

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

Albumin in liver disease

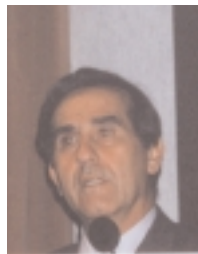
Summary of sessions of the 21st International Symposium on Intensive Care and Emergency Medicine (ISICEM) held at the Brussels Congress Centre, March 20-23, 2001

Introduction

The International Symposium on Intensive Care and Emergency Medicine continues to be the major congress in this therapeutic area, attracting larger numbers each year and providing a forum for discussion, education and presentation of research results. The Chairman, Professor Jean-Louis Vincent, welcomed nearly 4000 delegates to 21st International Symposium at the Brussels Congress Centre.

Albumin - influencing the hepatorenal syndrome

In the Symposium session on Liver Failure, moderated by Nigel Webster (UK) and Marcel van Deuren (the Netherlands), Professor Vincente Arroyo (Spain) discussed the development of the hepatorenal syndrome (HRS) in patients with advanced liver disease.



*Professor
Vincente Arroyo*

The syndrome involves functional renal failure due to intense constriction of the renal arteries that induces a marked decrease in renal perfusion and in the glomerular filtration rate. There are two types of HRS. The commonest is designated Type II and involves a moderate renal failure that remains steady over months; the increases in creatinine levels can stay steady over quite long periods. Patients do not respond to diuretics and, therefore, develop refractory ascites that require frequent therapeutic paracentesis.

Type I HRS is a rapidly progressive renal failure, with sharp increases in serum creatinine that reach high levels in days or weeks. This is the most serious condition in hepatology, almost all patients dying within a few days or weeks of onset. It is often precipitated by some event, commonly severe

bacterial infection, perhaps spontaneous bacterial peritonitis (SBP), or gastro-intestinal haemorrhage or a major surgical procedure. Once the syndrome develops, despite management of the precipitating event, renal impairment follows a progressive course.

The mechanism of HRS in cirrhosis is related to a marked impairment in circulatory function. Arterial pressure is decreased in patients with cirrhosis, but is more markedly decreased in patients with HRS despite a significant increase in cardiac index, indicating an intense arterial vasodilation, and also a marked overactivity of the renin angiotensin system and of the sympathetic nervous system. This activation of the renin angiotensin and sympathetic nervous systems are homeostatic mechanisms to maintain arterial pressure. Hepatorenal syndrome has traditionally been considered to be secondary to the renal vasoconstriction induced by these endogenous vasoactive systems. It is now known that the aetiology of HRS is more complex and, in addition to the endogenous

vasoactive systems, there are intrarenal mechanisms that are important in the pathogenesis of the syndrome. For example, in cirrhosis, there is an increase in synthesis of renal prostaglandins, in the activity of nitric oxide and probably also an increase in intrarenal production of natriuretic peptides. These vasodilators maintain renal perfusion by antagonising the effects of angiotensin II and noradrenaline, endothelin and adenosine. Hepatorenal syndrome can be reproduced in experimental animals by inhibiting prostaglandin synthesis and nitric oxide synthesis, suggesting that in HRS there could be not only activation of the systemic vasoconstrictor system, but also an impaired renal production of vasodilators.

In addition, the kidney also produces vasoconstrictor substances such as adenosine and endothelin, with evidence that these substances are activated whenever there is renal ischaemia. It may be possible that Type II HRS could be secondary to the activation of the systemic vasoconstrictor systems and sympathetic nervous system. When the precipitating event develops, such as bacterial infection, the systemic circulation produces more renal ischaemia and the renal ischaemia impairs the synthesis of vasodilators and increases the intrarenal production of vasoconstrictors, precipitating the rapidly progressive form of Type 1 HRS.

This is a suggested mechanism of HRS. In cirrhosis with ascites and HRS, portal hypertension plays an important role and this is mediated by a marked splanchnic arterial vasodilation. The mechanism is not known, but may be related to an increase in production and release of local vasodilators, particularly NO, leading to arterial hypotension, activation of the systemic vasoconstrictor system, renal vasoconstriction, and Type II hepatorenal syndrome. When there is a complication, such as SBP, there is a further deterioration in the systemic circulation, more activity of the systemic vasoactive systems, renal vasoconstriction, renal ischaemia, impairment of renal vasodilators, activation of intrarenal vasoconstrictors and then Type I HRS.

This is a vicious circle that maintains Type I HRS and, despite removing the precipitating event, the syndrome follows a rapidly progressive course.

Therapy for Type I HRS

Approaches to therapy of HRS have been made on the premise that, if the initial event of HRS is splanchnic arterial vasodilation, a splanchnic vasoconstrictor could be of benefit. It is now known that HRS can be reversed by treating cirrhotic patients with plasma volume expansion and splanchnic vasoconstrictors. Plasma volume expansion with albumin and splanchnic vasoconstriction with ornipressin, or preferably terlipressin, increased arterial pressure, produced a marked

suppression of plasma renin activity (PRA) relative to baseline levels and a significant suppression of plasma noradrenaline concentration, indicating an improvement in circulatory function. The therapy normalised serum creatinine and, significantly, when ornipressin was withdrawn, HRS did not recur. There is also the suggestion that this therapy may improve survival in patients with HRS.

Prevention of Type I HRS

Development of Type I HRS is particularly associated with SBP. In cirrhotic patients with SBP, renal impairment occurs in around 33% and, in most cases, involves Type 1 HRS and its associated high mortality rate. For example, in patients with SBP who do not develop HRS, the hospital mortality rate is around 7%; in patients who do develop HRS, the hospital mortality rate is around 40%.

Professor Arroyo's group have investigated whether plasma volume expansion with albumin, at the time of diagnosis of the infection, could prevent deterioration of renal function in patients with SBP. In a randomised trial, 126 patients with SBP received either cefotaxime at standard dose of 2g every 8 hours, or cefotaxime by the same dose and schedule, plus an intense plasma volume expansion with albumin, 1.5g/kg body weight at diagnosis and 1g/kg on day 3.

When a patient develops SBP, the PRA increases significantly,

indicating an impairment of circulatory function, leading to development of Type 1 HRS. In patients who received albumin as well as cefotaxime at the time of diagnosis, not only was there no further increase in PRA, but also a significant decrease was observed, indicating an improvement in circulatory function (Figure 1).

Figure 1 Plasma renin activity - indicative of circulatory and renal function - in patients with spontaneous bacterial peritonitis treated with cefotaxime alone () or cefotaxime plus volume expansion with albumin ()

The results obtained during hospitalisation in this trial are summarised in Table 1. The rate of resolution of infection was high; SBP is not an intrinsically serious infection, but is serious because it occurs in patients with cirrhosis. It is readily cleared by third generation cephalosporins and over 90% of patients were cured of their infection. However, the incidence of HRS and the hospital mortality were significantly reduced in the group of patients treated with cefotaxime plus albumin, compared with those treated with cefotaxime alone.

	Cefotaxime alone (n=63)	Cefotaxime / Albumin (n=63)	P value
Resolution of infection	59 (94%)	62 (98%)	N.S
Circulatory dysfunction	17 (27%)	3 (5%)	<0.01
SBP-related HRS	21 (32%)	6 (10%)	<0.01
Hospital mortality	18 (27%)	6 (10%)	<0.01

HRS; hepatorenal syndrome (progressive or steady); NS, not significant

Table 1 Hospital outcomes in cirrhotic patients with SBP treated with cefotaxime alone or with cefotaxime plus albumin

Therefore, it can be concluded that:

- * Although HRS is an extremely serious condition in cirrhotic patients, there is now an effective therapy, which consists of administration of splanchnic vasoconstrictors, particularly terlipressin, associated with albumin. In some patients survival may be improved long enough to achieve liver transplantation.
- * HRS can be prevented in patients with infections, the most frequent precipitating event for Type I HRS, by expanding the plasma volume at the time of diagnosis.

Albumin solutions in liver cirrhosis

Professor Arroyo also spoke about the use of albumin in the treatment of patients with massive / tense ascites. Currently these patients are treated with therapeutic paracentesis (TP) associated with plasma volume expansion, because previous approaches, with diuretics, were

very slow in achieving an effect and require a long hospital stay. Therapeutic paracentesis is very rapid. Ten percent of cirrhotic patients do not respond to diuretics and develop refractory ascites. There are very few ascites that are refractory to paracentesis, but also a considerable body of data showing that, in patients with tense ascites, TP is associated with a lower incidence of complications than diuretics (Table 2).

	Diuretic (5 studies, 332 patients)	TP and plasma volume expansion (12 studies, 412 patients)
Renal impairment	84 (25.3%)	11 (2.6%)
Hyponatraemia	94 (28.3%)	33 (8.0%)
Encephalopathy	86 (25.9%)	34 (8.2%)

Table 2 Incidence of complications in 17 studies of treatment of patients with ascites receiving either diuretics or therapeutic paracentesis with plasma volume expansion (using albumin, hemagel, dextran 70 or dextran 40)

Paracentesis is now considered the treatment of choice in patients with cirrhosis and tense ascites, but there is debate about how this should be done and which plasma volume expander should be used, the choice being between albumin, which is considered expensive, or synthetic plasma expanders. Although further trials are needed, the current data suggest that albumin is safer in this patient group than other plasma expanders.

In a randomised study of paracentesis alone (n=53) versus paracentesis plus intravenous albumin (n=52), PRA was measured in about half the patients in each group before and after paracentesis. Plasma renin activity is the most sensitive marker of circulatory function and an increase, in cirrhotic patients, indicates deterioration; PRA increased among the patients treated with paracentesis alone, but remained stable in those receiving albumin. The PRA effect is not due to change in plasma volume as such, but due to peripheral vascular dysfunction.

To discover whether albumin could be substituted by less expensive plasma expanders, a large trial was conducted in patients with massive ascites; 289 patients were randomised to receive albumin 8g/L, dextran 70 8g/L or polygeline and PRA measured sequentially before and 2 days, 6 days, and in some cases 1 and 6 months after paracentesis.

The incidence of paracentesis-induced circulatory dysfunction was 34-40% in association with dextran or polygeline, but 18% with albumin. If cirrhotic patients are confined to bed, but left untreated, there is spontaneous deterioration of circulatory function in around 15%; therefore, albumin almost totally prevents the circulatory dysfunction induced by paracentesis, while the synthetic plasma expanders are less effective. The incidence of circulatory dysfunction is related to the amount of ascitic fluid removed in patients given synthetic plasma expanders, but is independent of this parameter in patients given albumin. Long term follow up has shown that once circulatory dysfunction develops and there is an increase in PRA, the PRA remains elevated, indicating that the circulatory dysfunction is not spontaneously reversible. Comparing the patients who did or did not develop circulatory dysfunction, despite the fact that both groups were similar regarding hepatic and renal function, the mean interval to further hospital admission was significantly shorter in those patients who developed circulatory dysfunction. Although paracentesis-induced circulatory dysfunction is an asymptomatic problem, it appears to adversely affect the course of cirrhosis and steps should be taken to avoid this complication. Professor Arroyo concluded that if a patient has massive ascites and it is required to prevent circulatory dysfunction, albumin should be used.

Supporting the failing liver

In the inaugural session of the symposium, Julia Wendon (United Kingdom) summarised the advances that have been made in techniques of supporting the failing liver. This should be done with the objectives of:

- * improving outcomes,
- * allowing time for regeneration and recovery with the hope of avoiding the need for liver transplantation,
- * supporting the liver until full orthotopic liver transplantation can be arranged,
- * avoidance of other organ dysfunction.

The techniques now available include:

- * transplantation (whole, split or auxiliary)
- * "Artificial organ" systems (cellular + dialysis, with or without adsorbent components)
 - Extracorporeal liver assist devices
 - Berlin extracorporeal liver system
 - Bioartificial liver system
 - Whole liver perfusion systems
- * Dialysis methods
 - MARS®
 - Ash charcoal dialysis
 - High volume haemofiltration
 - Plasmapheresis

If a full orthotopic liver transplantation is undertaken, the whole necrotic liver is replaced not only the hepatocytes, but also the sinusoidal system with its endothelial cells and also the Kupffer cells. However, partial

transplantation can also be used, replacing a left lateral segment, up to about 300g, which is a useful technique for paediatric patients and, in adults, a right lobe transplant, using about 800g of liver, is possible in some circumstances. Techniques of extracorporeal support with human livers not suitable for transplantation and with transgenic porcine livers have been reported, to reduce prothrombin times, serum bilirubin and ammonia levels and control intracranial pressure. These methods are highly labour-intensive.

High volume haemofiltration and plasmapheresis can also be used to bridge patients until the opportunity for liver transplantation arises. Among the bioartificial liver devices reviewed by Dr Wendon, were hollow fibre systems coated with hepatocytes, systems using hepatoblastoma cell lines and the Molecular Adsorbent Recirculating System (MARS®), the last of which has achieved impressive results and was described by Steffen Mitzner (Germany) in the session on Liver Failure.

Extracorporeal albumin dialysis (MARS)

The basis of the Molecular Adsorbent Recirculating System (MARS) is a dialysis-like recycling system with albumin as the molecular adsorbent. Albumin is the common transport medium for different potentially harmful end-



Dr. Steffen Mitzner

products of metabolism like:

- * Bilirubin
- * Bile acids
- * Tryptophan (precursor of serotonin)
- * Fatty acids

The MARS device was developed to attempt to remove effectively the strongly albumin-bound metabolites, those usually removed by the liver, and substances thought to be involved in secondary organ dysfunction, with the assumption that the patient would be helped by their removal. The basic technique is relatively simple to those familiar with dialysis and adsorption (Figure 2).

membrane that does not allow passage of albumin and a closed-loop circuit pre-filled with 600mL human serum albumin 20%. The albumin is recycled in the loop and carries metabolites that cross the membrane to columns of charcoal and an anion exchanger. To complete the system, there is a standard dialysis set-up with aqueous, bicarbonate-buffered, dialysate to remove water-soluble substances, plus excess water. Different substances, that exert toxic effects if not sufficiently cleared by the liver, can be removed efficiently by the system. These are, among others:

- * Bilirubin
- * Bile acids
- * Tryptophan - as the precursor of serotonin, with a potential role in metabolic encephalopathies
- * Short and medium chain fatty acids
- * Aromatic amino acids
- * Water-soluble substances like ammonia, creatinine or lactate

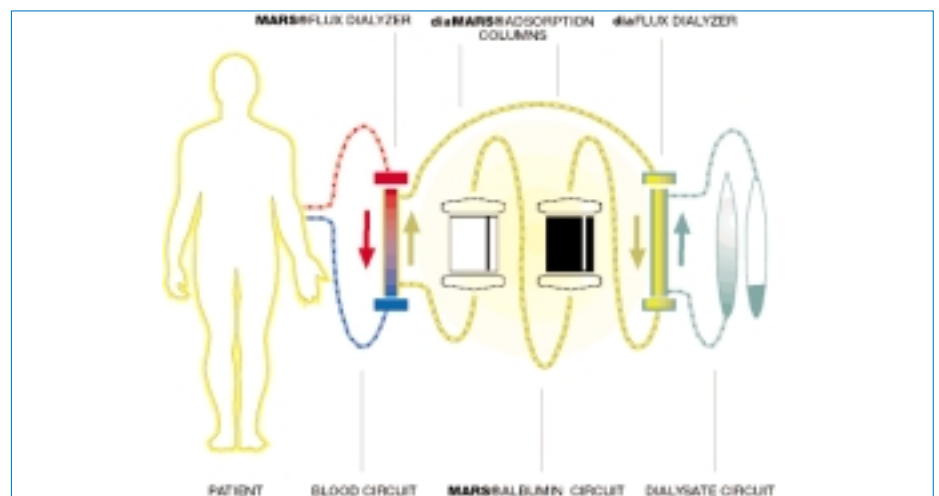


Figure 2 The Molecular Adsorbent Recirculating System (MARS(r))

There is a standard extracorporeal blood circuit (with heparin anticoagulation), a module with a

The removal of albumin-bound as well as water-soluble toxins results in different clinical effects. Different studies have shown the following changes in patients with

severely decompensated liver function:

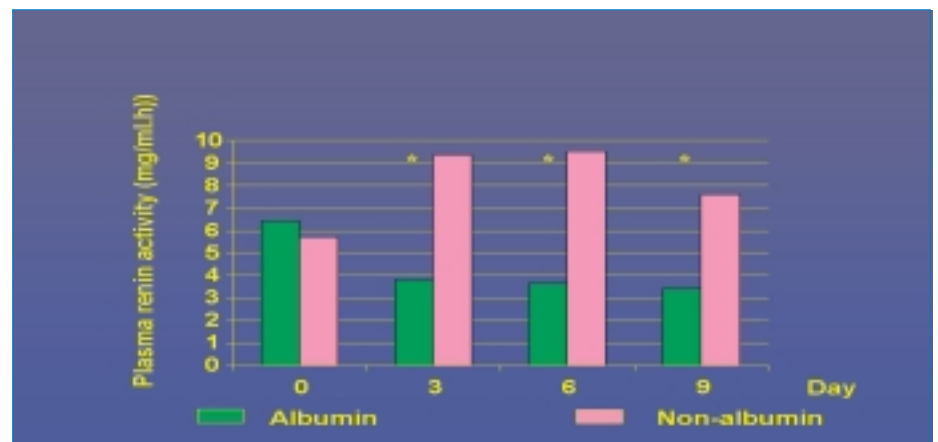
- * increase in cerebral blood flow in decompensation of chronic liver disease
- * reduction in encephalopathy grade
- * increase in systemic vascular resistance during treatment, leading to increases in mean arterial pressure
- * improvement in kidney function, which may be directly linked to increase in blood pressure, but also to a decrease in plasma renin activity; in addition, urine excretion increased
- * improvement in liver function - controlled and uncontrolled pilot trials conducted by groups throughout Europe and the US, report an increase in liver synthesis parameters, with rises in prothrombin activity (Quick), antithrombin III, factor VII and albumin synthesis.

Uncontrolled pilot trials have included alcoholic patients, chronic decompensated patients and patients with chronic hepatic failure. A register has been set up to collect case data in acute hepatic failure and in primary dysfunction and non-function after transplantation.

Controlled clinical studies are now being conducted and reported. One small study in HRS Type 1 patients (Mitzner *et al*, *Liver Trans*, 2000, **6**, 277) involved 13 patients treated at two centres. They were Child's Class C patients, with bilirubin higher than 20mg/dL and

all had indications for extracorporeal support. They were treated with the MARS or with haemodiafiltration (HDF, control patients). As illustrated in Figure 3, MARS treatment resulted in significant falls in plasma concentrations of creatinine and bilirubin, while there were no significant falls in these levels in the control patients.

Figure 3 Plasma concentrations of serum creatinine (S-creatinine) and total bilirubin in patients with Type I HRS before (()) and after (()) treatment with the MARS method or before (()) and after (()) haemodiafiltration (HDF) and standard management



In MARS-treated patients there was a significant increase in serum sodium, not seen in control group patients and, similarly an increase in the prothrombin activity. There was a tendency for the mean arterial pressure to be increased after MARS treatment, although this was not statistically significant, but no such tendency was seen in control group patients. Of eight patients, four started to produce urine, while none of the controls improved urine output. Control patients died within a week

without transplant. Without transplantation, two MARS-treated patients survived to days 45 and 105, respectively.

The results appeared to indicate that MARS was useful for these patients, but that perhaps treatment had been started too late. A second two-centre trial included chronic liver failure patients with acute severe decompensation showing an intrahepatic cholestasis with bilirubin higher than 20mg/dL, who had not responded to standard medical treatment within 3-5 days (Heeman *et al*, submitted). Of 46 patients recruited and initially managed

with best medical care, 22 improved or dropped out, leaving 24 patients who had not improved on detoxification within a pre-phase of 5 days and who were randomised to continuing standard care or to additional MARS, limited to a total of 10 treatments. These patients were Child's Class B and C, with very high bilirubin levels (>30mg/dL), some encephalopathy, some impairment of synthesis function and some initial creatinine increases.

There was a significant difference in 30-day survival between the two treatment groups; one MARS-treated patient died, compared with six control-treated patients. On this basis, the trial was stopped after 24 patients. Total bile acids were markedly reduced by MARS treatment within one week of treatment; MARS was continued for a total of 12 days from randomisation. Bile acids rose once treatments stopped. The Child-Turcotte-Pugh index was reduced and maintained in MARS patients throughout the 30-day observation period. The mean arterial pressure (MAP) tended to reduce over 30 days in controls, but no such tendency was seen in MARS-treated patients, with MAP tending to increase rather than decrease. Creatinine levels tended to increase in control patients, but not in the MARS group, and there were improvements in hepatic encephalopathy during MARS treatment.

As Dr Mitzner summarised:

- * MARS has been used clinically since 1993 to treat more than 400 patients in 56 centres worldwide.
- * The indications for MARS are acute decompensation of chronic liver disease, acute liver failure and primary malfunction of transplant.
- * The MARS effectively removes albumin-bound as well as water-soluble substances.
- * Treatments have been tolerated well, with no serious adverse events reported.
- * Clinical effects include improvements of cerebral,

haemodynamic, kidney and liver function.

- * Randomised control studies suggest there may be significant improvements in survival associated with MARS.

Further controlled randomised trials are currently in progress to give more information about the capabilities of the MARS system.

In a session on Extracorporeal Techniques for Liver Failure and Sepsis moderated by Julia Wendon and Didier Journois (France), Pierre Lamesch (Germany) described his experience gained over the last 2 years of the use of the MARS in liver failure. Potential indications for liver assist devices are acute and acute on chronic liver disease and there is also some experience with MARS in patients with liver failure after liver resection and after transplantation in patients with severe graft dysfunction.

From the United Network for Organ Sharing (UNOS) data, it is obvious that there is a great discrepancy between the numbers of patients on the waiting list for liver transplantation, with a trebling in numbers in the last 10 years, and the number of transplants available which has increased by only 30% over the same time.

Therefore, the practising hepatologist is increasingly required to manage patients on transplant waiting lists. Extracorporeal liver perfusion can involve major logistical problems and liver assist devices with hepatocytes from pigs or

hepatoma cell lines are still under investigation.

The MARS (Figure 2) is based on a filter with pores allowing the transport of 50kD molecules and an isolated albumin circuit. The membrane allows filtration of small and medium sized molecules, allowing the passage of these, albumin-bound molecules. The quantities and dynamics of the filtration process are yet to be fully defined.

Dr Lamesch's own experience has been with 17 patients, of median age 44 years (range 17-74 years, 8 male, 9 female). The indications for MARS treatment were acute on chronic liver failure (n= 9), after transplant with graft dysfunction, intoxication (paracetamol and mushroom poisoning) and other indications. Four patients were treated with the intention of bridging to transplant. A median of 4.5 treatments were administered per patient, lasting a median of 18 hours. Patients were usually treated every day. Results are summarised below.

- * nine patients treated for cirrhosis, four survived; four patients who died were in an advanced state of liver disease.
 - * Of the four patients treated for bridging to transplant, three survived and were discharged from hospital within 3-4 weeks of transplant.
 - * Two patients were treated after liver resection; one recovered initially then failed from other complications, the other recovered well.
-

- * patients who were treated for graft dysfunction went on to receive another transplant, but one died from sepsis.
- * The two patients treated for intoxications and one trauma case all survived.

Three of the cirrhosis patients who survived received between two and seven MARS treatments, with no infectious complications. In the cirrhotic patients who received several treatments, there was a dramatic decrease in bilirubin levels from a median 450mM per mL to below 300mM per mL. In parallel to this, there was an increase in prothrombin time. In the non-cirrhotic patients who received multiple treatments, findings were similar, but with more improvement in the coagulation parameters.

From his own experience, Dr Lamesch concluded that: MARS liver support therapy -

- * Has no negative side effects
- * Can be rapidly instigated
- * Leads to a decrease of intracranial pressure
- * Results in a decrease in encephalopathy
- * Has the following indications:
 - Acute on chronic liver failure
 - Acute liver failure (limited data)
 - After transplantation
 - Liver failure after liver resection

The value of MARS in patients with a long past medical history, especially those with recurrent oesophageal bleeding, remains to

be investigated. Further controlled clinical studies are necessary, but because of the lack of reliable parameters this may be difficult. Dr Lamesch finished his presentation by quoting Professor Vincent - "Randomised controls trials, although admittedly providing strong evidence in favour or against interventions, are not necessarily appropriate, especially in the intensive care environment." This is especially true for complex patients and illnesses such as acute on chronic liver failure.



Dr. Patrick Sorkine

Patrick Sorkine (Israel) also presented his experience with MARS, in patients with acute exacerbations of chronic liver disease and patients with fulminant liver failure.

The course of chronic liver disease is sometimes complicated by acute exacerbations due to sepsis or upper gastro-intestinal bleeding; patients then deteriorate to multi-organ failure and death. In fulminant hepatic failure, the clinical picture is of jaundice and encephalopathy and patients may die rapidly due to high intracranial pressure and intracerebral hypertension. The best treatment to date is liver transplantation, but there is a severe shortage of donated organs. Dr Sorkine has

started to investigate the MARS in a one-year prospective study and he presented the results from 11 patients, all with acute exacerbation of liver disease or acute liver failure. They had at least Grade II encephalopathy and had not responded to standard supportive therapy.

The MARS mimics the physiological system in that albumin-bound substances from plasma cross the membrane against the concentration gradient through the membrane and are released to the exogenous albumin, in the dialysate. A conventional haemodialysis double lumen catheter was used for these patients and each treatment session lasted an average of 9 hours. No fluid or inotropic support was given during the treatment and patients were kept normothermic. It is difficult to define the number of sessions that a patient may need, because of individual requirements.

Metabolic monitoring has shown good ammonia and lactate clearance, and no changes in albumin levels have been noted. Creatinine and glucose levels have been maintained in the normal range. There have been no significant changes in platelet counts, as has been reported in bioartificial systems, and no changes in liver enzyme levels. Very rapid decreases in intracranial pressure have been noted and these have been maintained for over 3 hours after the treatment session has finished.

The complexity of the liver is such that it is not possible to provide full replacement of all liver functions for any significant length of time with any of the existing systems, including ex vivo perfusion with intact human liver. Therefore, the MARS system appears very promising in that it is:

- * A liver support system that appears to arrest or reverse the rapid development of

intracranial pressure leading to brainstem herniation and death

- * A bridge to orthoptic liver transplantation in fulminant hepatic failure
- * A means of providing effective metabolic and physiological support

Hepatology was a major topic at the 21st ISICEM and it is clear that albumin has a number of roles in

this therapeutic area:

- * As plasma expansion for cirrhotic patients with HRS
- * As part of the management of cirrhotic patients with SBP helping to prevent development of HRS
- * As part of the novel and highly promising MARS system for supporting patients in liver failure.

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