

Excess mortality after human albumin administration in critically ill patients

Clinical and pathophysiological evidence suggests albumin is harmful

Papers p 235
Letters p 277
Science commentary
p 240

Albumin is a medium weight colloid which plays an essential role in generating the colloid-osmotic pressure. It facilitates fluid retention in the intravascular space. Human albumin is often given to critically ill patients with life threatening hypovolaemia. Low serum albumin concentrations are seen in various disease states and may be due to leakage, increased metabolism, or insufficient synthesis in the liver. The serum albumin concentration in critically ill patients seems to be inversely related to mortality.¹ Yet does this observation imply that hypoalbuminaemia should be treated with albumin? In this week's issue a systematic review—published simultaneously in the Cochrane Library² and a sequel to a paper on the controversy of whether critically ill patients with hypovolaemia should be given colloid or crystalloid fluids³—evaluates the use of human albumin in various clinical settings (p 235).⁴

The paper is clinically important because it suggests that a respected and widely used treatment given to neonates, children, and adults with hypovolaemia, burns, or hypoalbuminaemia is associated with increased mortality: on average six extra deaths for every 100 patients treated. The authors conclude that human albumin should not be given any more “outside the context of a rigorously conducted randomised controlled trial.”

Can we trust these findings? As systematic overviews of the medical literature are becoming more prevalent, it is important for clinicians to understand how to decide whether an overview is credible and how to interpret its results. Guidelines to help assess the scientific quality of a systematic review focus on the definition of the question, the comprehensiveness of the search strategy, the methods of choosing and assessing the primary studies, and the technique of combining the results and reaching appropriate conclusions.^{5,6}

The present overview addressed a focused clinical question, the relation between one determinant—administration of human albumin versus no albumin or crystalloids—and a clinically important outcome (death); the criteria used to select articles for inclusion were appropriate; and it is unlikely that relevant studies were missed. The validity of the studies included was appropriately appraised. The authors also make explicit what the data are, and the assessments of studies are reproducible. Patients from many different hospitals were studied, but the results were similar in the three

different settings: volume expansion, burns, and treating low serum albumin. The review therefore seems to be scientifically robust. What adds to the credibility of these results is that if results are consistent across studies they are likely to apply to this wide variety of patients.⁵ However, favourable effects of albumin administration in certain patients may have been obscured in the analysis and cannot be totally excluded.

Another requirement is that there is a plausible pathophysiological mechanism to explain the excess mortality. Without one, it is hard to understand and accept study results of this kind. A low serum albumin value is a marker for serious disease associated with high mortality. However, a direct causal relation between low albumin values and mortality has not been established, and it is difficult to justify maintaining serum albumin values within the “normal” range without clinical evidence that this improves patients' outcome. On the contrary, there are several reasons why albumin supplementation might make things worse for critically ill patients.

Firstly, cardiac decompensation may occur after rapid volume replacement with 20% albumin since this leads to an increase in volume retention (of up to four-fold). Indeed, an older study in baboons found that interstitial pulmonary oedema develops after albumin infusion in haemorrhagic shock.⁷ Secondly, in patients with increased capillary permeability or the capillary leak syndrome albumin administration may become detrimental when albumin and water cross the capillary membrane and cause or worsen (pulmonary) oedema, thus compromising tissue oxygenation and finally leading to multiorgan failure. Thirdly, the antithrombotic and platelet lowering properties of albumin may increase blood loss in postsurgical or trauma patients.⁸ Finally, albumin administration in the resuscitation of hypovolaemic shock may impair sodium and water excretion and worsen renal failure.⁹ Thus, although not fully understood, several potential mechanisms may explain how human albumin administration may worsen the condition of critically ill patients, but they need to be delineated in more detail.

Alternatives to albumin are available for most acute situations—hypovolaemic shock, burns, and in post-surgical patients with hypovolaemia. Unfortunately, they are not without drawbacks. The newer synthetic colloids like hydroxyethyl starch (high molecular weight hetastarch) are larger in molecular size and

hopefully do not leak into the extravascular spaces. Indeed, in recent studies volume replacement using hetastarch in patients with the capillary leak syndrome led to improved haemodynamics with a lower incidence of pulmonary oedema than with saline solutions.¹⁰ Hetastarch, however, reduces platelet aggregation, prolongs bleeding time, and decreases the levels of circulating factor VIII.¹¹ Gelatin based plasma substitutes (such as Gelofusine) can cause anaphylactic reactions and impair primary haemostasis and thrombin generation. The defect in primary haemostasis seems to be related to a gelatin induced reduction in von Willebrand factor activity, whereas the decreased thrombin generation is due to dilution.¹² Dextran infusion may also lower plasma factor VIII, and it prolongs bleeding time. Although high quality comparative studies in critically ill patients are not yet available, clinicians should be aware of these adverse effects on the haemostatic system. Crystalloids do not influence haemostasis but more volume needs to be infused to reach adequate clinical effects. This is usually unwanted in young children and patients with renal failure, who are at increased risk of volume overload, oedema, and subsequent compromised oxygenation.

How then should we use albumin from now on? Although albumin administration is surely harmful in certain categories of patients, favourable effects in particular patients cannot yet be excluded. An effort must be made to identify these patients. As agreed in the North American consensus conference,¹³ albumin should not be used for the treatment of septic shock. Hypoalbuminaemia in patients without circulatory failure is a symptom that should not be treated: instead the cause should be identified and treated. In other clinical circumstances synthetic colloids and crystalloids may offer an effective,² relatively cheap, and safe (no viral or prion risk) alternative.

After evaluating the evidence that a treatment is not beneficial and may even be harmful, deciding on subsequent actions may not be simple. If one accepts that the results of this systematic review are valid, the differences in mortality are clinically relevant, and

plausible mechanisms exist to explain these differences, and if one thinks that the results apply to patients in one's own practice then one has to decide whether to continue to administer human albumin. Given the succession of positive answers to these questions the administration of albumin should be halted until, as the authors suggest, the results of a high quality large clinical trial are available.

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A generous birthday present to the NHS

But spending it wisely may be difficult

New Labour has paid its tribute to the one symbol of Old Labour's achievements that has stood the test of time. The British government's 50th birthday present to the National Health Service has, at £21bn over the next three years, turned out to be even more generous than expected. It implies an annual growth of 4.7% in the NHS's budget, well above the rate conventionally assumed to be necessary to accommodate demographic pressures and technological change.¹ Whatever the doubts about the precise significance of the figures announced by the chancellor of the exchequer, and whatever the reservations about how the money is to be spent, this represents morale boosting reassurance that the government's commitment to the NHS is more than rhetorical.

The planned 4.7% growth rate in real terms depends on one key assumption. This is that the rise in the costs of the inputs to the NHS—in particular, salaries—will not exceed 2.5% a year. This is unrealistic. The gap between pay in the public and private sectors has been widening. To the extent that salaries in the NHS are brought into line with the rest of the economy, so there will be less scope for translating the extra funds into extra resources. Only consider the case of nurses, who account for almost half the NHS's total salary bill. If the government is to succeed in its intention of recruiting 15 000 more nurses, it may well have to offer better salaries and to change the pay structure to offer stronger incentives to stay in the profession.

Nurs p 231

BMJ 1998;317:224-5

But why does the NHS need an extra 15 000 nurses? Or, come to that, another 7000 doctors? These are the targets set by Frank Dobson, the secretary of state for health, in his House of Commons statement on health expenditure. But it is far from clear why these particular figures have been chosen. Why not 10 000 (or 20 000) nurses and 5000 (or 10 000) doctors? Are these figures more than extrapolations of existing trends? If so, what is their rationale? And where will the extra bodies come from? The expansion in training places for nurses and doctors will certainly not graduate the extra staff in time to meet Mr Dobson's targets for the next three years.

Such questions prompt a larger worry. This is that the extra funds will be used to achieve headline catching targets rather than to pursue a coherent strategy for the NHS. This worry is compounded by another feature of the new expenditure strategy. This is the emphasis on making increasing expenditure contingent on the achievement of specific objectives, a process of "continuous scrutiny and audit" to be monitored by a cabinet committee.² In principle this is eminently sensible: there is little point in pouring extra funds into the NHS (or education) if the investment does not yield an improved performance. However, everything depends on how the performance is to be measured. If the wrong benchmarks are chosen, the result may be to offer perverse incentives to increase activity without necessarily improving outcomes.

This risk is all the greater given that activity is easier to measure than outcomes. So, for example, Mr Dobson's targets include an increase of 3 million in the number of patients treated in NHS hospitals and a reduction in waiting lists. It is not self evident that the NHS's performance should be judged by the number of patients being processed through hospitals: the number of patients successfully treated outside hospitals, or illnesses prevented, might be a better indi-

cator. Nor is it self evident that a reduction in waiting lists, rather than in waiting times for urgent conditions demanding speedy treatment, should have high priority. The Department of Health has published a range of possible indicators^{3,4} designed to capture the various dimensions of performance, including quality, but it remains to be seen how these will be used. Indicators are welcome in so far as they give visibility to what the NHS is doing but, given the problems of interpreting them, potentially dangerous as tools of central control.

Yet greater central control is the price that the NHS will have to pay for the extra funds. Thus the £5bn modernisation fund, included in the birthday present, will presumably be distributed by the centre. In this the expenditure review reinforces the centralising thrust of the 1997 white paper.⁵ It is far from obvious that the NHS Executive has the managerial capacity to take on this extra burden. Nor is it clear that ministers have thought through the implications of such a centralising strategy. For even with the extra £21bn the NHS will still be allocating scarce resources between competing demands: ministers will not change the reality of rationing by expunging it from their vocabulary. And the greater the degree of centralisation, the more difficult will it be for ministers to absolve themselves from responsibility.

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Evidence based patient information

Is important, so there needs to be a national strategy to ensure it

Information in Practice
pp 263, 264

Leaflets and other information packages (video and audio tapes, computer programs, and web-sites) have long been seen as integral to educational strategies designed to promote health, persuade people to adopt healthy lifestyles, and increase uptake of screening. They have also been developed to educate patients in self care of such chronic conditions as arthritis, hypertension, stress related psychological problems, gastrointestinal diseases, and back pain, and how to take medicines correctly. There is now growing interest in providing information to support patients' participation in choosing treatments and deciding on strategies for managing their health problems.¹ Much well intentioned effort goes into developing such material, but good intentions are not enough to guarantee quality and usefulness, as two papers in this week's issue show (pp 263, 264).^{2,3} If patients are to be active participants in decisions about their care the information they are

given must accord with available evidence and be presented in a form that is acceptable and useful. Information materials are no substitute for good verbal discussions, but consultations are usually short and plenty of evidence exists that patients do not receive the information they want and need.⁴ Leaflets and other materials can therefore play an important part in supplementing and reinforcing information provided by clinicians, but the information they contain must conform to the highest standards of scientific accuracy and must be tested for comprehensibility and relevance.

Unfortunately few of the patient information materials currently in use meet these standards.⁵ Far too many adopt the paternalistic view that patients cannot cope with bad news and must be kept ignorant of medical uncertainties. Patients are seen as ignorant children in need of instruction and reassurance, rather than as experts in their own needs and preferences. Benefits of interventions are emphasised, risks and side

effects glossed over, and scientific controversies hardly ever mentioned. In too many cases the information contained in patient information leaflets is inaccurate or misleading.

Various checklists have been proposed to enhance the quality of health information.⁶⁻⁸ These cover issues such as accessibility, acceptability, readability, and comprehensibility; style and attractiveness of presentation; accuracy and reliability of content; coverage and comprehensiveness; currency and arrangements for review and updating; reference to sources and strength of evidence; reference to sources of further information; credibility of authors, publishers, and sponsors; relevance; and utility. In general far more attention has been paid to presentation and readability than to content. Ironically the insistence on aiming for the lowest possible reading age as measured by readability formulas may have contributed to the infantile quality of many materials. There are many problems with the standard readability formulas,⁹ and they are no substitute for researching patients' information needs and involving them in developing and testing materials. But accuracy of the content is arguably even more important, and there is no excuse for palming patients off with unscientific clinical opinion which does not conform to the standards required for evidence based medicine.

The growth and wider availability of the internet will greatly increase access to health information. Already over 10 000 health related websites exist, and over a third of internet users access the web to retrieve health and medical information.¹⁰ Much of this material is inaccurate or misleading, but it is difficult for non-specialists to sort out the wheat from the chaff.^{11 12}

Failure to pay attention to the quality of information obtained by patients could have serious consequences. An overoptimistic view of medical treatments could foster demand for inappropriate interven-

tions, leading to iatrogenic harm, increased dissatisfaction, and unnecessary costs. On the other hand, accurate information which patients find useful has the potential to enhance the quality and appropriateness of health care. It is time to develop a national public health information strategy which recognises the advantages in raising standards and the risks of not doing so. This will require investment in the production of better materials, training for clinicians and other information providers in how to use them, and the development of an accreditation system to help users to judge the quality of health information.

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Intravenous β blockade in acute myocardial infarction

Should be used in combination with thrombolysis

In the 1980s two large randomised controlled trials showed a reduction in early mortality when intravenous β blockers were given acutely to patients presenting with suspected myocardial infarction,^{1 2} and the use of β blockers in acute myocardial infarction has since been recommended.³ Yet intravenous β blockade is rarely used in Britain. In the ISIS-4 trial, for example, it was given to only 5% of patients enrolled in Britain compared with about 30% of those enrolled in Italy and America.⁴ This is consistent with anecdotal evidence that few British hospitals routinely use intravenous β blockade in acute myocardial infarction.

The evidence is persuasive. In the Gothenburg metoprolol trial, metoprolol 15 mg was given intravenously as soon as possible after the arrival of the patient in hospital followed by oral metoprolol 100 mg twice daily.¹ At 90 days there was a 36% reduction in total

mortality in the group treated with metoprolol. In ISIS-1 atenolol 10 mg was given intravenously immediately on admission followed by a dose of 100 mg every day for seven days or until discharge from hospital if earlier.² Vascular mortality fell by 15% during the treatment period in those given atenolol, mainly in the first 24 hours. This study suggested that treating 1000 patients would save five lives and prevent five reinfarctions.

Moreover, the costs are minimal. The ISIS-1 results² suggest that the direct cost per life saved is £400, which is impressive compared with other routine treatments. For example, the front loaded alteplase regimen of the GUSTO trial⁵ (which may save up to 9 lives per 1000 patients treated) is commonly used at a direct cost of £80 000 per life saved. Even this may be an underestimate as fewer than 9 lives per 1000 would probably be saved.^{6 7}

BMJ 1998;317:226-7

Why then is intravenous β blockade so infrequently used in Britain? An important factor is clinicians' lack of awareness. Intravenous β blockers have not been heavily promoted—unlike, for example, calcium antagonists—which may in fact be harmful in acute myocardial infarction.⁸ Anecdotal evidence also suggests that many clinicians worry about the adverse effects of combining intravenous β blockers with thrombolytics, particularly streptokinase. The major concern is excessive hypotension, although no published data support such an adverse effect. There also seems to be a perception that intravenous β blockade is somehow no longer effective now that thrombolysis has become established.

In the post-thrombolytic era the evidence in support of giving intravenous β blockade immediately on hospital admission is even more overwhelming. Cardiac rupture is an early hazard of thrombolytic therapy and may contribute to the excess mortality seen with thrombolysis within the first 24 hours.⁹ Conversely, intravenous β blockade reduces the incidence of cardiac rupture,² so the two treatments may have synergistic effects.

In both the GISSI-2¹⁰ and GUSTO⁵ trials of thrombolytic agents intravenous atenolol was administered according to the ISIS-1 regimen as standard therapy—that is, not as part of any randomisation process. In each trial about 45% of patients received intravenous atenolol, and no adverse events in relation to use of β blockade were reported in either trial. In the GISSI-2 trial fewer patients given atenolol developed advanced atrioventricular block (4.3% *v* 12.3%), a need for temporary pacing (1.9% *v* 5.6%), sustained ventricular tachycardia (2.8% *v* 4.5%), heart failure (7.1% *v* 12%), ventricular fibrillation (4.9% *v* 8%), or cardiac rupture (0.5% *v* 1.4%) or died (5.1% *v* 11.9%).¹¹ Transient hypotension was more common in patients treated with streptokinase than in those receiving alteplase (9.3% *v* 4.8%), but the rate of sustained hypotension did not differ between the two groups (4.6%). These data are observational but support the contention that the acute administration of intravenous β blockade with thrombolysis is safe.

In Sweden intravenous metoprolol has long been standard therapy for acute myocardial infarction. A retrospective analysis of the incidence of hypotension during streptokinase infusion with and without simultaneous intravenous metoprolol has been reported.¹² Data were collected on unselected patients at two hospitals. Thirty four per cent of all patients receiving streptokinase had a systolic blood pressure <90 mm Hg at some stage during the infusion. Mortality was related to

the presenting systolic blood pressure but not to the transient values during streptokinase infusion. Patients treated with simultaneous streptokinase and intravenous metoprolol had significantly less hypotension than those treated with streptokinase alone (23% *v* 47%). Possibly metoprolol has a protective effect against hypotension, but the most plausible explanation is that patients who received metoprolol were selected and, for example, had higher systolic blood pressures at presentation. This observation should lay to rest any suggestion that the simultaneous use of streptokinase and intravenous metoprolol causes unacceptable and harmful hypotension.

In summary, administering intravenous β blockade with thrombolytic therapy is safe and does not result in excessive hypotension. Impressive evidence exists that additional lives can be saved by using both treatments together. Swedish and Italian patients have been benefiting from these therapies for many years. Why should British patients be denied them?

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Objective measures and the diagnosis of asthma

We need a simple diagnostic test—but don't yet have one

Diseases represent extremes of continuously distributed characteristics, and defining exactly where and why in that distribution normality ends and disease begins may be difficult. The use of objective markers can be helpful, but these often force us to change our concept of a disease to accommodate

the new information they provide—such as the identification of subclinical disease or adverse prognostic factors in otherwise healthy people. These conceptual changes are part of the natural evolution of disease definition and are justified if, in the long run, patients benefit.

Asthma has always been a clinical diagnosis, recognised on the basis of a characteristic history of variable wheezing, cough, and breathlessness and supported by objective, though non-standardised, evidence of variations in airflow. Many attempts have been made to define this diagnosis. Since 1958¹ all have highlighted the fundamental abnormality of variable airflow obstruction, and some have also invoked concepts such as airway hyperresponsiveness² or airway pathology.³ None has yet provided objective criteria for the component parts of this process, and there remains no standardised definition of the type, frequency, or severity of symptoms or the degree of airflow variability necessary to diagnose asthma.

Nevertheless, measurements of peak flow variability and airway responsiveness have gained widespread use as markers of asthma, particularly in epidemiological studies, and a recent editorial in the *BMJ* suggested that where doubts linger after a careful history and spirometry a "positive" result from peak flow monitoring or methacholine challenge (a measure of airway responsiveness) is enough to diagnose asthma.⁴ Is this assertion justifiable, and what are its implications for our concept of asthma?

There are unresolved methodological issues arising from the need to provide standardised methods of measuring and expressing peak flow variability or airway responsiveness, not to mention the arbitrariness of current definitions of positivity for these tests. More important, however, is the fact that if we define asthma in terms of extreme values of these objective measures we would have to label as asthmatic many people who we do not now recognise as clinically asthmatic.

Individuals with hyperresponsiveness or increased peak flow variability include not only those with a diagnosis of asthma but also those who are simply atopic, smoke, are older, are female, have other diagnosed obstructive airways diseases, or indeed have normal but low lung function.⁵⁻⁶ Some are completely normal, and many are asymptomatic. Even among people reporting symptoms, those with increased peak flow variability may be more likely to report current or relatively recent wheeze or cough, whereas those with hyperresponsiveness are likely to report longer term morbidity,⁷ which includes asthma but also the non-specific condition described by breathing that is "never quite right."⁸

These observations, combined with the lack of specificity to clinical asthma and the poor concordance between the populations identified as abnormal by these different objective measures,⁷⁻⁹⁻¹⁰ show that populations defined by symptoms or either increased peak flow variability or hyperresponsiveness are different from, and generally embrace a much broader range of disorder than, our current concept of asthma, however ill defined. Have we reached a stage in our understanding of the pathogenesis, prognosis, or natural history of this disorder at which such a major change in the characteristics of the population we define as having asthma is justified?

There is no evidence that we have. Except for one study of newly presenting symptomatic asthma, which suggested that early intervention with inhaled steroids may preserve lung function in the longer term,¹¹ there is no evidence that any therapeutic intervention in asthma does anything other than improve morbidity in

people with symptoms. If we adopt an operational definition based on a response to treatment, therefore, there is no asthma without symptoms, no point in attempting to recognise asymptomatic disorder, and no justification for including asymptomatic individuals in our definition of disease.

If we are to adopt a prognostic definition based on these objective measures, we need to know the independent relation between hyperresponsiveness or increased peak flow variability and the long term risk of morbidity or mortality, over and above that provided by the characteristics used to make a clinical diagnosis. To date these relations are poorly defined. If we opt for a statistical definition, declaring that the highest 5% or 10% of the distributions of airway responsiveness or peak flow variability indicate asthma, we will have a definition that is attractively convenient but divorced from concepts of clinical abnormality without obvious justification. Thus, on present evidence, there seem to be few compelling reasons to abandon clinical criteria.

This is not to argue that attempts to refine the diagnosis of asthma should be abandoned. Peak flow variability does at least reflect the expression of the fundamental abnormality of asthma encompassed in the available definitions,¹⁻³ and peak flow is an established means of monitoring asthma therapy. If the identification of early, asymptomatic, or just different disease by objective methods proves to have a practical application then our concept of disease should change to accommodate this. We have no such evidence, however, and the suggestion that decisions on long term management of people with equivocal symptoms should be based on the results of such tests⁴ is simply unjustified. We certainly need a simple objective diagnostic test for asthma, but we don't have one yet.

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