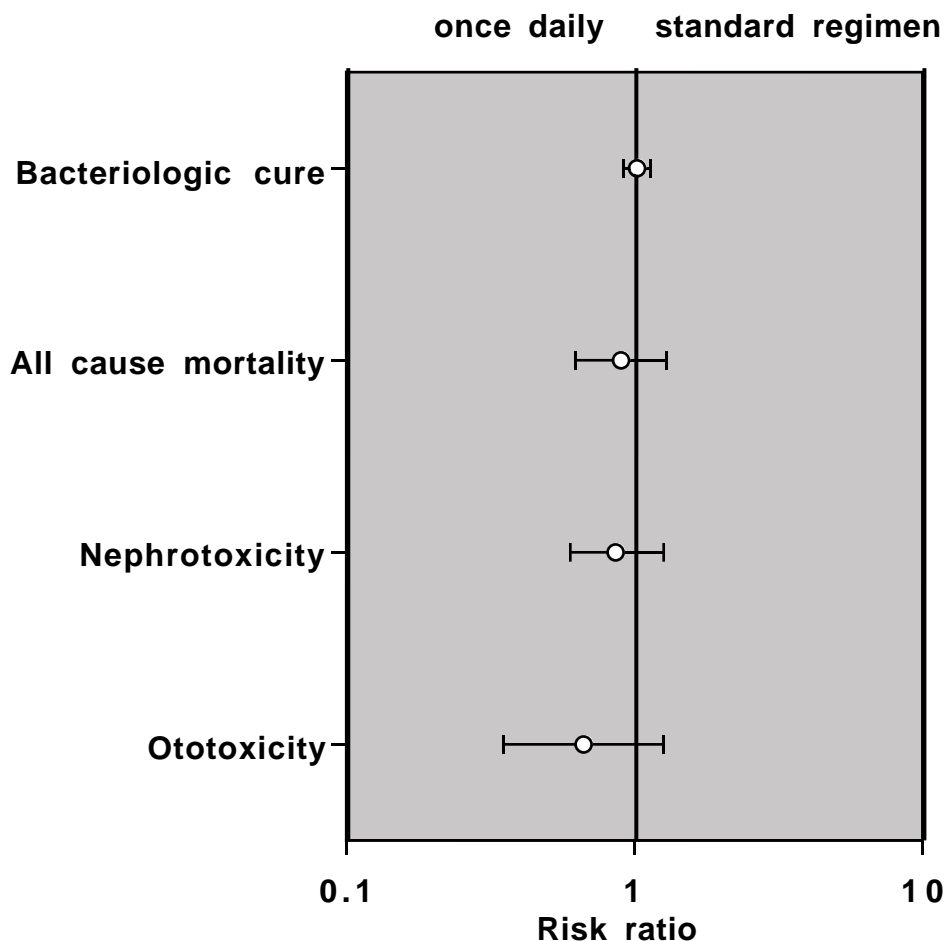
Comment

The meta-analysis showed that once-daily aminoglycoside dosing is equivalent to standard dosing in terms of bacteriological cure, and may be associated with reduced nephrotoxicity, ototoxicity and mortality. The authors have a useful discussion of the limits of their analysis because of the availability of trials, and point out some of the areas for research in this complicated area.

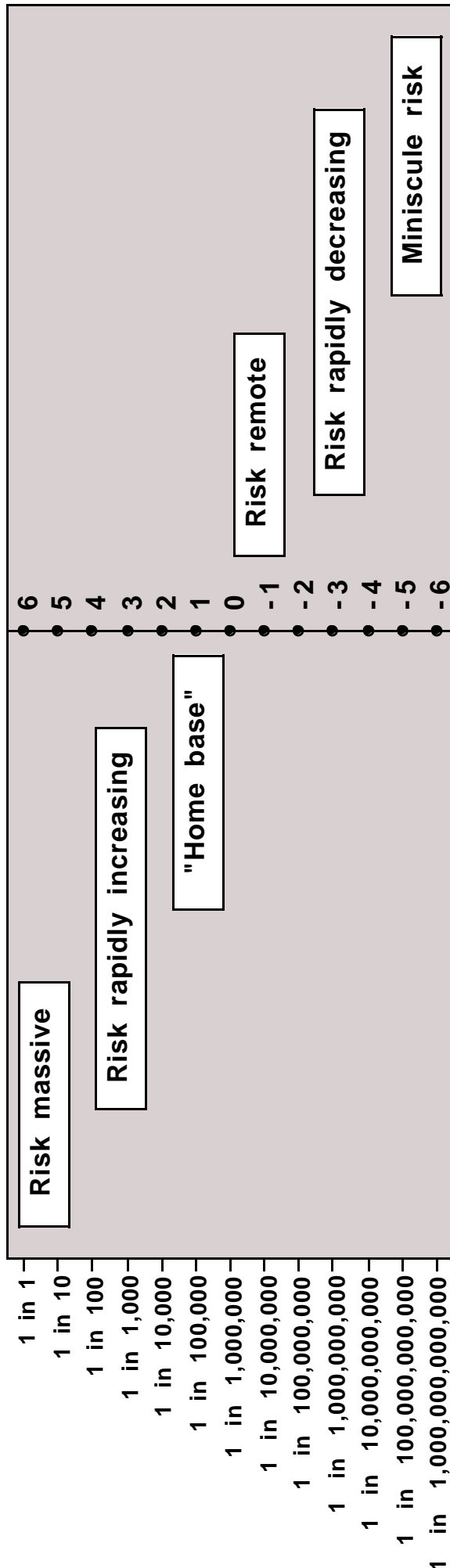
Reference:

- 1 R Hatala, T Dinh, DJ Cook. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Annals of Internal Medicine* 1996 124:717-25.

Results of aminoglycoside dosing frequency, meta-analysis favouring:



The Paling Perspective Scale



"If all the risks about you seem as dangerous as alligators, and you don't know which way to turn....." then reach for the Paling Perspective Scale. This is a simple way of communicating risks (to the public and each other), and is the central feature of a book "Up to yourArmpits inAlligators" by John Paling, ex of Oxford (and co-founder of Oxford Scientific Films) and now of California. Many thanks to Jim Falconer Smith of Leicester Royal Infirmary for bringing it to *Bandolier's* attention.

Paling Perspective Scale

Bandolier has been unable to do justice to the graphical representation of the scale featured in the book. The idea is that various numerical or verbal representations of risk - from 1 in 1 to 1 in 1,000,000,000 are rated logarithmically between +6 and -6, like a pH scale. Like pH also, the middle is comfortable neutral territory. In risk terms, the kinds of everyday risks we live with in the home or with consumer products, like being injured by falls, or gardening equipment, or by the television, fall in the region of +2 to +4.

At either end come the extremes. So at about -4 comes the risk of anything happening to anyone in the whole world, and at -1 to -2 the risk of anything happening to anyone in the UK. At the other extreme the odds of a child being born to unmarried parents in the UK is +5.4, and the risk of dying from cancer by smoking 20 cigarettes a day for 20 years is +5.

Paling's book comes with a plethora of examples, and with references and source material. There is also a pull-out scale with some simple messages about what the bottom line numbers translate into, ranging from "paranoia paradise" at -6 to -2, to "just take normal care" at +1 to +2, "change something" at +4 to +5 and "bye!!!" at +5 to +6.

An excellent and engaging read, with much food for thought for those presenting risk information to the media and the public. Some of *Bandolier's* media readers might like to take this up.

Reference:

Up to Your Armpits in Alligators. John & Sean Paling, 130pp, 1993. The Environmental Institute, 5822 NW 91st Boulevard, Gainesville, Florida 32653. ISBN 0-9642236-0-0. Cheque for \$20 to John Paling & Co, Ltd. Tel 001 904 377-2142.