

One in a series of reports concerning meetings on topics relevant to the clinical use of human serum albumin

Selected topics concerning

## Intravenous fluid therapy and management of acute liver failure

from the 23<sup>rd</sup> International Symposium on Intensive Care and Emergency Medicine held in Brussels, Belgium, in March, 2003.

### Introduction

The International Symposium on Intensive Care and Emergency Medicine, which is essentially an educational Symposium, continues to expand in scope and in the numbers of delegates attending. Each year brings new discoveries and theories concerning the processes of sepsis,

but some basic problems remain the same. One of these is the appropriate choice of fluid for resuscitation, and the session on intravenous fluids is always well attended. Presentations from this session are included in the report. The session on gastrointestinal crises was very crowded as many

delegates sought advice on dealing with such crucial emergencies. Part of the session concerned the treatment of acute liver failure, an area where definite advances have been made in the last few years.

### Intravenous fluid therapy

The session on intravenous fluid therapy for the critically ill patient, moderated by Jean-Pierre Revelly (Switzerland), mainly concerned the appropriateness of intravenous fluids, both in general and in relation to suitability for particular patients.

#### Normal saline induced abnormalities

Monty Mythen (UK) argued that normal saline is far from normal as an agent for fluid resuscitation. In fluid management, the major questions are:

- What to give?
  - How much to give?
- in order to achieve the endpoints of improvements in:
- Heart rate, blood pressure, central venous pressure, cardiac output
  - pH, base excess, lactate
  - Mentation – if the patient is not comatose

- Peripheral perfusion
- Urinary output

#### Normal saline

Normal saline may be of normal osmolality, but while the sodium content approximates to normal plasma levels, the chloride content does not. Administration of a 0.9% solution of sodium chloride produces hyperchloraemia and acidosis – a situation which has been named hyperchloraemic metabolic acidosis (HCMA), almost as if this constitutes a disease in itself. It should be remembered that all colloid resuscitation fluids are in a saline solution formulation.

#### Hyperchloraemic metabolic acidosis (HCMA)

In human studies of 0.9% saline solution in comparison with Hartmann's solution, which contains lactate, potassium and calcium, as

well as sodium chloride, saline was associated with HCMA, with the risks of:

- Decreased mental acuity
- Abdominal discomfort
- Reduced urine flow
- Tendency to increased bleeding

#### Mental acuity and abdominal discomfort

In a crossover comparison of lactated Ringer's solution (LR) and normal saline in 18 healthy volunteer subjects, Williams *et al* (*Anesth Analg*, 1999, **88**, 999) found saline to be associated with some degree of central nervous system (CNS) change in over 80% of subjects, while LR was not associated with these changes. The degree of CNS change was the equivalent of ammonium chloride poisoning. Abdominal discomfort was reported by 10 subjects given normal saline, but by only one volunteer when given LR.

In 47 elderly surgical patients, who received either 6% hydroxyethyl starch (HES) in normal saline or “balanced fluid” consisting of Hartmann’s solution and 6% HES in balanced electrolyte and glucose (HEXTEND), over 60% of the normal saline/HES recipients experienced HCMA, compared with none of those given the “balanced fluid” (Wilkes *et al*, *Anesth Analg*, 2001, **93**, 811).

### Reduced urine flow

A number of authors have reported the impact of normal saline on renal function in animals, in normal volunteers and in patients. In dogs, hyperchloraemia produced a progressive renal vasoconstriction and detectably lower glomerular flow rate;

the changes in renal blood flow correlated with plasma chloride levels (Wilcox *et al*, *J Clin Invest*, 1983, **71**, 726).

In the crossover study with 18 volunteer subjects (Williams *et al*), the time to first urination was significantly longer ( $P < 0.001$ ) after normal saline compared to LR (Figure 1). In the elderly patients (Wilkes *et al*), urine output was greater following HEXTEND, 320ml, compared to 175ml after normal saline/HES, at the same time interval from infusion.

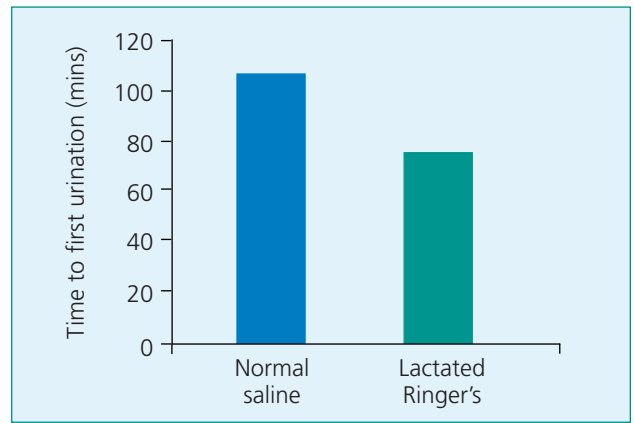


Figure 1 Time to first urination in normal volunteer subjects following normal saline or lactated Ringer’s solution

This evidence leads to the conclusion that there is little that is normal about normal saline and the use of more physiologically balanced intravenous fluids may be associated with an improved outcome.

## Hypertonic fluids in polytrauma

David Hoyt (USA) reviewed data from the Birmingham Accident Hospital (UK), recorded between 1961-66 that showed that trauma victims who bleed to death usually do so within 5 to 6 hours of sustaining the trauma (Table 1). Although these are old data, the same would probably be true today. US Military experience is similar. In the Vietnam War, bleeding was the cause of death in 24% of fatalities, all of whom died within 6 hours.

Type of trauma	% dying within 6 hours
Head injury	20%
Spine injury	70%
Chest	80%
Ruptured diaphragm	100%
Ruptured heart or aorta	100%
Haemothorax	100%
Abdomen	
Liver	100%
Spleen	100%

Table 1 Percentages of patients dying within 6 hours of sustaining trauma

## Classification of haemorrhagic shock

Haemorrhagic shock can be classified

according to the extent of blood loss (blood volume is 7% of body weight) (Box 1).

<b>Compensated shock – BP &gt;90mm Hg</b>	
Class I	10–15% blood loss
Class II	20–25% blood loss
<b>Uncompensated shock – BP &lt;90 mm Hg</b>	
Class III	30–35% blood loss
Class IV	>40% blood loss

Box 1 Classification of haemorrhagic shock. Loss of >50% of blood volume leads to death

## Choice of suitable resuscitation fluid for the polytrauma patient

Deciding whether a polytrauma patient will benefit from fluid resuscitation depends on the type of trauma, but essentially any major haemorrhage must be controlled before fluid resuscitation is started.

An analysis of the state of the art for fluid resuscitation for casualties was undertaken for the US military in 1999 (Fluid Resuscitation, State of the Science for Treating Combat Casualties and Civilian Injuries, Institute of Medicine, Pope A, French

G, Longnecker DE (Eds), National Academy Press, Washington, DC). There were concerns with respect to LR and to colloids, but hypertonic saline has become increasingly attractive as an option because of its:

- Haemodynamic properties – higher pressure achieved with the same volume
- Effects on intracranial pressure (ICP)
- Immunological effects

Hypertonic saline is available as 7.5% solution and as 7.5% saline plus dextran 3%. Management of haemorrhagic shock using small volume resuscitation with 7.5% saline leads to:

- Rapid haemodynamic restoration
- Increased organ blood flow
- Inotropic effects
- Effects on the microcirculation
- Less endothelial swelling, decreased red blood cell (RBC) volume and systemic vascular resistance (SVR) as a result of the fluid shift induced by hyperosmolarity.

## Immunological effects

The immunological effects of hypertonic saline solutions are of interest and probably of clinical value in the polytrauma patient. Coimbra *et al* (*Shock*, 1995, 4, 45) found that *in vitro*, hypertonic/hyperoncotic fluids reverse prostaglandin E2-induced T-cell suppression. In an *in vivo* study Coimbra and colleagues (*J Trauma*, 1997, 42, 602) showed that hypertonic saline resuscitation decreases susceptibility to sepsis after haemorrhagic shock. In a mouse "two hit" model using haemorrhage and caecal ligation and puncture (CLP), the outcomes for study were survival and organ function. Survival was superior in animals resuscitated with hypertonic saline compared with those given LR (Figure 2) and there were marked improvements in lung and liver injury.

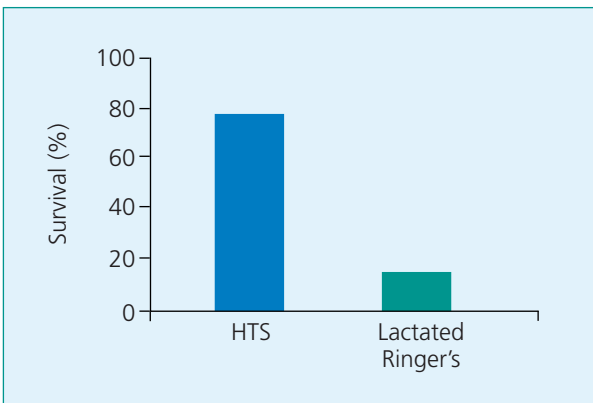


Figure 2 Survival after haemorrhage and CLP in mice given hypertonic saline (HTS) or LR

Junger *et al* (*J Trauma*, 1997, 42, 457) showed that hypertonic saline triggers a T-cell signalling pathway that includes increased phosphorylation of several cellular proteins and activation of MAP kinase p38. While hypertonic saline itself does not result in interleukin (IL)-2 mRNA expression, IL-2 expression or T-cell proliferation, in combination with other stimuli, hypertonic saline augments IL-2 expression and T-cell proliferation. Haemorrhage, trauma or burns may

result in immune suppression, but hypertonic saline may aid the recovery mechanism and promote immune responses by promoting MAPK p38 activity.

## Effects of hypertonic saline on neutrophils

Saetzler (*Surg Forum*, 1996, 47, 41) in a hamster microcirculation model showed that hypertonic saline reduced neutrophil rolling and sticking. Angle *et al* (*J Trauma*, 1998, 45, 7) found that hypertonic saline significantly decreased neutrophil L-selectin expression, but had little effect on endothelial P and E selectins. Rhee *et al* (*J Trauma*, 1998, 44, 313), in an animal model, showed that LR resuscitation after haemorrhage activated neutrophils, as measured by superoxide burst activity, but that there was no such activation after resuscitation with shed blood or with hypertonic saline.

## Clinical studies

A multicentre study in the USA compared 250mL 7.5% saline plus 6% dextran (HSD) and 250mL normal crystalloid

administered before routine pre-hospital and emergency centre resuscitation of 422 patients, 211 of whom subsequently underwent surgery. There were no differences between the groups in overall survival, but among the patients requiring surgery there were significantly better rates of survival among those patients who received HSD ( $P=0.02$ ) and also a lower incidence of complications (Mattox *et al*, *Surgery*, 1991, 213, 482).

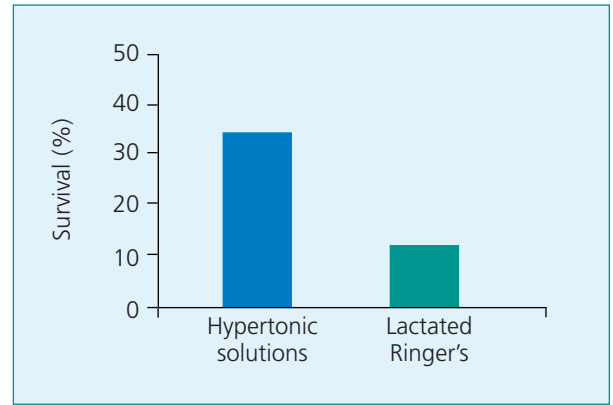


Figure 3 Survival of patients with low baseline Glasgow Coma Scores (<8) receiving initial resuscitation with hypertonic solutions or LR

In another multicentre study, 250mL hypertonic saline, with or without dextran, was compared with LR for correction of hypotension in trauma patients before helicopter transport to hospital. Further treatment was with conventional isotonic solutions. Overall survival was no different between the groups and there was no obvious benefit of dextran. However, subgroup analysis, showed improved survival of patients with low baseline Glasgow Coma Scores (<8) treated with hypertonic solutions compared with LR (Figure 3) (Vassar *et al*, *J Trauma*, 1993, 34, 622).

To date, basic research into hypertonic saline solutions has shown:

- Improved microvascular flow
- Less organ dysfunction
- Control of ICP and brain oedema
- Immunomodulatory properties of value
- Improved understanding of the mechanisms involved

However, the FDA has not currently approved hypertonic saline and there are no studies of infectious/inflammatory complications. Additional multicentre trials are needed.

## Artificial Colloids

The most recent Cochrane Review on the topic of colloid solutions for fluid resuscitation (Issue 4, 2002, Bunn *et al*) concerns a meta-analysis of randomised and quasi-randomised trials comparing colloid solutions in critically ill and surgical patients thought to need volume replacement that had the main outcomes of death, the amount of blood transfused and incidences of adverse reactions. The analysis concluded that:

- There is no evidence that one colloid is more effective or safer than another.
- Confidence intervals are wide and do not exclude clinically significant differences between colloids.
- Larger trials of fluid therapy are needed if clinically significant differences in mortality are to be detected or excluded.

Therefore, Philippe Van der Linden (Belgium) proposed that the choice of synthetic colloid in the intensive care unit depends on a balance between:

- Volaemic expansion
- Side effects in relation to
  - pulmonary oedema
  - anaphylaxis
  - haemostasis
  - tissue storage in kidney, liver
  - infectious risk
- Cost

A comparison of gelatin versus starch on this basis is illustrated in Table 2.

### Synthetic colloids and renal function

Acute hyperoncotic renal failure syndrome (Box 2) has been reported in the past to be associated with dextrans, starches, concentrated albumin solutions and possibly gelatins. Osmotic nephrosis-like damage has also possibly been associated with starches. It could be concluded that hyperoncotic colloidal solutions should be avoided, especially in patients at risk for renal complications.

- *Generation of high plasma colloid osmotic pressure which counteracts the hydraulic pressure gradient in the glomerulus*
- *Predisposing factors include*
  - Age
  - Pre-existing or latent renal disease
  - Dehydration
  - High dose colloids for non surgical reasons (stroke, claudication, sudden hearing loss)

Box 2 Hyperoncotic acute renal failure

Boldt *et al* (*Anesth Analg*, 2003, **96**, 376) in an analysis of 14 studies addressing intravascular volume therapy and renal function, found

only a few with evidence of adverse effects of HES on renal function, and those involved renal transplantation from brain-dead kidney donors (Legendre *et al*, *Lancet*, 1993, **342**, 248; Cittanova *et al*, *Lancet*, 1996, **348**, 1620) or patients with mild, pre-existing renal dysfunction (Schortgen *et al*, *Lancet*, 2001, **357**, 911). Otherwise there were no significant differences in outcomes.

The molecular weight of the starch and the substitution ratio influence intravascular persistence and tissue storage, which, in turn, influence both volaemic expansion and side effects.

The primary goals of volume therapy are to correct absolute or relative volume deficits to optimise tissue oxygen delivery. Results with individual solutions in situations such as:

- Peri-operative volume expansion during cardiac surgery, to maximise stroke volume as guided by oesophageal Doppler;
  - Optimisation of intra-operative fluid therapy during orthopaedic surgery;
  - Intra-operative fluid maintenance during major abdominal surgery;
- lead to the conclusion that it is the optimal amount rather than the type of fluid infused that is important. Further studies are needed:
- To improve monitoring measures that recognise fluid deficits and can guide volume therapy.
  - To better define patients who may benefit from a particular kind of fluid.

	<b>Gelatin</b>	<b>Starches</b> (medium molecular weight: 200,000 Da)
<b>Volaemic expansion</b>		
Immediate Duration	70–90% Short	100–145% Intermediate – long
<b>Secondary effects</b>		
Pulmonary oedema	Hydrostatic pressure	Hydrostatic pressure
Allergy	++	± to +
Haemostasis	±	+ to ++
<b>Maximum daily dose</b>	No	20–33 (50?) mL/kg/day
<b>Price (€)</b>	4	9–12

Table 2 A comparison of gelatin and starches

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## Hypertonic colloids in the surgical patient

Louis Riddez (Sweden) discussed some of the known beneficial and adverse effects of hypertonic colloids.

### Effects of hypertonic colloids

- Volume expansion is increased due to fluid passage from the intracellular to the extracellular compartment.
- The volume expansion is prolonged by the colloid and is equal to three to four times the infused volume.
- A possible inotropic and chronotropic effect on the heart, combined with peripheral vasodilation, increases blood flow distribution.
- Endogenous fluid is mobilised from the microvascular endothelium and the red blood cells.
- Intestinal mucosal blood flow is improved.
- Diuresis is improved.
- There is some enhancement of cell mediated immune function *in vivo*.

### Adverse effects of hypertonic colloids

- A rapid increase in blood pressure and blood flow will increase the risk of haemorrhage if the source of bleeding is not controlled.
- Hypernatraemia is common. However, levels of sodium >165mMol have been recorded, without adverse effects.
- Anaphylaxis does not seem to be a problem when HSD has been used in trauma. However, when hypertonic colloids have been used in other situations, anaphylactic reactions have been described, although they have been very rare. No allergic reactions have been described with hydroxyethyl starch.

## Timing of administration of hypertonic colloids for the surgical patient

If during any phase of the surgical treatment, a situation will develop that causes or stimulates a hypovolaemic condition or if haemodynamics are at risk due to the surgical technique, for example, aortic clamping or cardiopulmonary bypass, then hypertonic colloids may be appropriate. If this is so, should they be administered before, during or after the operation?

### Pre-operative administration

In an estimate of the effects of hypertonic colloids when administered to normovolaemic patients prior to surgery, HSD in normovolaemic and hypovolaemic healthy volunteers increased interstitial and intravascular volumes (Tølløfsrud *et al*, *Acta Anaesth Scand*, 1998, **42**, 145). Nine fasting subjects received 4mL/kg HSD as a 10-minute infusion in a normovolaemic situation and also 7 days later after withdrawal of 10 % of blood volume. In the normovolaemic state, HSD caused a transitory unpleasant sensation of headache and heat in the thorax up to the throat. A transitory increase in heart rate, mean arterial pressure (MAP) and central venous pressure (CVP) was noted at the end of the transfusion, but these effects were greater in the hypovolaemic state.

### Before elective cardiac or coronary bypass surgery

Tølløfsrud and Kramer reviewed this topic in the 2000 Yearbook of Intensive Care and Emergency Medicine (Vincent J-L, Ed: Springer, page 476). Their analysis of published studies revealed findings of increased cardiac output, a significant reduction of positive fluid balance after less than

400mL of infused hyperosmotic-hyperoncotic solutions and a decrease in SVR.

### Peri-operative administration in specific surgical populations

#### Abdominal surgery

There are no published studies in elective abdominal surgery. In urgent surgery for appendicitis, diverticulitis or cholecystitis, there is probably no need for a change in the traditional approach. The patients may be haemo-concentrated already due to fluid losses from vomiting and diarrhoea. In the situation of a mechanical bowel obstruction, the intracellular fluid compartments are probably already depleted and there is a need for intravenous administration of fluids to compensate for fluid derangements due to fluids in the bowel or vomiting.

#### Neurosurgery

Gemma *et al* (*J Neurosurg Anesthesiol*, 1997, **9**, 329) found that hypertonic colloids reduced intracranial pressure.

#### Cancer surgery

In cancer surgery, the requirement is more to reduce perfusion, to eliminate that aspect of the risk of metastasis.

#### Plastic surgery

Waagstein *et al* (*Eur J Vasc Endovasc Surg*, 1997, **13**, 285), using an animal model, showed that small volume hypertonic saline, especially in combination with 6% dextran, will effectively reverse limb ischaemia-induced haemodynamic and metabolic disturbances. Mazzoni *et al* (*Circ Shock*, 1990, **31**, 407), also in an animal model, concluded that HSD surpasses LR treatment in re-establishing capillary haemodynamics owing to a decreased hydraulic

resistance from osmotically-induced endothelium shrinkage.

These studies indicate that hypertonic colloids may have a place in plastic surgery, flaps or microvascular surgery.

### Orthopaedic surgery

There is little experience in orthopaedic surgery. Further studies are necessary to evaluate the significance of increased blood flow and possible prevention of thrombosis.

## Choice of fluids in head trauma

Peter Andrews (UK) summarised the basic mechanisms of volume control in the brain:

- Endothelial cell tight junctions, which are in the order of 7Å, whereas, systemically, the value is in the region of 65Å
- Brain crystalloid osmotic pressure gradient – 5000mg Hg
- Brain colloid oncotic pressure – 20mmHg

In brain injury, there is a deterioration of the blood/brain barrier (BBB) function with reduced oncotic pressure and leakage of sodium from the capillaries into the interstitium. Brain oedema is usually driven by a mix of hydrostatic pressure and cellular swelling. The skull is a closed box. As the intracranial volume increases, as a result of brain oedema, the intracranial pressure increases. As the brain lesion expands, the available compensatory volume decreases and the brain becomes stiffer or less compliant.

### Fluid therapy options in brain injury

The choice for fluid therapy lies between:

### Postoperative use

Tølløfsrud and Noddeland (*Acta Anaesth Scand*, 1998, **42**, 154) and Mazhar *et al* (*J Thorac Cardiovasc Cardiovasc Surg*, 1998, **115**, 178) found that hypertonic solutions mobilised the retained intra-operative fluid excess.

It can be concluded that hypertonic colloids in surgery:

- Increase cardiac output
- Reduce systemic vascular resistance and reduce blood viscosity, through haemodilution

- Crystalloids – isotonic or hypertonic solutions
- Colloids – albumin, plasma protein fraction, HES, gelatins, dextran, others (for example, diaspirin cross-linked haemoglobin)

The Cochrane reviews are, perhaps, the best single source of reliable evidence on the effects of healthcare interventions, concentrating on patient-orientated outcome measures. Review number 002045, compares hypertonic versus isotonic crystalloids in trauma, burns and surgical patients and shows that hypertonic solutions are associated with lower relative risk (RR) in trauma and surgical patients.

### Hypertonic versus isotonic solutions in traumatic head injury

To investigate the value of hypertonic solutions, Wade *et al*, (*J Trauma*, 1997, **42** (Suppl), S61) conducted a cohort analysis of individual patient data from previous prospective randomised clinical trials (RCT) that compared hypertonic crystalloid plus colloid with isotonic

- Decrease endothelial swelling
  - Enhance capillary blood flow
- These effects are of special interest for patients who will undergo surgery for cardiovascular diseases, when haemodynamics may be deranged. Dose titration might be necessary to avoid fluid overload.

crystalloid. The patients had abbreviated injury scores  $\geq 4$  and hypotension (systolic blood pressure  $\leq 90$ mm Hg). The analysis investigated survival to discharge after treatment with standard of care (SOC) or SOC plus HSD. All variables and endpoints were defined before initiation of data handling and the investigators were blinded to the treatment received. Of the patients in the analysis, 223 patients met the inclusion criteria for traumatic brain injury (TBI).

Survival to discharge was significantly better for HSD-treated patients, compared with those receiving SOC alone ( $P=0.80$ ) (Figure 4). The RR of survival to discharge was 2.12 for HSD compared with SOC alone.

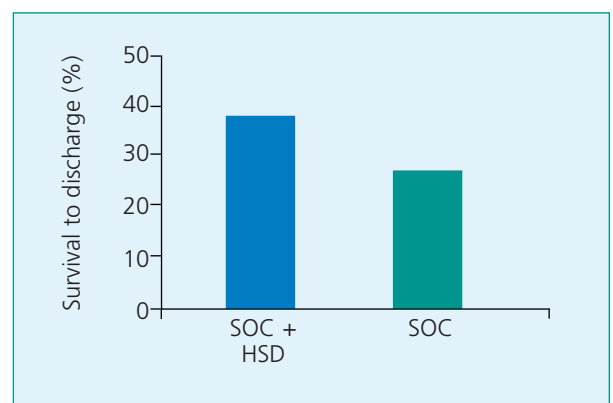


Figure 4 Survival to discharge in TBI patients receiving standard of care (SOC) or SOC plus hypertonic saline/dextran (HSD)

## Prognosis and intracranial pressure

Signorini *et al* (*J Neurol Neurosurg Psychiatry*, 1999, **66**, 26) assessed the prognostic value of summary measures of secondary physiological insults, in addition to baseline clinical variables, in a series of 110 patients with TBI. Of the eight secondary insults measured, only ICP added significantly to prediction of survival in the first 72 hours after injury. The study confirmed early intracranial hypertension as a sign of poor prognosis in patients with TBI, even controlling for baseline clinical variables.

## Osmotherapy as an approach to management of TBI

Osmotherapy depends on creation of an osmotic gradient across the BBB, the barrier being impermeable to the agent, which leads to efflux of water from the brain tissue, and consequently reduced brain volume. Possible agents include mannitol, urea, sorbitol glycerol, hypertonic saline or tris-hydroxymethyl aminomethane (THAM) buffer.

### Mannitol

The potential advantages of mannitol in the management of TBI patients include:

- Increased cerebral blood flow (CBF) due to transient hypervolaemia, haemodilution and alteration in RBC deformability.
- Improved oxygen delivery
- Reflex vasoconstriction
- Decreased cerebral blood volume
- Reduced cerebrospinal fluid production
- Mannitol is a free radical scavenger

### Clinical study

Cruz *et al* (*Neurosurgery*, 2001, **49**, 864) evaluated clinical outcomes and

post-operative physiological findings for 178 comatose patients with acute subdural haematomas who received pre-operative high dose mannitol (HDM,  $n=91$ ) with those of control patients treated with a lower pre-operative mannitol dose ( $n=87$ ). Pre-operative improvement of abnormal pupillary widening was significantly more frequent with HDM and there was better postoperative control of ICP. Pre-operative HDM was associated with significantly better clinical outcomes at 6-month follow up evaluations ( $P<0.01$ ).

However, there have been problems with this type of osmotherapy:

- Diuresis leads to hypovolaemia and hyperosmolarity
- Osmolarity  $>320$  mosmol/kg decreases the effect
- Tachyphylaxis
- Rebound hypertension, especially if the BBB is breached

## Hypertonic saline

Original work on management of ICP was evaluated with hypertonic saline. Hypertonic saline is:

- Proven treatment for raised ICP resistant to other measures (Horn *et al*, *Neurol Res*, 1999, **21**, 758).
- As effective as mannitol and may have a longer duration of action (Qureshi *et al*, *Neurosurgery*, 1999, **44**, 1055).
- Effective for volume replacement without diuresis.

## Hypertonic saline/ dextran (HSD)

There is renewed interest in small volume hypovolaemic resuscitation. Animal studies showed HSD to be as effective as mannitol in reducing raised ICP following trauma (Berger *et al*, *Neurosurgery*, 1995, **37**, 98). The Wade *et al* analysis (see above) in patients with TBI and hypotension,

showed HSD-treated patients were more likely to survive to discharge than those who received SOC.

HSD (7.5% saline and 6% dextran 70 solution) is given over 2–5 minutes, and can provide effective intravascular volume expansion of up to 1 litre through recruitment of intracellular water to the vascular compartment. Dr Andrews' group is now studying the solution. It has theoretical advantages in head injury (Box 3). To date, HSD has been given to 10 patients and has been found to be at least as effective as mannitol.

- Plasma volume expansion leads to raised cerebral perfusion pressure (CPP)
- Reduced endothelial oedema leads to raised CPP
- Reduced cerebral oedema (and hence reduced ICP) leads to increased CPP
- Reduced extracellular glutamate leads to reduced rates of cell death
- Leucocyte margination leads to reduced risks of infection and perhaps decreased inflammation

Box 3 Theoretical advantages of HSD solution in head injury.

In conclusion:

- The processes after head injury are complex and its unlikely that one approach will be appropriate for all patients. It will be necessary to identify subgroups of patients for whom particular treatments are more appropriate.
- Better understanding of the pathophysiology of head injury is required.
- Adequately powered prospective RCT are urgently required.

## Fluid management in ARDS

Greg Martin (USA) discussed manipulation of oncotic and hydrostatic pressure in acute respiratory distress syndrome (ARDS) in terms of:

- Hydrostatic pressure in acute lung injury (ALI)
- Colloid osmotic pressure (COP) in ALI
- Colloid and diuretic therapy in ALI

## The role of hydrostatic forces in ALI

In large scale trials in patients with ALI, more than 80% of enrolled patients have intermittent pulmonary capillary wedge pressures (PCWP) greater than >18mmHg. Indeed, mortality in ALI patients can be stratified by PCWP (Figure 5) (Ferguson *et al*, *Int Care Med*, 2002, **28**, 1073; Neff *et al*, *Am J Resp Crit Care Med*, 1999, **159**, A716).

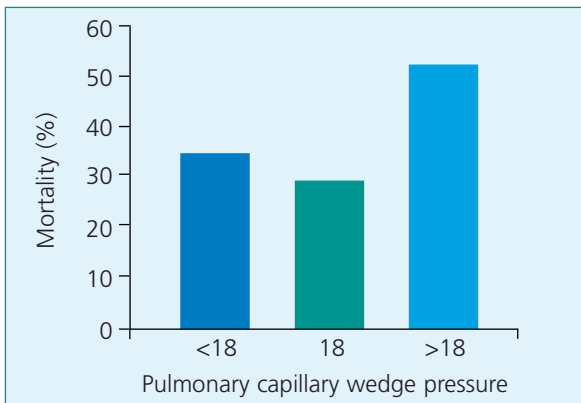


Figure 5 Mortality in ALI patients stratified according to pulmonary capillary wedge pressure

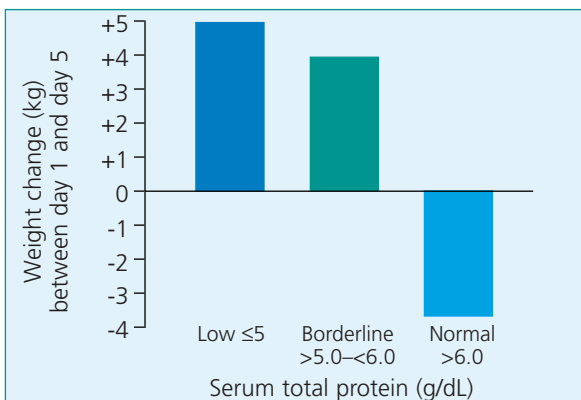


Figure 6 Weight change between days 1 and 5 of study in relation to serum protein levels in 178 patients who developed ARDS

## Fluid restriction in ALI

Mitchell *et al* (*Am Rev Respir Dis*, 1992, **145**, 990) concluded that fluid restriction in ALI:

- Reduces extravascular lung water
- Reduces the duration of mechanical ventilation
- Reduces the ICU length of stay
- May influence mortality

## Oncotic effects on oedema generation

In normal circumstances, lung oedema begins to form at left atrial pressure (LAP) >24mmHg. If the circulation is hypo-oncotic, oedema begins to form at LAP >11mg Hg (Guyton and Lindsay, *Circ Res*, 1959, **7**, 669).

## The role of oncotic pressure in ARDS

The ibuprofen in human sepsis trial (Bernard *et al*, *N Engl J Med*, 1997, **336**, 912) was a multicentre study conducted between 1989 and 1995.

Of the 445 patients studied, 178 developed ARDS; 92% of these 178 patients were hypoproteinaemic.

Regression analysis of clinical variables (Mangliardi *et al*, *Crit Care Med*, 2000, **28**, 3137) showed that reductions oncotic pressure, assessed by changes in serum total protein, predict:

- Positive fluid balance
- Weight gain
- Development of ARDS
- Prolonged mechanical ventilation
- Mortality

Weight gain in relation to serum protein levels in the 178 patients who developed ARDS is illustrated in Figure 6.

Therefore:

- Reductions in hydrostatic forces are beneficial in ALI / ARDS patients
- Hypoproteinaemia is associated with fluid retention, weight gain, ARDS, prolonged mechanical ventilation and increased mortality.

## Albumin and diuretics in ALI

These conclusions provided the rationale for a clinical study (Martin *et al*, *Crit Care Med*, 2002, **30**, 2175) with the hypotheses:

- Combined colloid and diuretic therapy will favour lung fluid resorption, thus improving pulmonary physiology.
- Colloid and diuretic therapy in patients with ALI will improve minute ventilation, dead space fraction, oxygenation and duration of mechanical ventilation.

## The study

The study protocol is summarised in Box 4 and the eligibility criteria in Box 5.

Of the 37 patients enrolled to the study between February 1997 and July 1998, 19 were included in the active treatment group and 18 in placebo control group. The mean age of the study population was 42 years and there were no differences between groups with respect to age, race, gender, aetiology of ALI or severity of illness. Trauma was the major cause of ALI.

## Results and findings

Serum total protein increased in the active treatment group more rapidly than in the controls (Figure 7). Values stabilised after completion of the 5-day treatment in the active group, but continued to increase in the placebo group.

- *Randomised, double-blind, placebo-controlled trial of human serum albumin plus furosemide or placebo plus placebo*
- *Treatment – given for 5 days. Either:*
  - *Albumin 25g intravenously every 8 hours (25% albumin = 100mL)*  
*Placebo was substituted if serum total protein >6.0g/dL, plus:*  
*Furosemide – given by continuous intravenous infusion. Or:*
  - *Placebo plus placebo by the same schedules*  
*Titrated to net negative fluid balance and weight loss*  
*Held for hypotension, Na+ >155 or K+ <2.5meq/L*
- *Goals*
  - *negative fluid balance*
  - *weight loss*
  - *increase in serum total protein*
- *Outcome measures*
  - *haemodynamics*
  - *respiratory mechanics and oxygenation*
  - *serum chemistries*
  - *days of ventilation*
  - *mortality*

Box 4 Albumin and diuretics in ALI – study protocol

- |  |  |
|--|--|
| <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>ALI or ARDS of acute onset</li> <li>bilateral chest X-ray infiltrates</li> <li>PaO<sub>2</sub>/FiO<sub>2</sub> ≤300mg Hg</li> <li>PCWP ≤ 18mm Hg</li> <li>Ventilated ≥ 48 hours</li> <li>Serum protein ≤ 5.0g/dL</li> <li>Nutritional support</li> </ul> | <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Haemodynamic instability</li> <li>Renal failure</li> <li>Chronic hepatic failure</li> <li>Na+ &gt;155 or K+ &lt;2.5meq/L</li> <li>Pregnancy</li> <li>Age &lt;8 or &gt; 80 years</li> <li>Study drug allergy</li> </ul> |
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Box 5 Albumin and diuretics in ALI – eligibility criteria

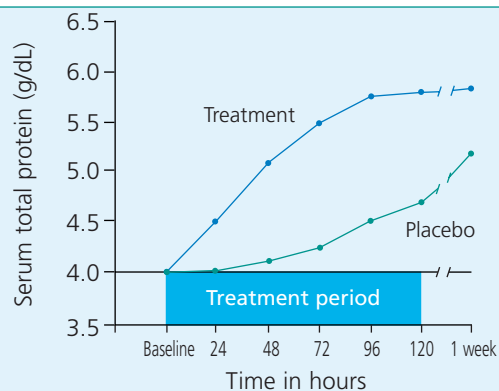


Figure 7 Serum total protein in ALI patients treated with albumin/furosemide or placebo for 5 days

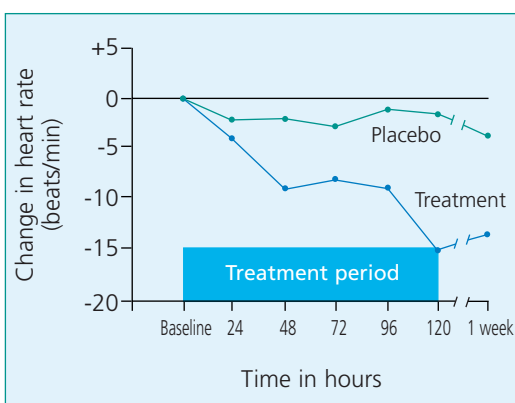


Figure 8 Changes in heart rate in ALI patients treated with albumin/furosemide or placebo for 5 days

Heart rate reduced in the placebo group, but the reduction was variable. In the active treatment group, heart rate was reduced more consistently (Figure 8).

#### Respiratory function

Respiratory function, measured by changes in PaO<sub>2</sub>/FiO<sub>2</sub> ratio, was improved within a day of active treatment, by around 70mm Hg, and varied thereafter, but were never less than 35mm Hg greater than baseline. Respiratory function worsened with placebo to 48 hours, but then was substantially improved, maintaining the improvement to completion of observations at 1 week.

#### Mortality and ventilation requirement

Mortality rates and ventilation requirements are summarised in Table 3. There were no statistically significant differences between the two groups, but trends favoured the active treatment combination.

#### Diuresis and weight loss

Over the 5 days of treatment, actively treated patients diuresed, with a weight loss a mean of 5.3kg more than placebo-treated control patients (P=0.04).

#### Haemodynamics

Mean arterial pressure increased steadily throughout active treatment from 80 to 88 mm Hg, but was variable in the placebo group, with the maximum increase (5.5mm Hg) seen after 4 days of treatment and falling thereafter.

Dr Martin concluded that:

- Hydrostatic pressure is a dominant force in pulmonary oedema and directly correlates with mortality.
- Oncotic pressure plays a role in the generation and/or persistence of pulmonary oedema.
- Albumin/furosemide-treated ALI patients:
  - Diurese and lose weight.
  - Improve oxygenation.
  - Increase haemodynamic stability.
  - May require fewer days of mechanical ventilation.

	Albumin/furosemide	Placebo/placebo
Mortality rate	16%	17%
Duration of mechanical ventilation	20.1 days	25.9 days
Ventilator-free survival	15.5 days	10 days

Table 3 Mortality rates and ventilation requirements in ALI patients treated with albumin/furosemide or placebo for 5 days

# Management of acute liver failure

A session on gastrointestinal crises, moderated by Paul Hebert (Canada) and Pierre Singer (Israel) included three presentations on the management of acute liver failure, focusing on treatment advances in this situation that gives so much cause for concern.

## Acute liver failure

As part the first of these presentations, Julia Wendon (UK) defined acute liver failure (ALF) and outlined some of the complications contributing to the severity of the condition.

Acute liver failure involves encephalopathy in a patient with no previous liver disease and can be due to a variety of causes (Box 6).

- Complications of diagnosis and assessment
- Speed of deterioration and management planning

Renal failure is common, occurring in 45% of all cases, and infection rates are high. Rolando *et al* (*Hepatology*, 2000, **32**, 734) reported that the magnitude of systemic inflammatory response syndrome in ALF patients with bacterial infection correlated with mortality.

Adrenal insufficiency is clinically important in acute hepatic dysfunction. Harry *et al* (*Hepatology*, 2002, **36**, 395) used the short Synacthen test (SST), a dynamic test of adrenal function, as part of their management and investigations in

Development of encephalopathy in patients with ALF is correlated with arterial ammonia concentration. Clemmesen *et al* (*Hepatology*, 1999, **29**, 648) and Kramer *et al* (*Hepatology*, 2000, **31**, 30) reported that the partial pressure of ammonia correlates more closely than total ammonia with the degree of clinical and electrophysiological abnormalities.

Concluding her presentation, Dr Wendon said that there is much to be done in the future for management of the patient in ALF and that research is driving the patterns of care.

Transplantation techniques are evolving, using organs and cells, and the appropriate use of the limited supply of organs must be considered. Haemofiltration removes ammonia as such and use of relative hypothermia has an anti-enzymatic effect, reducing the production of ammonia. Innovative treatment options include various liver support systems and controlled trials are in progress or needed in ALF and in chronic liver disease, but also in liver dysfunction and in sepsis.

## Novel therapies for liver failure

Samir Awad (USA) outlined the state of the art approaches to management of ALF, which address the problems of:

- Management of encephalopathy
- Management of cerebral oedema
- Ventilator management
- Nutrition
- Fluid balance
- Sepsis

However, replacing the detoxification function of the liver remains a challenge.

<i>Viral hepatitis</i>	<i>Hepatitis viruses A, B D or E, cytomegalovirus, or seronegative hepatitis</i>
<i>Drug ingestion</i>	<i>Paracetamol, anti-tuberculous drugs, lipid therapies; Recreational drugs</i>
<i>Toxins</i>	<i>Idiosyncratic reactions to compounds including anticonvulsants, non-steroidal anti-inflammatory drugs and cyclosporine</i>
<i>Vascular / ischaemic events</i>	<i>Carbon tetrachloride, Amanita phalloides</i>
<i>Other</i>	<i>Veno-occlusive disease, Budd-Chiari syndrome (idiopathic hepatic vein thrombosis)</i>
	<i>Heatstroke</i>
	<i>Acute fatty liver of pregnancy, liver rupture, Wilson disease, lymphoma, carcinoma, trauma</i>

Box 6 Causes of acute liver failure

In addition to encephalopathy, ALF is associated with a range of problems affecting patient management:

- Cardiovascular failure
- Renal failure
- Coagulopathy
- Insulin resistance
- Disturbances of glucose, sodium, potassium, magnesium and phosphate
- Energy requirements
- Metabolic acidosis

45 patients with acute hepatic dysfunction. The results were compared with haemodynamic profiles, severity of illness and outcomes. Abnormal SST were common (62% of patients); those who required noradrenaline for blood pressure support had a significantly lower increment following Synacthen compared with patients who did not. The increment was lower in those who fulfilled liver transplant criteria than in those who did not.

For selected patients the only proven curative therapy is liver transplantation, but a severe shortage of donor organs has mandated the development of liver assist devices, which can be divided to cell based and non-cell based approaches.

### Cell based techniques Hepatocyte transplantation

The advantages of hepatocytes, versus transplantation of the whole organ, are:

- The absence of operative mortality
- One donor can provide cells for multiple recipients
- Hepatocytes can be used as a temporary measure
- Autologous cells may be used in certain circumstances

There have been reported cases of spontaneous recovery of liver function, or a successful bridge to transplantation using hepatocyte transplantation, but there have been no prospective randomised studies to allow an adequate evaluation of efficacy in either ALF or chronic liver failure. The adverse effects of concern are:

- Worsening portal hypertension
- Pulmonary artery hypertension
- Destruction of the infused hepatocytes
- A need for immunosuppressive therapies

Published evidence so far has consisted of case reports of patients with acute ALF who have been treated chiefly for enzyme deficiency states.

### Extracorporeal cell-based approaches

Cell-based cartridge devices, supporting hepatocyte growth, have been developed, using both porcine and human liver cells. The methods include perfusing blood through a hollow fibre cartridge with

hepatocytes seeded in the extracapillary spaces. Some bioartificial liver devices are in Phase II/III trials; others, such as the extracorporeal liver assist device (ELAD) and modular extracorporeal liver support (MELS), which uses primary human liver cells from explanted organs, are at the Phase I stage.

### Non-cell based approaches

Non-cell based approaches including haemodialysis, plasma exchange, charcoal haemofiltration and haemodiadsorption have all been investigated, but none have proven satisfactory.

### Molecular Adsorbents Recirculating System (MARS)

Albumin dialysis using the Molecular Adsorbents Recirculating System (MARS), system has received more attention and has been studied in randomised trials. As Helena Isoniemi explained later in the session, the MARS involves selective haemofiltration with albumin dialysis Figure 9. The extracorporeal circuit includes a haemofilter with a low molecular weight cutoff (MWt=60KDa, less than the MWt of albumin =65KDa)

and countercurrent dialysis using an albumin solution. The flow of the dialysate through adsorbent columns results in regeneration of albumin molecules with free binding sites.

Data from the International MARS registry summarised in Table 4 (Steiner and Mitzner, *Liver*, 2002, 22 [Suppl 2] 20), show that the main indication for treatment has been acute-on-chronic liver failure.

### The place of the MARS in the intensive care/intensive treatment unit

Many of the patients who develop hepatic failure in the ICU / ITU are not transplant candidates. Accumulating experience (see below) has demonstrated the safety and efficacy of MARS, which may allow the liver to recover successfully through regeneration by efficiently removing hepatic toxins. It is easy to use, and similar in this respect to continuous venovenous haemofiltration.

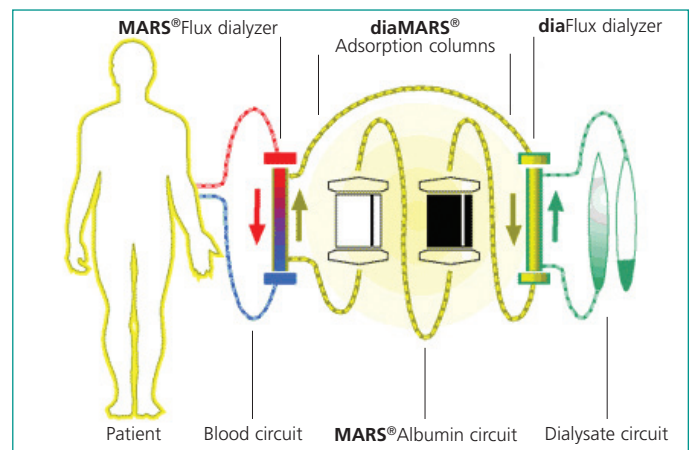


Figure 9 The Molecular Adsorbents Recirculating System (MARS)

Indication	Percentage of patients*
Acute-on-chronic liver failure	56
Acute liver failure	22
Liver failure following liver transplantation	15
Liver failure following liver surgery	4
Other reasons	3

\* percentage of patients on the MARS registry

Table 4 Indications for treatment using the MARS – patients on the International MARS Registry

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## The future for liver assist devices

There is a need for more understanding of hepatic support devices, although the preliminary results are encouraging and justify further investigation. Randomised clinical trials are in progress.

Acute hepatic dysfunction is potentially reversible, because the liver

can regenerate after injury; further studies must examine the effect of the support devices at the hepatocyte level and the extent of regeneration.

## Potential future therapy

An exciting prospect for the more distant future has been raised by the report from Lagasse *et al* (*Nature Medicine*, 2000, **6**, 1212–3). This

group have published their findings using a murine model of tyrosinaemia Type 1 that suggest that bone marrow stem cells can rescue biochemical function of the liver.

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## Experience with the Molecular Adsorbents Recirculating System (MARS) for liver support

Management of liver failure using extracorporeal liver support therapy has the chief aim of stabilising vital organ functions while waiting either for the liver to recover, or for a donor liver, that is using the method as a bridge to orthotopic liver transplantation.

Liver failure involves endogenous intoxication, with accumulation of metabolic products and ion imbalances leading to further liver damage with necrosis and apoptosis of hepatocytes. The MARS system removes water-soluble toxins by dialysis and protein-bound substances using an albumin dialysis method. Studies to date have investigated the impact of the MARS system on:

- Survival
- Haemodynamics
- Renal function
- Cholestasis
- Hepatic encephalopathy
- Intracranial pressure
- Liver function itself

Helena Isoniemi (Finland) presented a brief review of earlier work with the MARS system (see also Progress in Albumin Research – Albumin in Liver Disease – 2001). Although early studies were with small groups of

patients, the MARS Registry has now sought to compile findings of all patients treated by the device (Steiner and Mitzner, 2002).

## Impact on survival

Mitzner *et al* (*Liver Transplant*, 2000, **6**, 277) reported the impact of the MARS on the survival of patients with Type 1 hepatorenal syndrome (HRS). Mortality rates were 100% at day 7 in the control group managed by standard methods compared with 62.5% at day 7 and 75% at day 30 in patients managed by standard methods plus the MARS. Heemann *et al* (*Hepatology*, 2002, **36**, 949) also reported improved 30-day survival in patients with acute on chronic liver disease (cirrhosis). Eleven of 12 patients treated by MARS survived to 30 days, compared with six of 11 control patients treated by conventional methods only. There have also been reports of improved survival in patients with decompensated liver disease.

## Haemodynamics

Stange *et al* (*Artif Organs*, 2002, **26**, 103) summarising the findings with the MARS from 19 centres report that in treating liver failure with cholestasis, MARS was associated with haemodynamic stabilization and Schmidt *et al* (*Liver Transplant*, 2001, **7**, 1034) documented an increase in MAP and SVR. Although Awad *et al*

(*Surgery*, 2001, **130**, 354) found no significant changes in MAP, heart rate or systemic venous oxygen saturation in their Phase I study, they did conclude that albumin dialysis as a liver support device is effective in clearing hepatic toxins and associated with a decrease in hepatic encephalopathy and intracranial pressure.

## Removal of protein bound toxins

Heemann *et al* (2002) reported that bilirubin levels decreased by an average of 29% after one week of treatment that included the MARS, compared with no change in patients treated by standard therapy alone. Schmidt *et al* (*Liver Transplant*, 2001, **7**, 1034) also reported statistically significant ( $P<0.05$ ) reductions in bilirubin. The Registry data (Stange *et al*) have been encouraging.

## Impact on hepatic encephalopathy

Extending the findings of Awad *et al*, who found a significant reduction in hepatic encephalopathy, the MARS registry data have shown that the system can reduce the grade of HE in both adults and children, and after transplantation (Figure 10). Fourteen centres have reported that MARS treatment improved the mental status of patients with liver failure and hepatic encephalopathy (Stange *et al*).

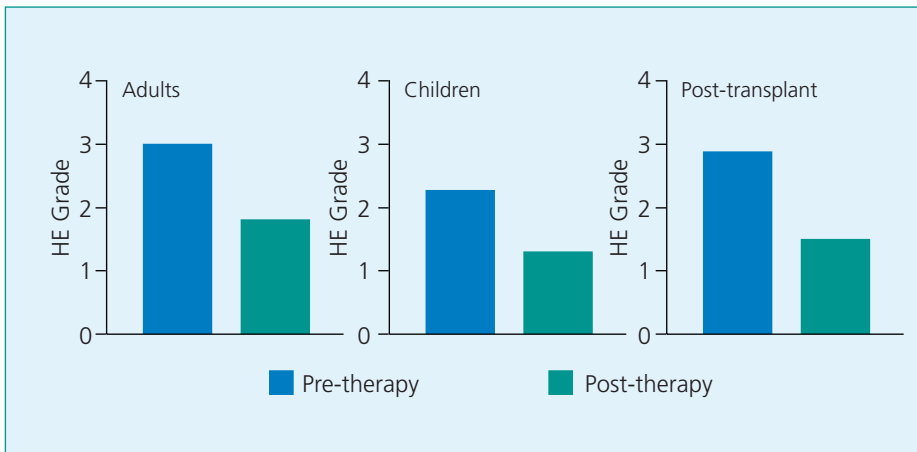


Figure 10 Grades of hepatic encephalopathy (HE) before and after MARS treatment in adults and children, and following liver transplantation

## MARS therapy in Helsinki

Dr Isoniemi reported the experience of her own group in Helsinki. The first patient was treated in May 2001 and, to December 2002, a total of 71 patients aged between 5 and 80 years have received treatment (Box 7).

Acute on chronic	21
Graft failure	7
Acute liver failure	39
Others	4

Box 7 Indications for MARS treatment among patients treated in Helsinki

Analysis is possible for the 30 patients with ALF who were treated between May 2001 and June 2002 (Table 5).

Cause of ALF	n
Unknown aetiology	14
Viral hepatitis	1
Pregnancy-related	1
Toxic liver failure	14
- paracetamol	6
- nimesulid	2
- mushroom poisoning (Amanita)	2
- anabolic steroid	1
- ethylene glycol + drugs	1
- disulfiram	1
- chemotherapy	1

Table 5 Causes of acute liver failure among 30 patients treated in Helsinki

At the start of MARS therapy, 12 patients (40%) were suffering from renal insufficiency and 13 (43%) were on a ventilator. Grade 2

encephalopathy was present in seven patients, Grade 3 in seven and Grade 4 encephalopathy in nine patients.

The outcomes for these 30 patients are summarised in Table 6 and the outcomes according to the original aetiology of ALF in Table 7.

Outcome	n
Native liver function recovered	13
Died	6
Bridged to liver transplantation	11*

\*, one patient subsequently died.

Table 6 Outcomes in 30 patients with ALF treated using the MARS

Aetiology of ALF	Alive	Died	Total
Pregnancy related	1		1
Viral hepatitis	1		1
Toxic	11	3	14
Unknown	10	4	14
<b>Total</b>	<b>23</b>	<b>7</b>	<b>30</b>

Table 7 Outcomes in patients treated with the MARS according to the original aetiology of acute liver failure

Parameter	Before first MARS	Worst value during treatment	After last MARS
Factor V	17%	10%	50%
Thromboplastin time (Factors II+VII+X)	13%	11%	22%
International normalised ratio	3.7	5.4	2.5

Table 8 Coagulation factors monitored in 30 ALF patients (median values)

## Coagulation parameters

Coagulation factors were monitored throughout the course of treatment in the 30 ALF patients. The findings are summarised in Table 8.

## Kidney function

Creatinine levels were a median of 203µmol before therapy (range 36–1318) and 91µmol (range 20–585) after MARS therapy (reference range 40–90µmol).

## Encephalopathy

Fifty-three percent of patients had Grade 3–4 hepatic encephalopathy before treatment. At the end of last MARS therapy 22% (five patients of 23) had Grade 3–4 encephalopathy. Seven other patients were still sedated at the end of last therapy and the real grade for those patients is not known (five were transplanted, one died due to myocardial infarction and one recovered without undergoing transplantation). Mean ammonia levels were reduced from 86µmol/L before treatment to 62µmol/L afterwards.

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## Other studies of albumin dialysis in ALF /Acute alcoholic hepatitis

Jalan *et al* (*J Hepatol*, 2003, **38**, 24) treated eight patients with severe acute alcoholic hepatitis. All were encephalopathic, five with HRS Type 1 and two with HRS Type II. Five patients were discharged from hospital and four of them remained alive at 3 months of follow up, compared with an estimated survival of about 20%. There were statistically significant improvements in serum

bilirubin ( $P=0.008$ ), creatinine ( $P=0.02$ ), prothrombin time ( $P=0.04$ ) and grade of hepatic encephalopathy ( $P=0.05$ ), and sustained improvements in mean arterial pressure, systemic vascular resistance and cardiac output were observed.

## Possible benefits of MARS in liver failure

- If the native liver has the ability to regenerate, then transplant can be avoided.

- If the liver is damaged beyond a critical point, there is unlikely to be regeneration, but the treatment allows bridging to liver transplantation by supporting vital organ function.

Dr Isoniemi concluded that the MARS is a promising device, but can become standard treatment only after verification in randomised controlled clinical studies.

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