

Bacteremia Using the Molecular Adsorbent Recirculating System in Patients Bridged to Liver Transplantation

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Objective: To retrospectively analyze the incidence and implications of bacteremia in patients supported by a molecular adsorbent recirculating system bridged to liver transplantation.

Material and Methods: From September 2000 to April 2003, 30 patients (17 males and 13 females, aged 15-70 years; median age, 52 years) presenting with acute-on-chronic liver failure were treated with a molecular adsorbent recirculating system.

Results: Nine patients (30%) developed bacteremia (positive blood culture) during treatment, 100% of them died during the same hospital admission. The most common isolates were *Pseudomonas aeruginosa* (44.4%) and *Escherichia coli* (33.3%). Sputum (44.4%) and ascites (33.3%) represented the most common sources of infection followed by urine and purely bloodborne infections (11.1% each). The isolate in the sputum was *Pseudomonas aeruginosa* 100% of the time, whereas *Escherichia coli* was found in 66.6% of the ascites cultures. The hemodynamic profile of patients who developed positive blood cultures showed significantly lower systemic vascular resistance indexes compared with those of nonbacteremic patients before and after treatment. There was a statistically significant difference ($P = 0.0002$) in survival between the bacteremic (who all died) and the nonbacteremic patients treated.

Conclusions: Bacteremia was found to be a negative prognostic factor for patients supported

with a molecular adsorbent recirculating system and therefore, a contraindication to starting and/or continuing treatment. Infection should be carefully ruled out prior to initiating treatment using a molecular adsorbent recirculating system. Moreover, prophylaxis with broad-spectrum antibiotics that provide double coverage against Gram-negative bacteria should be mandatory.

Key words: Liver failure, Artificial liver, Infection, Albumin, Dialysis

The molecular adsorbent recirculating system (MARS) (Teraklin, Aktiengesellschaft, Rostok, Germany) is an artificial liver support system first introduced into clinical practice in 1993 [1]. In contrast to bioartificial liver support systems, which replace some of the metabolic and synthetic functions of the liver by means of established hepatocyte or hepatoblastoma cell lines [2-3], MARS aims only at clearing the blood of metabolic waste products normally metabolized by the liver. Essentially, it is a modified dialysis system that uses an albumin-containing dialysate that is recirculated and perfused in-line through charcoal and anion exchanger columns. This effects the removal of albumin-bound toxins like aromatic amino acids, bilirubin, bile acids, phenols, short- and middle-chain fatty acids, copper, and more, together with free solutes like ammonia, creatinine, urea, and others that are removed by standard dialysis [1, 5-6]. It is noteworthy that the serum electrolyte concentration remains stable during MARS [7]. The MARS can cause noncardiogenic pulmonary edema [8] and may worsen coagulopathy [9]; however, MARS has shown specific efficacy in treating intractable pruritus [10] and acute-on-chronic hepatic failure, where it improves survival [11-12].

Patients with liver cirrhosis are more prone to

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develop infections because of impairment in the humoral as well as the cellular components of their immune systems. Liver cirrhosis is associated with decreased synthesis in the complement system that normally protects the organism against infection caused by Gram-negative bacteria [13]. Moreover, it has been reported that life-threatening infections are more common in cirrhotic patients/livers when the natural defense barriers are violated at the time of diagnostic and/or therapeutic interventions [14].

The hyperdynamic circulation characteristics of liver cirrhosis [15] and sepsis [16] are difficult to differentiate. They consist of high cardiac output, decreased vascular systemic resistance index, and hypotension. It appears that in cirrhosis, these changes are secondary to peripheral vasodilatation and are due mainly to increased nitric oxide production [15], whereas in sepsis, cytokines, cellular death (with release of inflammatory mediators), and free radicals are responsible for the same clinical picture. There is much evidence that decompensated liver cirrhosis is the prime indication for MARS treatment [11-12]; however, to date, it is unclear whether infection, sepsis, or both constitutes a limiting factor for the use of MARS. This study aimed to determine whether infection constitutes a contraindication to MARS treatment.

Materials and Methods

Data were retrospectively collected from a consecutive series of 30 cirrhotic patients (17 males and 13 females, aged 15-70 years; median 52 years), evaluated at the Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo, Italy, from November 2000 to April 2003, as potential candidates for liver transplantation who subsequently, during the pretransplant work-up or while awaiting liver transplantation, developed acute-on-chronic hepatic failure requiring MARS treatment. Patient demographics and indications for MARS are summarized in Table 1.

After obtaining informed consent, patients were considered for MARS if they presented with acute-on-chronic hepatic failure defined as the rapid development of at least 2 of the following 4 criteria: worsening encephalopathy despite intensive medical management; rising bilirubin (≥ 10 mg/dL); worsening renal function (serum creatinine ≥ 1.5 mg/dL, creatinine clearance < 40 mL/min, or urine

output ≤ 0.25 mL/kg/h) despite volume expansion (to a central venous pressure of ≥ 10 mm Hg or a pulmonary artery wedge pressure of ≥ 6 mm Hg); or worsening coagulopathy (need for fresh frozen plasma or a rising PT that was ≥ 18 seconds).

Patients were excluded from MARS treatment if they had culture-proven sepsis at the time of evaluation or developed sepsis (ie, in patients 1, 2, 6, and 8 in Table 1), pulmonary edema, or acute respiratory distress syndrome during MARS. Ideally, the protocol included 7 MARS sessions on consecutive days for each patient treated. A single MARS session was 6 hours. A second MARS treatment was started in cases of partial good response to the first treatment (ie, in patients 3, 7, and 9 in Table 1).

The primary endpoint of this study was to establish whether infection, sepsis, or both is a contraindication to starting/continuing MARS treatment; the secondary endpoint was to identify a general antibiotic prophylaxis recommendation for those patients undergoing MARS treatment.

MARS was performed through a hemodialysis double-lumen catheter. A flush of the extracorporeal circuit with 1 liter of heparinized saline solution (1000 U of heparin sulphate/L) was carried out before MARS commencement. Therefore, no systemic heparinization was obtained. The extracorporeal blood circuit was driven by a standard dialysis machine (D-85716, Baxter, Unterschleibheim, Germany) at a flow rate of 100 mL/minute initially, increased to 200 mL/minute if the patient remained hemodynamically stable.

Statistical Methods

Data are presented as the mean $\pm$ standard deviation. A 2-sample unpaired *t* test was used for comparison of the means.

Results

Nine patients (30%) treated with MARS developed positive blood culture during treatment; 100% of them died of sepsis during the same hospital admission (Table 1). Gram (-) bacteremia was observed in 77.7% of the cases, whereas Gram (+) bacteremia was diagnosed in 22.2% of the cases (Table 1). *Pseudomonas aeruginosa* (44.4%, 4 cases) and *Escherichia coli* (33.3%, 3 cases) were the most common isolates (Table 1). Sputum (44.4%) and ascites (33.3%) represented the most common sources of infection, followed by urine and a purely

Table 1. Causes and Risks of Recurrent Glomerulonephritis in Renal Allografts

Age/sex	Diagnosis/No. of treatments	Pathogen isolated in the blood	Source of infection	Antibiotic treatment	Outcome/cause of death	Follow-up (days)	Pre/post MARS vasopressors
54/F	AoCHF/2	Methicillin-resistant <i>Staphylococcus aureus</i>	Blood-borne	Vancomycin	Died/sepsis	3	y/y
61/M	AoCHF/5	<i>Escherichia coli</i>	Urine	Imipenem	Died/sepsis	2	y/y
49/M	AoCHF/11	Vancomycin-resistant <i>Enterococcus faecium</i>	Ascites	Imipenem	Died/sepsis	32	n/n
53/F	AoCHF/7	<i>Pseudomonas aeruginosa</i>	Tracheal aspirate	Imipenem	Died/sepsis	2	n/y
61/M	AoCHF/7	<i>Pseudomonas aeruginosa</i>	Tracheal aspirate	Piperacillin-tazobactam/gentamycin	Died/sepsis	6	n/y
56/M	AoCHF/4	<i>Escherichia coli</i>	Ascites	Imipenem	Died/sepsis	4	y/y
57/F	AoCHF/11	<i>Escherichia coli</i>	Ascites	Imipenem	Died/sepsis	5	n/n
52/F	AoCHF/6	<i>Pseudomonas aeruginosa</i>	Tracheal aspirate	Piperacillin-tazobactam/gentamycin	Died/sepsis	10	n/n
56/M	AoCHF/11	<i>Pseudomonas aeruginosa</i>	Tracheal aspirate	Imipenem	Died/sepsis	17	n/y

AoCHF: Acute-on-chronic hepatic failure

Table 2. Pre-MARS Cardiac Profile

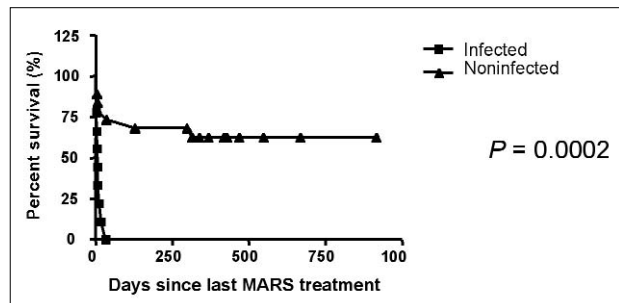
Indices	Bacteremic patients mean $\pm$ SD	Nonbacteremic patients mean $\pm$ SD	P value
Cardiac output (L/min)	10.9 $\pm$ 1.4	10.9 $\pm$ 3.4	ns
Cardiac index (L/min)	6.9 $\pm$ 0.9	10.1 $\pm$ 40	ns
Systemic vascular resistance index (dyne sec/cm ⁵ /m ²)	688 $\pm$ 170.2	1060 $\pm$ 692	< 0.05

Table 3. Post-MARS Cardiac Profile

Indices	Bacteremic patients	Nonbacteremic patients	P value
Cardiac output (L/min)	10.8 $\pm$ 1.4	12.6 $\pm$ 18.2	ns
Cardiac index (L/min)	6.8 $\pm$ 0.9	5.9 $\pm$ 1.5	ns
Systemic vascular resistance index (dyne sec/cm ⁵ /m ²)	685 $\pm$ 183.9	1068 $\pm$ 624.2	< 0.05

bloodborne infection (11.1% each) (Table 1). The isolate in the sputum was *Pseudomonas aeruginosa* 100% of the time, whereas *Escherichia coli* was found in 66.6% of the ascites cultures (Table 1). Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* were the other 2 isolates cultured, respectively, from the blood and ascites (Table 1). The hemodynamic profile of the patients who developed positive blood cultures showed systemic vascular resistance indexes that were significantly lower when compared with nonbacteremic patients before and after treatment (Tables 2 and 3). However, no significant difference was noted when cardiac output and cardiac index of bacteremic and nonbacteremic patients were compared before and after MARS (Tables 2 and 3). None of the noninfected patients required treatment with vasopressors (data not shown), whereas at some point before or after MARS commencement,

55.5% of the infected patients required continuous vasopressor infusion (defined as dopamine higher than the renal dose, norepinephrine at any dose, and epinephrine at any dose) to maintain a mean arterial pressure above 60 mm Hg (Table 1). There was a statistically significant difference ($P = 0.0002$) in survival between bacteremic and nonbacteremic patients treated with MARS (Figure 1).

**Figure 1.** Infected vs Noninfected Patient Survival after MARS

Conclusions

The daily struggle in a liver unit consists of maintaining the unstable patient (such as that diagnosed with acute-on-chronic hepatic failure) in a stable condition until a suitable donor organ becomes available. With the introduction of MARS, this task has been achieved with some success [11-12]. However, because infection, in larger studies, is the second cause of death for patients awaiting liver transplantation [13], it is unclear whether MARS is still indicated in the presence of bacteremia. We believe that our results, in terms of microbial flora and sites of infection during MARS treatment, are similar to those previously reported in cirrhotic patients and in accord with the increased infection rate for any invasive procedure performed in cirrhotic patients [13].

Based on the current results, infection and/or sepsis are contraindications to initiating or continuing MARS treatment. Therefore, every patient scheduled for MARS therapy should be pancultured before initiating treatment and closely monitored for infection during MARS. Prophylactic antibiotic therapy against Gram (+) and double coverage against Gram (-) bacteria are suggested during MARS. A hyperdynamic cardiac profile, per se, with or without the use of vasopressors is not a contraindication to MARS treatment unless it is associated with positive blood culture, which, along with decreased systemic vascular resistance index and use of vasopressors, is associated with an increased mortality rate.

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