

The second in an occasional series of reports concerning meetings on topics relevant to the clinical use of human serum albumin

## Fluid Therapy in Sepsis and Shock

Summary of the 4th Meeting of the International Therapeutic Fluids Group held at the UIC Convention Centre, Paris, France - June 14-15, 2000



**Professor  
Fabrice Brunet**

The International Therapeutic Fluids Group (ITFG) was formed in 1996 and has met each year to further its objectives of establishing a

strong, collaborative and internationally recognised group of clinicians and researchers with an interest in fluids for resuscitation, promoting evidence-based application of fluids for resuscitation and providing expert advice to clinicians, researchers and industry. In addition, the group seeks to assist in securing of funds

for quality research, to encourage both preclinical and clinical studies in areas where evidence is lacking. Currently, around 40 countries are represented in the group, with members from a range of specialities.

The fourth meeting of the group was held in Paris and sponsored by the Plasma Protein Therapeutics Association Europe. Professor Fabrice Brunet (Paris, France), Chairman of the ITFG, welcomed delegates explaining that the purpose of the meeting was to clarify strategies of fluid replacement therapy in critically ill

patients with polytrauma, sepsis and acute respiratory distress syndrome. Adequate guidelines in these situations are often lacking and recent controversies concerning the safety and efficacy of some products highlight the need for properly conducted research to assess the clinical effects of different fluids. The meeting sessions consisted of plenary lectures, presentations of clinical experience and preclinical research, and workshops on focused topics with the intention of promoting interactive exchange of opinions between delegates and those presenting their findings.

## Physiological roles of serum albumin

Plenary lectures concerning physiological roles of serum albumin formed the focus of each day of the meeting. Dr Marc Salit of the Hyland Immuno Division of Baxter Healthcare Corporation, USA, spoke on the role of albumin as a drug carrier and Professor Timothy Evans (London, UK) on "Albumin - new therapeutic perspectives".

### Albumin - a drug carrier



**Dr.  
Marc Salit**

resuscitation, that is carriage of drugs through the circulation, as well as carriage between the intravascular and interstitial

Dr Marc Salit described a physiological role of albumin not normally considered during its use as fluid

compartment.

Protein binding of drugs  
Albumin reversibly binds a number of different drugs (Table 1) and transports these to the therapeutic site of action and to excretory sites, the liver or kidney, for disposal, thereby influencing the pharmacodynamics of many drug moieties. Albumin also binds endogenous substances, including steroids, long chain and medium chain fatty acids and bilirubin.

- Antibiotics
- Anticonvulsants
- Anticoagulants
- Anti-inflammatory agents
- Cardiac drugs

Table 1 - Classes of drugs bound by albumin

## The free-drug hypothesis

The free-drug hypothesis proposes that it is only the free fraction of drug in the plasma that has a pharmacological effect. Albumin-bound drug is not free to interact in tissues and does not cause adverse effects. Similarly, albumin-bound drugs are more difficult to clear from the circulation.

For drugs bound by albumin, the concentration of free drug in the circulation depends on the number of binding sites on the albumin molecule for that drug and the dissociation constant of the interaction as well as the total drug and albumin concentrations in plasma. Drugs more than 90% bound by albumin have poor tissue penetration, are not accessible to privileged sites such as the eye and brain and are slow to be excreted via the liver and kidney. Conversely, it is the bound fraction that is subject to degradation or excretion, and that potentially elicits toxic effects.

## Albumin binding sites

Albumin is a flexible 66Kd protein, chiefly synthesised in the liver and present, in the normal range, at a concentration of 3.5-4.5g/dL. About 40% of the total albumin in the body (about 360g) is present in

the plasma. There are two high-affinity primary binding sites and numerous low-affinity, secondary binding sites. Binding site I of albumin binds, among other compounds, bilirubin and warfarin. In general, drug binding at site I limits the free fraction of these drugs to between 1-10%; thus, albumin binds 90-99% of these compounds while they are in plasma.

Binding site II binds valproate and non-steroidal anti-inflammatory compounds. It is known that drugs bound to binding site II are easily displaced by medium-chain fatty acids. The medium-chain fatty acid binding site overlaps binding site II and binding of free fatty acids to albumin induces conformational changes in the molecule. If a patient is lipaemic, with high free fatty acids, it is likely that drugs or compounds binding to albumin site II will be displaced, resulting in higher-than-expected free drug concentrations of these compounds.

## Characteristics of typical albumin interactions

Binding occurs through a variety of physical means, including hydrogen bonding, electrostatic interaction, hydrophobic and van der Waals forces. Body temperature, particularly fever, is known to alter albumin drug interactions.

Albumin concentration in plasma has been shown to correlate with the incidence of adverse drug reactions. For example, the incidence of adverse reactions to

diazepam and to steroids doubles in patients with albumin levels less than 2.5g/dL. As albumin levels and the levels capable of binding drugs fall, then free fraction of drug rises; it is the free fraction that has pharmacological effects, but also interacts with tissues producing adverse reactions.

High concentrations of drug may lead to albumin binding site saturation and free drug concentration will rise with total drug concentration. Some drugs given in the therapeutic dose range saturate albumin binding sites. If there is a very low drug concentration, the majority of the drug will be bound and, with low free drug concentration in the plasma, first-order elimination kinetics will no longer apply. If elimination half-life rises, then total drug concentration will rise.

## Albumin binding of drugs and displacement reactions

Drugs can be displaced from albumin binding sites either competitively, if drugs are competing for the same binding site, or non-competitively if binding of one compound, such as fatty acids, causing conformational changes resulting release of a drug bound to a second site. The clinical relevance of displacement reactions depends on drugs being highly bound, more than 90%, to albumin. Competing drugs must have a small volume of distribution and the displaced drug must have a narrow therapeutic index. If the free fraction is raised, by

displacement, outside of the limits of the therapeutic index, adverse reactions are more likely. Some examples are illustrated in Table 2.

- Fatty acids can be displaced by valproic acid, leading to increased levels of fatty acids in the circulation and obesity in epileptic patients.
- Displacement of warfarin by phenylbutazone can lead to increased haemorrhage.
- Urate displacement by various drugs can lead to acute attacks of gout.
- Bilirubin can be displaced, in neonates, by commonly used sulphonamides possibly leading to jaundice and kernicterus.

Table 2 - Examples of clinically relevant displacement reactions

## Albumin concentrations and free fatty acid levels in pregnancy and the neonate

During pregnancy total body water may rise by some 8L. Plasma volume may increase by 40 to 50%, and either due to haemodilution or some other factors, albumin concentrations decline significantly as pregnancy proceeds. Concomitantly there is a rise in free fatty acids. In pregnant women there is altered binding for valproic acid, phenytoin and some antibiotics. Oxytocin, used for inducing labour, reduces diazepam and lidocaine binding, increasing their free fractions. Therefore, in the natural state of pregnancy, there will be altered drug albumin interactions.

Hypoalbuminaemia can alter the physiological state of a newborn. A full term infant has an albumin concentration around 3.4g/dL. The pre-term infant has a significantly reduced albumin concentration and a higher concentration of unbound bilirubin. Free bilirubin depends on the total concentration of bilirubin, the total concentration of albumin and the binding capacity of albumin for this substance. All may be altered in jaundiced pre-term infants.

## Other clinically relevant albumin-drug interactions

Free fatty acid concentrations are lower in Crohn's patients than in healthy controls and it is known that there is a 40% increased binding of cortisol by albumin in such patients. There is increased binding of cortisol by albumin and less competition for albumin binding sites from fatty acids. Cortisol bioactivity and adverse drug reactions are lower, in general, in Crohn's patients, possibly because of albumin binding of cortisol in the plasma.

During cardiopulmonary bypass (CPB) in children, the mean albumin levels fall by around 18% in the six hours post-bypass, partially due to haemodilution. It takes some five days for albumin concentrations to recover, which may explain the unusual incidence of adverse reactions incidence in children after CPB.

For warfarin and phenprocoumon, the anticoagulant effects and rates of adverse events are related to the free drug concentration. In surgical patients, plasma fatty acid concentrations rise and albumin concentrations are reduced. As the free fatty acid level rises, warfarin will be displaced from its albumin binding site and may lead to excessive bleeding after surgery. Phenprocoumon binding is not changed significantly by free fatty acid rises, so coagulation with phenprocoumon rather than warfarin will be less sensitive to changes in plasma free fatty acid levels.

Patients with uraemia or liver disease may have altered albumin drug binding. Transplantation of liver or kidney, can result in normalization of drug binding of, for example, diazepam or furosemide, after transplantation.

Phenytoin anticonvulsant is used with antibiotics in patients with central nervous system infection. Strong displacement reactions can occur which lead to high free phenytoin levels and drug toxicity. Unbound concentrations of valproic acid and phenytoin are altered in patients with lipaemic serum. The increase in free fraction in response to lipaemic serum is more marked for valproic acid than for phenytoin. If patients are hypertriglyceridaemic, therapeutic monitoring of these drugs may be essential for proper patient management and prevention of drug toxicity.

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## Conclusions

- The physiological role of albumin as a drug-binding serum protein may not be fully appreciated.
- The clinical relevance of drug displacement reactions depend on drugs being greater than 90% bound and having a narrow therapeutic index.
- For drugs that have significant albumin interactions, low serum albumin concentrations may lead to increases in free fractions of drugs and an increased risk of adverse drug reactions.

## Albumin - new therapeutic perspectives



**Professor  
Timothy Evans**

Professor Evans spoke about new therapeutic directions that might emerge from interesting basic science concerning the

physiological roles of albumin, a compound that has been regarded as a basic therapy for nearly 50 years.

## The structure and metabolism of albumin

Albumin, is made up of 585 amino acids and in its reduced form, contains a thiol-containing cysteine. Many properties of albumin, particularly its potential as a redox-modulating molecule relate to the thiol-containing moiety. The degree to which thiols are important depends to what extent the albumin is in its oxidised or reduced form. In normal physiological circumstances it is reduced.

Albumin is synthesised in polysomes bound to hepatocytes at a variable rate, but usually 9-12g/day; there is no storage in the liver. Production is regulated by colloid osmotic pressure, hormonal influence, including that of insulin, and osmolarity. Both synthesis and metabolism of albumin may be regulated by the availability of the important amino acids, leucine, iso-leucine and arginine, but these are only likely to be rate limiting in cases of extreme malnutrition. Metabolism occurs in or adjacent to the vascular endothelium, at a rate equal to that of synthesis. It is thought to be pinocytosed at a rate related to concentrations of atrial natriuretic peptide. The albumin molecule has a strong negative charge which is important in regulation of colloid osmotic pressure and interaction with vascular endothelium.

## Transport, binding and colloid osmotic pressure

In the critical care setting, the transport function of albumin is important in relation to the number of drugs that can be bound either competitively, where ligands are competing for a single binding site and, therefore, influencing their apparent metabolism, or as a single ligand at a single binding site. Albumin is a circulating depot, and provides transport for, fatty acids, metal ions, thyroxine, bilirubin, amino acids.

Albumin probably accounts for around 80% of colloid osmotic pressure. Albumin is also present in

the intersitium, variably bound according to the site, and it is the difference between the oncotic pressure intravascularly and extravascularly, and the extent to which the membrane between the two is permeable, that influences the movement of water and solutes between the two compartments. Physiologically, shifts of water and protein will be different in a critically ill patient, with variability in synthesis, catabolism, permeability of the membrane and, therefore, distribution of protein and solute between the two compartments.

Following this introduction, Professor Evans turned to the potential of albumin to modulate redox via its thiol moiety, its anti-inflammatory potential and where new areas of research may emerge from basic scientific observations.

## Redox modulation by albumin

The redox state of an environment depends on the extent to which the molecules within it are, or are not, oxidised. Pro-oxidant factors present in variable quantities at varying sites and in varying quantities (Figure 1).

There is abundant clinical evidence of alterations to oxidant and antioxidant forces in sepsis and acute respiratory distress syndrome (ARDS). Protein thiol changes suggest oxidative damage in the plasma of such patients, but recent work shows that thiols can be variable in terms of antioxidant potential and the way in which

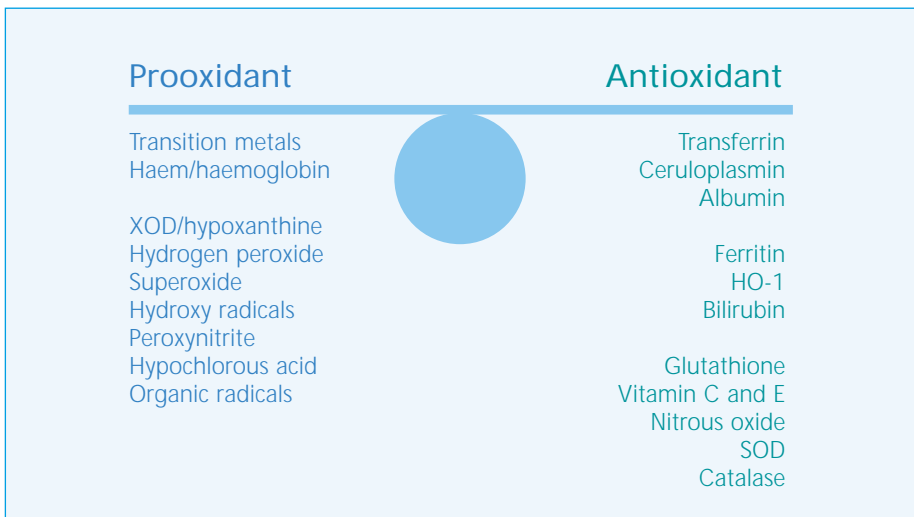


Figure 1 - Redox balance indices

patients differentially display plasma thiol levels in according to the stimulus that results in ARDS. A study of plasma thiols on the first intensive care unit (ICU) day in ARDS patients (Quinlan et al, Critical Care Medicine, in press) compared those developing ARDS after cardiopulmonary bypass (CPB, n=20), versus all other causes of ARDS (n=64). Significantly lower thiol levels were noted in CPB patients who survived, which may relate to the ability of thiols to recycle low molecular mass iron and become, paradoxically, pro-oxidant. In patients surviving after ARDS due to other causes, thiols were significantly higher, suggesting that the antioxidant effect of thiols is dominant in influencing outcome. This is obviously a complex situation.

- Main extracellular source of plasma thiols
- Iron / copper / nitric oxide binding
- Radical scavenging anti-oxidant
- Re-cycles other anti-oxidants
- Intra-cellular redox signalling

Table 3 - Antioxidant and related functions of albumin

### Albumin as a source of thiols

Albumin is the chief extracellular source of plasma thiols and these, in turn, are the chief extracellular antioxidants in physiological circumstances. Normally the redox-active exposed thiol of albumin is present in the reduced state; with aging, albumin is less reduced and thiols, and the redox active state of albumin may change with age.

### Potential of albumin as a binding

agent for iron and copper  
There is potential from a variety of reactive oxygen species, superoxide, hydrogen peroxide, hydroxyl radicals to generate cytotoxic effects and these may be modulated indirectly via transition

metals that catalyse the reactions. Albumin has the potential to prevent this. Additionally, albumin itself, with glutathione and vitamin C, may be an inorganic radical scavenger. Thus, albumin can, directly or indirectly, have antioxidant effects.

### Interaction with nitric oxide

Nitric oxide (NO) has a wide variety of properties and actions that relate to critical illness. Although NO has a very short in vivo plasma half-life, its actions may be prolonged in that it forms an adjunct or adduct as a nitrosothiol, with albumin in plasma. This prolongs the half-life of NO in terms of its vasodilator activity and cell signalling properties. Low molecular weight nitrosothiols are highly vasoactive and have relevance in cell signalling.

With regard to the relationship between an ischaemia-reperfusion injury and leucocyte and endothelial cell activation, NO can prolong the effects or activate NF(B, the ubiquitous cell signalling molecule that binds the promotor regions of many genes at a nuclear level and causes generation of pro-inflammatory substances, cytokines and adhesion molecule expression. Thus albumin interaction with NO is relevant to prolongation of NO half-life, vasodilatory properties and influence on cell signalling, although the level and extent of this influence is not yet known.

## Albumin as an oxygen recycling agent

Ascorbic acid is an anti oxidant- recycled from oxidized product to reduced form by chemical and enzymatic processes (DHAA reductase process). In rats, albumin has significant, glutathione-dependent DHAA reductase activity and therefore, not only has anti-oxidant activity in itself, but also the ability to recycle endogenous antioxidant (ascorbate) for further use.

## Cell signalling

Cell signalling is a complex area which remains to be fully investigated. Current research is examining the potential by which reactive oxygen metabolites, and therefore redox balance, modulates the extent to which NF(B is produced, thus directly influencing the transcription of a variety of pro-inflammatory genes. Redox balance is thought to have a role and the direct effect of albumin on redox balance and its indirect effects by binding NO, have important potential for modulating cell signalling processes and second messenger activation.

## Anti-inflammatory effects of albumin

Human serum albumin has been shown to suppress the respiratory burst in neutrophils following activation with tumour necrosis factor (TNF) and a variety of other complement-mediated processes. Albumin also decreased TNF-induced neutrophil spreading on membranes coated with fibronectin, a property specific to

human, rather than animal, serum albumin.

Albumin may protect in ischaemia-reperfusion inflammation. In cardiac myocytes there is evidence that albumin was protective against ischaemic damage and recovery of contractile function in isolated myocytes was improved.

Epithelial cell lines stimulated with TNF, with or without albumin and with or without glutathione synthase inhibitor, showed that TNF-induced alteration in mRNA expression was reduced or inhibited by presence of albumin by up to 80%, an effect independent of the antioxidant effects of albumin. Thus, albumin may have both antioxidant potential and more direct anti-inflammatory properties.

## New areas for research

From this basic scientific data, there are several potential areas for research relating to properties other than albumin's transportation properties and importance in modulating osmotic pressure and fluid shift.

The effects of administration of albumin on plasma thiol levels has been studied (Quinlan et al, Clin Sci, 1998, 95, 459-465) . In healthy individuals after administration of albumin, the serum albumin levels and total plasma thiol levels were increased and were just beginning to fall four hours after administration of the bolus. In sepsis patients, albumin rose initially and then fell

at four hours, probably due to redistribution through damaged membranes. However, there was no fall in plasma thiol levels in sepsis patients, probably due to interaction and exchange with other, unknown, molecules even though the plasma albumin levels had fallen (Figure 2). In subgroup of patients followed for 18 hours, thiols are sustained markedly in contrast to fall off in serum albumin levels.

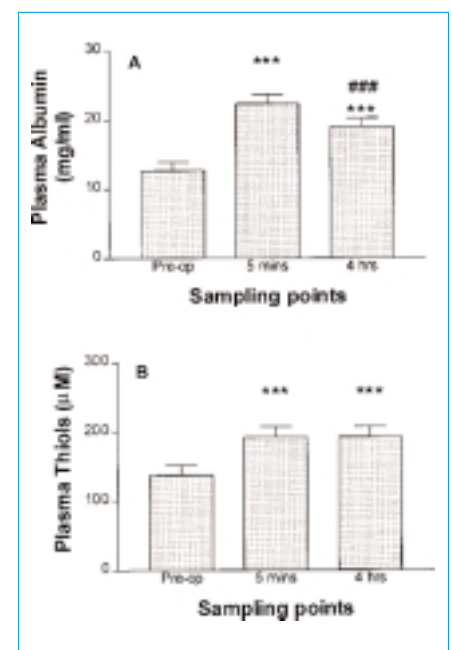


Figure 2 - Plasma albumin levels (A) and total plasma thiol levels (B) in patients with sepsis syndrome before and after albumin administration

\*,  $p < 0.01$  compared with pre-albumin administration. (,  $p < 0.001$  compared with 5 minutes after albumin administration.

These findings show that there is a range of factors affecting albumin in the critically ill and plasma albumin levels are not necessarily related to plasma thiol levels once albumin is administered.

## Future directions

Pathophysiology of sepsis is dependent on an interaction of vascular dysfunction, increased vascular permeability through cytotoxic effects, cellular and mitochondrial dysfunction, second messenger dysfunction and rheology (Figure 3).

Professor Evans' group are beginning to look at effects of albumin as fluid resuscitation on neutrophil rolling, adhesion and migration in post capillary venules using intra-vital techniques to look

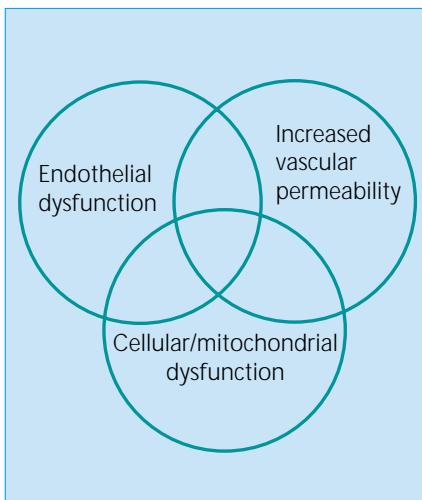


Figure 3 - Pathophysiology of sepsis

at rat mesentery subjected to a variety of inflammatory insults. This can be seen in real time and studying albumin versus crystalloid resuscitation on this process this seems an appropriate subject for ongoing research. Similar methods are being used to examine the different effects of volume resuscitation with crystalloid versus albumin on rat mesentery. Other groups are investigating the number of capillaries in animal muscle that are patent and non-patent in a variety of resuscitated and unresuscitated conditions.

## Conclusions

- The physical and transport properties of albumin are highly relevant to critical illness.
- The anti-oxidant potential of albumin is largely unexplored. Albumin has the theoretical potential to influence anti-oxidant activity.
- Albumin, directly by influencing redox balance, or indirectly via NO mechanisms, may influence cell signalling processes.
- Work on neutrophil spreading and inflammatory processes suggests the potential of albumin to influence the inflammatory process should be explored at a basic scientific level.

## Fluid therapy in sepsis and shock

During the two days of the meeting, sessions were dedicated to presentation and discussion of clinical approaches to fluid management of various patient groups.

## Fluid therapy in paediatric cardiac surgery

The current emphasis is on very early correction of heart defects, which results in better long-term function, but also results in increased inflammatory responses, more oedema and more difficulties of management in the intensive care unit (ICU). All neonates have immaturity of the coagulation system.



**Professor Desmond Bohn**

In his presentation on this topic Professor Desmond Bohn (Toronto, Canada) explained the clear differences

between adults and infants with respect to the relative volumes of blood and the CPB circuit (Table 4).

	Blood volume	Circuit volume
<b>Adult</b>	71.4 mL/Kg	29-35.8mL/Kg
<b>Child</b>	75mL/Kg	60mL/Kg
<b>Neonate</b>	80mL/Kg	125mL/Kg

Table 4 - Comparison of blood volume and CPB circuit volume in adults and children

It has been standard practice to use a non-blood prime for the circuit for adults and older children, as the fall in haematocrit has no clinically significant effect. Blood primes are used for infants where the discrepancy between the circuit volume and the patient is significant. For clear (non-blood) priming solutions for children, crystalloids are used, usually RL with or without added colloid. The most frequently used colloid is albumin, with 25% solution added to give a final concentration of 30g/dL, approaching the normal serum concentrations with a similar oncotic pressure. Studies have shown that use of colloid in the prime is associated with:

- higher colloid osmotic pressures;
- decreased extravascular lung water;
- lower intra-operative fluid requirements;
- lower filling pressures

compared with a crystalloid prime. Use of colloid in the prime for neonates is associated with less tissue oedema, a major complication of CPB operations in the very young. Studies of albumin compared with synthetic colloid have shown lesser effects on coagulation parameters, though this has not translated into decreased tendency to haemorrhage. Use of albumin in the prime has also been shown to have beneficial effects on in vitro platelet aggregation. Therefore, colloids should be used as the priming solution for CPB, especially in the very young, and experimental and clinical evidence suggests that the preferred colloid is albumin.

For the peri-operative period, trial evidence has concluded that hetastarch (the only FDA-approved synthetic colloid in the USA) at more than 20mL/kg should not be used for children during CPB due to development of abnormal coagulation profiles; children receiving albumin require less colloid support in the post-operative period.

Post-operatively, a randomised controlled trial comparing a bolus infusion of 100mL 25% albumin with an equivalent amount of normal saline to raise the filling pressure, to determine whether cardiac output was raised, found that the bolus administration of albumin improved cardiac output.

- Albumin remains the fluid of choice for paediatric cardiac surgery, for priming, peri-operatively or post-operatively.
- The effects of synthetic colloid, at least that available in North America, on coagulation preclude its use.
- Further comparative studies are needed to determine the optimum fluid, crystalloid or colloid, in the post-operative period.

*Table 5- Fluid use in paediatric cardiac surgery - conclusions*

### Fluid therapy for the paediatric patient in septic shock

During a workshop session, Professor Bohn presented a case history of a 14-year-old 55kg adolescent, with a brief history of fever and petechiae brought directly to the emergency department after diagnosis of meningococcaemia by her father, a doctor. She was tachypnoeic and hypotensive and, such was the bacterial burden, Gram negative organisms could be seen on blood smear. She was immediately placed on triple antibiotic therapy. She was in established multiorgan failure with profound immunosuppression.

This was a life or death situation and the workshop participants agree that there was immediate need for fluid resuscitation with whatever fluid was available. This would probably be saline or lactated Ringer's solution (RL), given at 20mL/kg immediately as a resuscitation bolus of fluid and, in the circumstances of a child on the

verge of cardiac arrest, without monitoring pressure. The response would then be assessed, with a view to switching to colloid infusion. The use of albumin would generally be favoured for paediatric patients. Some participants mentioned an initial use of large molecular weight starch before switching to albumin, although others queried the use of hydroxyethyl starches because of adverse effects on coagulation.

Albumin is the colloid of choice for intravascular expansion of paediatric patients in septic shock; it is possible to use smaller volumes than would be needed with crystalloid expansion. Another contributor would use albumin after initial crystalloid for this patient, perhaps using serum albumin levels as a guide. It could be guessed that the child is profoundly albuminaemic. Whilst crystalloids would be standard for adult patients, meningococcaemia is the most extreme paradigm of septic shock; in children and adolescents it is practice to use crystalloids initially and switch to colloids.

Subsequently, an intropene was administered because it was proving impossible to increase blood pressure with the practical rate of fluid resuscitation. In the emergency department the patient received 2.5L saline and 500mL 5% albumin and was transferred to the ICU. Once in the ICU, the patient received fresh-frozen plasma and another 500mL 5% albumin. Despite administration of

pressors, haemofiltration, corticosteroids and a trial of inhaled NO the patient went into irreversible cardiorespiratory failure and was put onto extra-corporeal mechanical oxygenation (ECMO) on the fourth day after admission. She died of massive intracerebral haemorrhage three days later.

## Fluid management of adult patients during non-cardiac thoracic surgery



Dr William Hurford (Boston, USA) spoke of problems in patients who had undergone pneumonectomy and subsequently

developed pulmonary oedema. The opinion that cautious fluid management during right pneumonectomy would be adequate to prevent this phenomenon guided practice for some 15 years. However, the conclusions of retrospective study of patients treated by Dr Hurford and his group indicate that that the amount and type of peri-operative fluids appeared unrelated to outcome.

It is now considered that increased morbidity post-pneumonectomy may be a result of increased blood flow to the remaining lung, possibly in combination with stress injury with endothelial damage rather than the amount or type of intravenous fluid used. The treatments proposed for minimisation and management of

post-pneumonectomy pulmonary oedema are summarised in Table 6. None of these have been proven in controlled trials, but a variety are used in combination.

- Fluid restriction and diuresis
- Positional changes - prone or lateral positioning
- Adequate analgesia and sedation to keep the pulmonary artery pressures low
- Maintenance of relatively normal oncotic pressure by use of albumin and blood products when appropriate
- Minimisation of barotrauma
  - ? inhaled nitric oxide
  - ? corticosteroids - to try to decrease any inflammatory response

*Table 6 - Post-pneumonectomy pulmonary oedema treatments*

As a result of implementation of these approaches, the mortality from post-pneumonectomy oedema has fallen from 80% in the patients reviewed in the retrospective survey, to 30% currently. Recent changes in ventilatory strategy for pneumonectomy patients may have altered the incidence of oedema after this operation, but it still occurs. When asked to comment on what fluids he used during cardiac surgery and by-pass, Dr Hurford referred to the illustration of the relative differences in volume between the patient and the by-pass circuit in adults and children (Table 4); usually, in adults, the type of fluid was not of major importance. In his own group, usually crystalloid

was used, perhaps with some albumin.

## Fluid management of the thermally injured patient

Daniel Wasserman (Paris, France) and Andrew Cooper (Toronto, Canada) discussed the case of a previously healthy 50 year-old-man, presenting in the emergency room four hours after a house fire. The patient had 40% body surface area (BSA) third degree burns, but no evidence of inhalation injury. He was hypotensive and has received 800mL normal saline through an intravenous line since the burn.

The injury severity indices used for burn patients would show that this is a high-risk patient and at the time of presentation the patient is under-resuscitated. The Parkland formula predicts that this patient should receive 2800mL fluid in the first four hours post-burn. The patient is hypotensive and is at major risk for shock. The risks of delay and under-resuscitation in burn patients are summarised in Table 7.

- Increased mortality both immediately and in the long term
- Deepening of burn tissue
- Secondary plasma leakage in non-burned tissue

*Table 7 - The risks of delay and under-resuscitation in burn patients*

The resuscitation goals are to restore critical organ perfusion, limit tissue and organ ischaemia (and consequent dysfunction), limit

tissue oedema which may lead to skin ischaemia and complications such as compartment syndromes and hydrostatic pulmonary oedema. For this patient, the Parkland formula predicts a need of 5600mL in the first 8 post-burn hours, but after the eighth post-burn hour there are only guides which are not necessarily applicable to individual cases, especially if they have been under-resuscitated initially. For resuscitation, RL plus colloid would be used from the time of admission. As the colloid, human serum albumin might be used or HES 6% to a maximum of 33g/kg, but in practice more than 1.5L of HES is never used because of concerns about coagulation and renal elimination in these patients. Human serum albumin is the fluid of choice to achieve rapid plasma expansion; a relatively high concentration would be used on the following basis (Table 8).

- The SFAR (French Society of Anaesthesia and Resuscitation) consensus proposes the use of albumin with greater than 30% BSA burns.
- When a patient has been under resuscitated and is at risk of shock, a rapid plasma expansion is needed.
- There is clinical and experimental evidence favouring the use of colloid for severely burned patients.
- Colloids can:
  - achieve rapid plasma expansion
  - limit oedema formation.

*Table 8 - Rationale for the use of human serum albumin in burn patients*

The amount of fluid will be perfused to obtain haemodynamic stability, normal blood pressure and diuresis greater than 1mL/kg/hour, somewhat more than the recommendation of the American Burn Association consensus, that is 30-50mL/hour in adults and, for children. Pulmonary artery catheters (PAC) are recommended only where requirements are greater than predicted, for very volume-sensitive patients or for those with a history of cardiac insufficiency. Fluid management of adult patients with septic shock and organ failure

### Choice of colloid for the intensive care patient



**Professor Bertrand Guidet**

Bertrand Guidet discussed the choice of fluid for a patient admitted to intensive care for septic shock. In the case presented, the patient had been well prior to urinary tract infection six weeks earlier, for which he was given a three-week course of fluoroquinolones. He was hypotensive and tachycardic on admission, with a one-day history of fever and rigors. This patient had sepsis, probably of urinary tract origin, and it was not known how he might respond to plasma expansion. He probably had metabolic acidosis and, as he was agitated, he might have had cerebral hypoperfusion.

- Associated mortality risk
- Volume expansion
- Risk of immediate and long-term side effects
- Volume limitation considerations
- Cost

*Table 9 - Factors influencing the choice of fluid for an adult in septic shock*

The available meta-analyses show efficacy of crystalloids compared with colloids for trauma patients, but for non-trauma patients colloids are equivalent or slightly superior to crystalloids. However, methodological limitations preclude choosing fluids on the basis of these mortality meta-analyses.

In relation to volume expansion requirement, physicians should be fully aware of the characteristics and pharmacodynamics of albumin, gelatins, dextrans and starches; the molecular structure, especially of starches, influences the properties and hence the choice in specific situations. A product with an initial high-volume effect, 20% albumin or a high- or medium-molecular weight starch, may be selected. The duration of action should be considered, especially if there is a risk of volume overload, although this does not apply to albumin. Dextrans and gelatins have around 10-fold higher incidence of allergic reactions than do albumin and starches. With dextran and high- and medium-molecular weight starches, there may be problems with coagulation and, with starches there is debate concerning the relevance of tissue accumulation in the reticulo-

endothelial system of HES. Accumulation in the kidney has been associated with osmotic nephrosis, but the evidence of impaired renal function is equivocal. There is histological evidence of hepatic accumulation, particularly in cirrhosis patients, but the effects on portal pressure, ascites and hepatic dysfunction are debatable. Pruritus is a significant effect of accumulation of HES in the skin.

Although Professor Guidet dismissed the findings of the Cochrane study (Brit Med J, 1998, **317**, 225-240), he considers that the use of albumin should be restricted on grounds of cost. For the case under consideration, sepsis related to urinary tract infection in a previously healthy patient has a good prognosis. As in burn patients, quick restoration of volaemia is paramount and both crystalloids and colloids, specifically a medium- or low-molecular weight starch would be used in this case.

## Management of cirrhotic patients with spontaneous bacterial peritonitis (SBP)



**Dr. Pau Sort**

Dr Pau Sort (Barcelona, Spain) discussed a second case of a patient in septic shock, a man with a history of alcoholic cirrhosis,

admitted to surgical intensive care a week after evacuation of ascites. The patient was oliguric and

hypotensive. Although it was probable that the patient was in septic shock as a result of SBP, most patients with cirrhosis and ascites are hypotensive and the blood pressure in this case would not be uncommon. Similarly, the daily urine output in this case would be the normal output in a patient with cirrhosis and ascites. Plasma expansion with saline infusions cannot be recommended, as it is normal to restrict salt intake of patients with ascites.

The presence of SBP in cirrhotic patients is defined by presence of polymorphonuclear cells in the ascitic fluid in the presence of fever with no other evidence of infection; 15-20% of patients admitted to hospital for ascites present with SBP or develop the infection during the admission. Usual treatment is the administration of third generation cephalosporins. A striking feature of SBP is the high incidence of renal impairment, with a third of patients developing this complication. This, in turn, is associated with high mortality rates (Table 10).

	Mortality rate
No renal impairment	7%
Renal impairment	42%
progressive	100%
steady	31%
transient	5%

*Table 10 - Hospital mortality in patients with SBP*

Previously published work has shown the utility of albumin in maintaining haemodynamic and

renal function in patients undergoing paracentesis, and the superiority of albumin to dextran 70 and polygeline in this respect. A recent randomised study, conducted by Dr Sort's group (New Engl J Med, 1999, **341**, 403-409), enrolled 126 cirrhotic patients with SBP, comparing a third-generation cephalosporin (the standard treatment) with or without intravenous albumin, 1.5g/kg on day 1 and 1g/kg on day 3 of treatment.

It was anticipated that by improving haemodynamics, the renal function would also improve and this was so. Blood urea nitrogen and serum creatinine levels remained stable in albumin-treated patients, but increased significantly in patients receiving cefotaxime only. Serum sodium levels were stable in patients receiving albumin, but decreased significantly in those not receiving additional albumin. These results indicate that administration of albumin prevented the deterioration of renal function in cirrhotic patients with SBP. Results are summarised in Table 11.

Plasma volume expansion with albumin at the time of diagnosis of SBP markedly reduces the incidence of circulatory dysfunction and renal impairment associated with the infection, and improves hospital survival. It can be concluded that all cirrhotic patients with SBP should be treated with albumin as well as antibiotics. In the patient presented, Dr Sort would not hesitate to give

	No additional albumin	Additional albumin
Hospital stay (days)	14±1	13±1
Antibiotic treatment (days)	6±1	5±1
Resolution of infection	59 (94%)	62 (98%)
Renal impairment	21 (33%)	6 (10%)
Hospital mortality	18 (28%)	6 (10%)

Table 11 - Treatment parameters and incidence of renal impairment and hospital mortality in cirrhotic patients with SBP treated with cefotaxime with or without albumin

antibiotics and albumin to improve the chance of survival.

## Fluid therapy in acute lung injury

Dr Gregory Martin (Nashville, USA) spoke on the subject of appropriate fluid therapy in acute lung injury, (ALI) or the acute respiratory distress syndrome (ARDS), reviewing the mechanisms of pulmonary oedema formation, what role oncotic pressure may play in ALI/ARDS and what is known about albumin and/or diuretic therapy in the clinical setting of acute lung injury.

It is known that hydrostatic pressure is of prime importance in the setting of altered capillary permeability, and that reducing lung water, for example by diuresis, decreases the duration of mechanical ventilation and intensive care stay. It is known theoretically that oncotic pressure gradients play a role in pulmonary oedema formation (Table 12), although the nature of the role remains to be elucidated. Recent analyses reported from clinical trials of sepsis reveal that patients with low serum total protein concentrations gain weight, are more likely to suffer

ALI/ARDS, experience prolonged mechanical ventilation, and have nearly 3-fold higher mortality rates than patients with normal total protein concentrations. (Mangialardi, et al. Crit Care Med 2000 ;28 : 3137-45)

- Reductions in plasma colloid oncotic pressure increase lung lymph flow, altering one of the protective mechanisms preventing pulmonary oedema.
- Shrinking the oncotic pressure gradient between the plasma and the interstitial space favours pulmonary oedema formation.
- Exogenous, administered albumin does not increase oedema formation when hydrostatic pressures remain unchanged.

Table 12 - The role of oncotic forces in ALI

A prospective randomised, double-blind controlled trial of albumin plus furosemide versus placebo plus placebo administered over five days to 37 patients with hypoproteinaemia and ALI/ARDS. The majority suffered ALI/ARDS related to trauma, with pneumonia and sepsis accounting for the remaining etiologies. The protocol was based on the hypothesis that combined administration of

albumin and diuretic (furosemide) would expand the oncotic pressure gradient while minimizing hydrostatic components of pulmonary oedema, and thus improve pulmonary physiology and intensive care outcome. The study concluded that, in hypoproteinaemia and ARDS, albumin and furosemide-treated patients, diurese and lose weight, show improved oxygenation and haemodynamic stability and may have reduced mechanical ventilation requirements. The benefits reported from this trial are likely attributable to the combined effects of colloid and diuretic therapy, the specifics of which benefit are currently unknown. The tangible benefits from each therapeutic component is being investigated in an ongoing clinical trial.

Professor Evans and his co-workers are now collaborating with Gregory Martin and Gordon Bernard, looking at thiol levels in the acute lung injury patients given albumin and furosemide, versus placebo. Professor Evans reported their very preliminary findings at the meeting. Six sets of samples had been examined and appeared to be divided into two groups; the study is blinded and the code has not been broken. In some patients there was no overwhelming relationship between albumin and thiols and albumin and total antioxidant potential. There are low levels of albumin in patients with sepsis. In the second group albumin levels are higher - presumably as a result of

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exogenous albumin administration, and there is a relationship between thiols and plasma albumin and with antioxidant potential.

## Fluid management of the trauma patient

Both presentations and workshop sessions dealt with management of the trauma patient, particularly the differences in approach between North America and the UK ("scoop and run") and continental Europe ("stay and stabilise"). Professors Pierre Carli (Paris, France), Jean-Emmanuel de la Coussaye (Nîmes, France) and Stephen Cohn (Miami, USA) discussed the various approaches. As was pointed out in most sessions, this is not an either / or situation; management must depend on the type and severity of the injury and the circumstances - including how long it will take to transport the patient to the appropriate treatment centre.

The continental European / Scandinavian approach to early resuscitation of the trauma patients may involve placement of an endotracheal tube and an intravenous line at the site of the accident. Fluid resuscitation, if required would be with crystalloid, although the need for medical assessment is needed in the field was stressed. In the case of haemorrhage, fluid loading should be enough to keep the patient alive long enough to get them to the surgical team. Use of vascular loading in a non-hypovolaemic patient is inefficient and may be hazardous.

In the US, the trauma patient would be taken to the treatment centre after assessment. Crystalloid might be given as a temporising measure until blood were available. The emergency centre would have been made aware that a hypotensive trauma patient was about to be admitted and un-crossmatched blood would be made available.

Patrick Goldstein (Lille, France) pointed out that the goal is to treat the patient, not the specific cardio-circulatory or respiratory distress. He firmly believes in fluid resuscitation of the polytrauma patient in the pre-hospital setting, but for selection of crystalloid versus colloid, there is no direct answer. The French Guidelines for fluid resuscitation for the polytrauma patient in the pre-hospital setting are as follows:

- Fresh plasma, albumin or dextran are not used in this setting;
- Colloids or crystalloids (RL rather than saline, unless the patient has a head trauma) are used;
- Recommended colloids are gelatin or hydroxyethyl starch (HES), the latter being preferred as it appears to attenuate the acute inflammatory response.

Low amounts of starch may be given, according to French guidelines, in a manner and dose considered to be without influence on coagulation and the best results have been achieved with moderate volume substitution using rapid infusions. However, many physicians are reluctant to give large volumes of starch partly

because of effects on clotting, partly because of accumulation of starch in tissues and, finally, if the patient is likely to arrest, because of accumulation in organs that may later be used for transplantation.



**Dr. Patrick Goldstein**

Professor Paul Pepe (Dallas, USA), defending a relative "scoop and run" approach, emphasized that the discussion should be concerned what should or could be done for the patient before they were brought to the operating theatre. Although fluid resuscitation sufficient to restore blood pressure may be standard practice, this traditional approach assumes that raising blood pressure is always beneficial. However, it may not always be so. One large, prospective, controlled clinical trial has shown in the pre-hospital and emergency department setting IV fluid resuscitation, that hypotensive patients with penetrating torso injuries, who received aggressive IV isotonic fluid resuscitation pre-operatively had higher mortality rates and a higher incidence of post-operative complications when compared to those patients who were given fluid only on arrival in the operating room.

Professor Pepe cautioned, however, that such studies must be interpreted carefully. Trauma is not a generic condition and different disease processes are involved in

each patient according to the mechanism of injury (blunt vs penetration) and its anatomic locations. In the end, all contributors to these sessions agreed that there is no hard and fast difference between “stay and stabilise” and “scoop and run”. Some patients in each country will need stabilisation before transport (particularly those with head trauma), others in each country (such as those with penetrating truncal trauma) will do better with immediate transfer to a surgeon. Once it has been decided to transport the patient, co-ordination of services to bring the patient to the most appropriate treatment centre as quickly as possible, not necessarily the nearest, is vital.

## Clinical trials of techniques of fluid resuscitation



**Dr. Bruno Riou**

An assessment of current research in fluid resuscitation was presented by Bruno Riou (Paris, France) focusing on the specific

point that is important for all past and future randomised trials in this area, that is, the distribution of probability of survival. Lack of statistical power can produce a situation where the heterogeneity of the population may explain any observed differences between two treatment groups, rather than the treatment itself.

A data base of severe trauma patients has been used to simulate

what could happen in a randomised trial with a theoretical drug that could improve survival, studying the distribution of probability of survival in trauma patients and its consequences on hypothesis testing. In the data base of 350 patients, the mean TRISS score (a function of age, injury severity score, revised trauma score and type of injury) was 0.75, indicating 75% of patients survived. An analysis was performed to simulate the effects of a drug or intervention that would increase the probability of survival by various percentages. For example, if 30% of patients in a group survive, with a drug or intervention that would improve the rate of survival by 10%, there would be 33% survivors from that group.

The same analysis was made, but using the individual, rather than group, probabilities of survival. The calculations revealed bi-modal distribution of probability of survival amongst severe trauma patients, the majority having TRISS scores  $<0.10$  and  $>0.90$ . This resulted in major discrepancies between the number of patients that would need to be included in trials to demonstrate specific percentage improvements with an intervention, when the probability of survival of a group of patients or the individual probability of survival were compared. For example, based on a mean group TRISS score of 0.75, 12,018 patients would have to be included in a study with power to demonstrate a 10% improvement in survival, and

2,848 to demonstrate a 20% improvement. Based on individual survival probabilities, rather than group survival, the numbers would be 312,400 and 63,202, respectively. The full significance of this bimodal distribution of survival probability with regard to trial design has not previously been recognised. Dr Riou's proposals are summarised in Table 13.

- Distribution of the probability of survival should be considered in the design of the trial, especially in trauma patients - because of the bimodal distribution of this probability.
- Where the number of patients that would need to be included to detect differences is not realistic, alternative statistical methods that could include the a priori probability of survival, to increase the power to detect an effect should be used.
- Selection of a sub-population of patients with a more homogeneous degree of severity or use of endpoints other than mortality should be investigated. It is not feasible to study mortality as an endpoint if some 300 000 patients have to be studied to detect a difference.
- A composite endpoint including death, incidence of acute respiratory distress syndrome (ARDS), acute renal failure and multiple organ failure (MOF) should be devised.

*Table 13 - Proposals for clinical trials in emergency medicine*

These are important findings with respect designing clinical research protocols and also important for evidence-based practice and analysis of the literature on which current practice is based. If the demonstration is true, many of the studies on which clinical practice today is based were not well, or even poorly, designed. For example, the Cochrane analysis (Brit Med J, 1998, **317**, 225-240) of different clinical trials of crystalloid and colloids may be based on poorly designed trials.

A number of speakers commented on the shortcomings of the meta-analyses published by the Cochrane Group and by Schierhout and Roberts (Brit Med J, 1998, **316**, 961-964) which compared crystalloid and colloid solutions for resuscitation. Both Andrew Cooper and Professor Guidet stated that the studies subjected to analysis had been conducted over three decades, there was heterogeneity with respect to the timing of resuscitation, the patient populations in different studies, the way that colloids, particularly albumin, were used and the assessment of outcomes. There

was general criticism of these meta-analyses on these grounds, emphasising the need for prospective studies with good trial design and homogeneous patient populations.

## Conclusions

- The choice of fluids for resuscitation remains a matter of debate, but the use of albumin for paediatric patients, for thermally injured patients and for patients with cirrhosis and SBP was endorsed.
- The meeting was, as intended, highly interactive and a range of opinions was expressed on all topics. The areas where there were some elements of disagreement were usually those where clinical trial evidence to corroborate animal findings is lacking.
- The need for properly designed and powered clinical studies was stated repeatedly, but, as Dr Riou pointed out, these may be difficult to conduct.

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Gaea Consulting Limited (Managing Editor: [ngg@gaea.co.uk](mailto:ngg@gaea.co.uk))

PPTA EUROPE  
Boulevard Brand Withlock 114 (5<sup>th</sup> floor)  
1200 BRUSSELS  
Belgium  
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