Albumin: don't confuse us with the facts

Rather than fulminating, seek to answer the questions raised

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Goodness, what a reaction. You would think that the Cochrane Injuries Group had really gone too far with its systematic reviews of the outcomes in patients treated with colloid solutions and human albumin.[1 2] Worse, the *BMJ* has colluded in publicising this dangerously subversive material. One couldn't miss the incandescent letters that these rather routine, workmanlike reviews have elicited (p 882).[3 4] It's as though they had desecrated Osler's grave.

So what is going on here? Scepticism about most uses of albumin is not new[5] and is reflected in clinical guidance in the United Kingdom.[6] The new factor is that a group that is expert in the business of finding and sifting clinical evidence has revisited this aspect of the crystalloid *v* colloid argument that has been grumbling on since the Vietnam war. The authors are not clinical experts in emergency medicine, burns, or intensive care and don't claim to be. All they have done is unearth all the papers that compare mortality in patients treated with albumin according to licensed indications,[7] line up the results according to a defined set of criteria, and write down what they found. Capable patients or their lawyers might reasonably tackle a project like this.

Moreover, the authors' discussion and conclusions about the albumin review are less than hysterical: "Based on relatively small trials in which there were only a small number of deaths the results must be interpreted with caution. Nevertheless … a reasonable conclusion from these results is that the use of albumin in critically ill patients should be reviewed."

I had believed that a main purpose of a systematic review was to stimulate practitioners to look again at conventional ways of doing things and come to a measured decision about the need for change, clinical trials, or whatever. Because transparency of methods is one of the strengths of a systematic review, constructive criticism, reanalysis of the data, and debate about interpretation are all appropriate and important responses. The critics are right to point out that the trials analysed are small, elderly, and mostly do not reflect today's practices. But where are the trials that do?

For some reason (could it be related to the economic survival of a beleaguered blood industry?) this particular topic has elicited a fusillade of responses that appear to be defending current practice by attacking both the paper and the authors' credentials. On the other side, the *BMJ* helped set the scene for sensational press reports by sound biting the conclusions in the "This week" paragraph,[8] and proposals to sue the doctor and refuse participation in a clinical trial[9] have helped to up the ante.

In the United States the Food and Drug Administration has just written to doctors stating that these findings deserve serious attention, encouraging further clinical trials and urging "treating physicians to exercise discretion in use of albumin and PPF based on their own assessment of these data."[10] The UK Committee on Safety of Medicines has been similarly reluctant to offer much in the way of support to clinicians facing the press, anxious patients, and nervous managers.[11]

Colleagues who have over the years continued to review the use of albumin mostly agree that there is little solid evidence to specify the precise clinical situations where albumin would be better than a crystalloid or an alternative colloid. However, they do point out that some patients require such vast volumes of crystalloid and become so oedematous that management is very difficult.

So what should the conscientious intensivist, traumatologist, liver transplanter, or burns doctor do with tomorrow's patient? Will he or she risk legal action if a patient succumbs after receiving albumin or another colloid solution, rather than gallons of saline? And if their clinical team is accustomed to using colloids will they easily adapt to sudden changes in management protocols that require the much larger infusion volumes demanded by crystalloids.

Despite the colourful reactions to these two important papers, this is a moment for a bit of cool reflection and planning rather than rushing to defend current practice or to change treatment protocols—an action that could itself create risks. We know there are huge variations in the use of albumin and colloids,[12] but neither descriptive studies nor the systematic reviews identify subpopulations of patients who may do better if infused with colloids. New and probably large trials will be needed. Meanwhile, what fluid should I give to Mrs X? Here are a few simple proposals:

- Published guidance from the UK transfusion services[6] already emphasises, "There is no evidence to support the use of albumin rather than crystalloid in acute volume resuscitation; albumin solutions are more likely to cause circulatory overload than are crystalloids; 20% albumin can produce severe acute circulatory overload; 5% albumin should be used with care in patients at risk of sodium retention." The guidance also points out, "All the colloids other than albumin have known potential for adverse effects such as: acute allergic reactions and anticoagulant effects (dextrans); anticoagulant effects and long persistence in the reticuloendothelial system (starches); acute reactions (gelatins). The origin of gelatin solutions (bovine tissue) may also worry some people."
- In view of the above guidance it would seem sensible to review protocols for fluid replacement, if this has not been done recently, to document any changes made (and why), and to record the use of the protocol in patients' notes.

And how could the experts speed up the process of getting the evidence that patients and clinicians both need?

- The Cochrane Injuries Group and the objecting clinicians could cooperate to re-examine the studies included in the albumin meta-analysis to see if specialist experience can enlighten the interpretation of the data.

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- Specialist teams could get together and plan some well focused clinical trials to provide the evidence on which to base improved clinical guidelines.
- Those who fund clinical research should take a proactive position and encourage proposals for these trials.
- The licensed indications for albumin (and crucially the summary of product characteristics on which manufacturers base their documents[7]) must surely be given a thorough and prompt overhaul as it appears that these are divorced from both clinical opinion and the conclusions of the systematic review.

Meanwhile—for the next six years or so—if I have the misfortune to be seriously sick, I hope I can choose my doctor, take the fluid he or she decides on, and worry about all the other hazards of being in hospital.[13]

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1 Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ* 1998;316:961-4.
2 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in crtically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317:235-40.
3 Human albumin administration in critically ill patients [letters]. *BMJ* 1998;317:882-6.
4 Fluid resuscitation with colloid or crystalloid solutions [letters]. *BMJ* 1998;317:277-9.
5 Soni N. Wonderful albumin. *BMJ* 1995;310:887.
6 McClelland DBL, ed. *Handbook of transfusion medicine*. 2nd ed. London: HMSO, 1996.
7 Committee for Proprietary Medicinal Products. *Core summary of product characteristics for human albumin*. Brussels: Commission of the European Communities, 1992.
8 Giving albumin increases mortality in critically ill patients [This week in the BMJ]. *BMJ* 1998;317 (7153).
9 Chalmers I. What is going on behind the scenes in the debate about albumin. www.bmj.com/cgi/eletters/317/7153/235#EL9.
10 Fergal D. *Letter to doctors*. Washington, DC: Food and Drug Administration, Center for Biologics Evaluation and Research, 1998. (www.fda.gov/medwatch/safety/1998/plasma.htm)
11 Rawlins MD. *Human albumin therapy in critically ill patients*. London: Committee on Safety of Medicine, 1998. (CEM/CMO/98/11.)
12 Sirchia G, Giovanetti AM, Baele PL, Carrington da Costa RB, Drouet N, ten Duis HJ, et al. Use of blood products for elective surgery in 43 European hospitals. *Transfus Med* 1994;4:251-68.
13 Brennan TA, Leape LL, Laird NM, Hebert L, Logalio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. *New Engl J Med* 1991;324:370-6.

Flushing away the fat

Weight loss during trials of orlistat was significant, but over half was due to diet

Obesity (body mass index >30 kg/m^2) is a serious disease which predisposes to heart disease, hypertension, stroke, diabetes, osteoathritis, obstructive sleep apnoea, gallstones, and some cancers sensitive to sex hormones. It accounts for 2-7% of total healthcare costs and a substantial proportion of disability pensions. Obesity is out of control in most affluent countries of the world, and its prevalence is increasing rapidly in developing countries. The World Health Organisation describes it as a global epidemic.[1] This week, with the launch of orlistat, hopes have been raised that there is a new, effective weapon against the rising prevalence of obesity.

In 1976 in the United Kingdom an expert committee sounded a warning that obesity was "one of the most important medical and public health problems of our time."[2] In 1980 a survey showed that 6% of men and 8% of women were obese,[3] and in 1992 the government set a target that the prevalence of obesity (then 8% of men and 12% of women) should be reduced back to the 1980 levels by the year 2005.[4] Despite these brave words the prevalence continues to increase: the latest data show that 13% of men and 16% of women are obese.

The excitement about a potential new drug treatment for obesity is not new: at the beginning of this decade there were high hopes for the efficacy of fenfluramine. The largest multicentre trial enrolled patients who were initially about 36 kg overweight and who were randomised to either diet and fenfluramine 15 mg twice a day or diet and placebo. After 12 months the dropout rate of the drug group and the placebo group was 37% and 45% respectively and the weight loss among completers 9.82 kg and 7.15 kg.[5] However, enthusiasm for centrally acting appetite suppressants was waning even before the recent cardiovascular side effects were reported: the annual number of prescriptions dispensed in the community in England fell steadily from 384 000 in 1991 to only 81 000 in 1997.

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Orlistat, which last month was licensed for prescription in the UK and the rest of the European Community, is a powerful inhibitor of pancreatic lipase, so some 30% of dietary fat is not digested but is excreted in faeces. In a two year double blind multicentre trial 743 obese patients (average weight 100 kg) were prescribed a diet in which 30% of the energy was from fat and which provided 600 kcal/day less than calculated expenditure.[6] The 688 patients (93%) who were compliant during a four week run in period on this diet and placebo capsules, during which they lost about 2 kg, were then randomised to either 120 mg orlistat three times daily or placebo for 12 months, during which the orlistat group lost 10.3 kg compared with 6.1 kg in the placebo group. As usual, almost all of this loss occurred in the first six months. At the end of the year patients were randomly reassigned to orlistat or placebo and a weight maintenance diet. At the end of the second year those continuing on orlistat had regained about 2 kg, while those switched to placebo had regained 4.6 kg. The drop out rate was low.

Many patients taking orlistat experienced fatty stools, increased defaecation, and oily spotting (so the test was not completely double blind), and after two years on orlistat up to 5.8% of them had abnormally low blood concentrations of β carotene, vitamin D, or vitamin E.

It is too early to know the contribution which this new drug will make to the control of obesity. The weight losses achieved are statistically and clinically significant, but the diet accounts for more than half of

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