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Is MARS system enough for A.phalloides-induced liver failure treatment?

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Abstract

Patients with Amanita phalloides-induced liver failure (LF) have a high mortality, despite significant advances in intensive care managemet. Our study evaluated the effect of Molecular Absorbents Recirculating System (MARS) comparative with optimal intensive care (OIC) in adults with this condition, in the absence of liver transplantation (LT). Six consecutive patients (women, range 16–61 years) affected by A.phalloides-induced LF were treated with OIC (3 patients) and MARS (3 patients). Laboratory parameters and hepeatic encephalopaty were evaluated 15 min before and 24 hours following each MARS treatment. Three 6-hour sessions per patient were performed in MARS group, with a statistically significant decrease in ammonia (p value 0.011), alaninaminotransferase (ALT) and prothrombin time (PT) (p value 0.004). Two patients had a significant rebound in bilirubin (+116%; p value 0. 04) 24 hours following MARS. Mortality in MARS group was 66.7%. Survival rate in OIC was 0%. Negative prognostic markers: lack of PT and hepatic encephalopaty improvement, rebound in bilirubin, and delay of MARS therapy initiation. No significant adverse reactions occurred during MARS. MARS is an effective depurative therapy in adults with A.phalloides-induced LF, but alone is not enough. Survival is predicted by the results of the initial MARS, amount of mushroom consumed, and time from toxin exposure.

Keywords

MARS, liver failure, Amanita phalloides

Introduction

Fulminant liver failure (FLF) is defined as sudden onset of severe LF associated with jaundice and altered mental status known as hepatic encephalopathy (HE) in the absence of preexisting liver disease.[1] FLF, the most severe form of liver failure (LF) is produced, among other causes, by toxins, such as those from the Amanita phalloides.[1,2] As reported in literature, the mortality rates for patients with FLF without liver transplantation (LT) approaches 80%, despite advances in intensive care management.[3-5] LF associated with excretory insufficiency and jaundice results in an endogenous accumulation of toxins (involved in the impairment of cardiovascular, kidney, cerebral function) and damage the liver itself by inducing hepatocellular apoptosis and necrosis, thus creating a vicious cycle of the disease.[6] Treatment is directed to early recognition of the complications and general supportive measures, but the only proven therapy for patients unlikely to recover remains LT.[7]

More than 90% of all fatal cases of mushroom poisoning are secondary to A.phalloides.[8] Its rapid evolution towards FLF makes poisoning with A. phalloides a medical emergency. Due to the development of acute tubular necrosis, and subsequent renal failure worsening LF, and rising ammonia levels occur hepato-renal syndrome, hepatic coma and convulsions, followed by respiratory failure, hemorrhage, and death by days 6–16.[8,9]

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Once a diagnosis of A.phalloides poisoning has been established, the patient's care is mainly supportive, as no specific antidote exists for its toxins. Controversy still remains whether hemoperfusion, hemodialysis, or both, are effective in averting the deleterious effects of amatoxins. Several studies have suggested that early hemoperfusion (<24 hours after exposure) over a charcoal filter should be considered if patients fulfill the criteria of time from ingestion, biochemical evidence of toxicity, ingestion of a potentially lethal dose and elevation of serum enzymes.[10] Orthotopic LT should be considered in patients who progress to HE with significant and worsening derangement of both clotting factors and liver enzymes.[11]

There is no evidence from randomized trials to support a standard intervention or therapy for FLF in A.phalloides poisoning. There were reports of using Molecular Absorbent Recirculating System (MARS) in the treatment of FLF secondary to mushroom poisoning, in children and in adults.[4,12-19]

MARS therapy has been shown efficiently to remove bilirubin, bile acids, tryptophan, aromatic amino acids, middle and short chain fatty acids, inflammation mediators, also decreased the HE grade, improved the liver synthesis function and most importantly, increased survival.[4,16,20]

The aims of the current study were to evaluate the feasibility, safety and efficacy of nine MARS sessions (three per patient), as well as impact on survival, comparative with optimal intensive care (OIC) in six consecutive adults poisoned with A.phalloides and secondary LF, in the setting of an intensive care unit (ICU) in Romania. We describe first Romanian experience with MARS therapy in A.phalloides-induced FLF in adult patients, considering that LT is not accessible in Romania for this etiology of FLF.

Methods

We studied retrospectively six consecutive patients accidentally poisoned with A.phalloides, who developed FLF, between September and November 2007. We analyzed this period because in 2007, we recorded 7 cases of A.Phalloides poisoning (of which 6 were consecutive cases, in 2007 fall), compared with 2 cases in 2008, and one case in 2009, and because MARS procedure was introduced in October 2007 for the first time in our ICU. Data were collected from hospital medical records. Inclusion criteria were FLF supported by clinical symptoms and biochemical parameters, with progressive clinical deterioration despite OIC over 72–96 hours, with increasing jaundice (bilirubin >7 mg/dL), and either HE (≥Grade 2) or renal failure or both, and A.phalloides spores detected by mycological analysis in gastric content or stool. There was no statistical significant difference in clinical and biochemical parameters between OIC group and MARS group (Tables 1 and 2). Exclusion criteria age was < 16 years old, more than 5 days from the moment of mushroom ingestion, or severe cardiorespiratory disease.

The MARS system consists of a 20% albumin closed-loop circuit, with two areas of depuration (Figure 1). In one area, the toxin-free 'albumin dialysate' is in contact with patient's blood though an asymmetric permeable polysulfone membrane – the MARS™ membrane (pre-perfused with albumin 20%, to saturation). Albumin-bound substances are transferred from patient's serum albumin to the unoccupied ligand binding sites of the system's albumin. In the second area, the 'albumin dialysate' is in contact with a standard bicarbonate dialysate through a high-flux membrane, which permits the elimination of water-soluble substances. The albumin toxin-charged solution is continuously regenerated by de-ligandization obtained by passage on charcoal and ion-exchange columns. This principle allows the replacement of the liver's detoxification function, which is life threatening while absent in LF.[4,20-23]

The following technical parameters were used: flow rates (Q) as follows – Q-albumin = 150 mL/min, Q-blood = 100–150 mL/min, Q-dialysate = 2000 mL/hour; P_{AA} was between 100 and 225 mm Hg (max = 400) and P_{AE} between 130 and 400 mm Hg (max = 500), as Figure 1 shows. MARS group (three patients) each received three MARS 6-hour sessions (a total of nine MARS sessions). Clinical course, biochemical parameters and survival was compared to that of OIC group (3 cases), matched for ALT levels and HE grade, hospitalized before the introduction of MARS therapy in our ICU.

The patients were evaluated clinically and biochemically (including liver and renal function tests, hematological and coagulation profiles) both 15 min prior to and 24 hours after each MARS session. The Child-Turcotte Pugh (CTP) score, the Model for End-stage Liver Disease (MELD) score were calculated at the same time.[24,25] These scoring systems are good predictors of the outcome in patients with liver disease and also in patients that are admitted with ALF.[26] The severity of HE was assessed using the

Table 1. Demographic, clinical parameters and outcome of patients included in study

Group	Case	Age (y.m)	BMI (kg/m^2)	Approx. amount of mushroom meal consumed (g)	Time to hospital admission (h) /time to first MARS session (h)	Encephalopathy grade (at MARS initiation)	SBP (mm Hg)/ HR (/min) at admission	Initial MELD score/GCS	ICU (d)/ Hospital (d)	Outcome/ after ingestion (d)
MARS	1	49.3	27.1	200	90 / 102	III	60 / 140	27 / 4	5 / 5	Death / 9
	2	16	24.7	150	16 / 89	II	100 / 110	17 / 7	5 / 8	Death / 8
	3	46.1	26.3	50	20 / 121	I	120 / 90	15 / 8	9 / 18	Survival / 90
OIC	4	30.3	31.2	200	24 / NA	NA	85/ 120	28 / 7	3 / 7	Death / 8
	5	61	33.1	250	36 / NA	NA	85 / 134	25 / 8	3 / 6	Death / 8
	6	25.2	27.3	150	48 / NA	NA	75 / 137	33 / 8	6 / 8	Death / 10
p value[a]		.94	.17	.18	.89/ NA	–	.62 / 0.47	.20/.26	.01/.44	–

BMI, body mass index; d, days; g, grams; h, hours; HR, heart rate; m, month; NA, not applicable (no MARS sessions performed); SBP, systolic blood pressure; y, year;GCS, Glasgow coma score.
[a] Comparison between parameters in MARS group and OIC group.

Table 2. Biochemical parameters of patients included in study

		Bilirubin (mg/dl)			ALT (IU/L)			Prothrombin time (s)			Ammonia (μmol/l)			Creatinine (mg/dl)		
Group	Case	b1/a1	b2/a2	b3/a3	b1/a1	b2/a2	b3/a3	b1/a1	b2/a2	b3/a3	b1/a1	b2/a2	b3/a3	b1/a1	b2/a2	b3/a3
MARS	1	6/5.2	7/4.6	6.9/5.9	16227/14320	12140/9360	3267/1860	101/56	65/55	70/63	193/54	91/73	150/108	3.8/2.6	1.9/.8	1.2/.8
	2	6.7/6.1	9.2/6.5	14.1/13.2	3397/3363	2388/1546	1541/863	140/125	129/105	108/95	298/68	416/330	270/219	4.2/1	2.9/1.8	.9/.6
	3	7.3/6.2	4.8/3.8	3.4/2.9	5514/4830	2188/1530	1656/969	74/35	29/21	22/15	167/56	66/46	39/27	5.9/ 3.6	6.6/3.8	1.7/.6
p Value[a]		.0015			.0045			.0044			.0110			.0043		
OIC	4	6	9.4	15.8	11836	5540	1746	104	64	69	91	150	108	1.6	1.8	2.4
	5	5.1	7.4	9.7	10508	8234	2468	62	104	319	87	169	306	2.8	3.9	5.1
	6	5.2	8.7	11.9	12916	8184	4276	86	127	205	69	135	203	5	6.24	6.4
p Value[b]		.36			.29			.20			.38			.43		

a1, parameter post MARS-1; a2, parameter post MARS-2; a3, parameter post MARS; 3b1, parameter pre MARS-1; b2, parameter pre MARS-2; b3, parameter pre MARS-3.
[a] Comparison between pre and post MARS parameters.
[b] Comparison between pre MARS parameters in MARS group and OIC group (the same interval from mushroom ingestion).

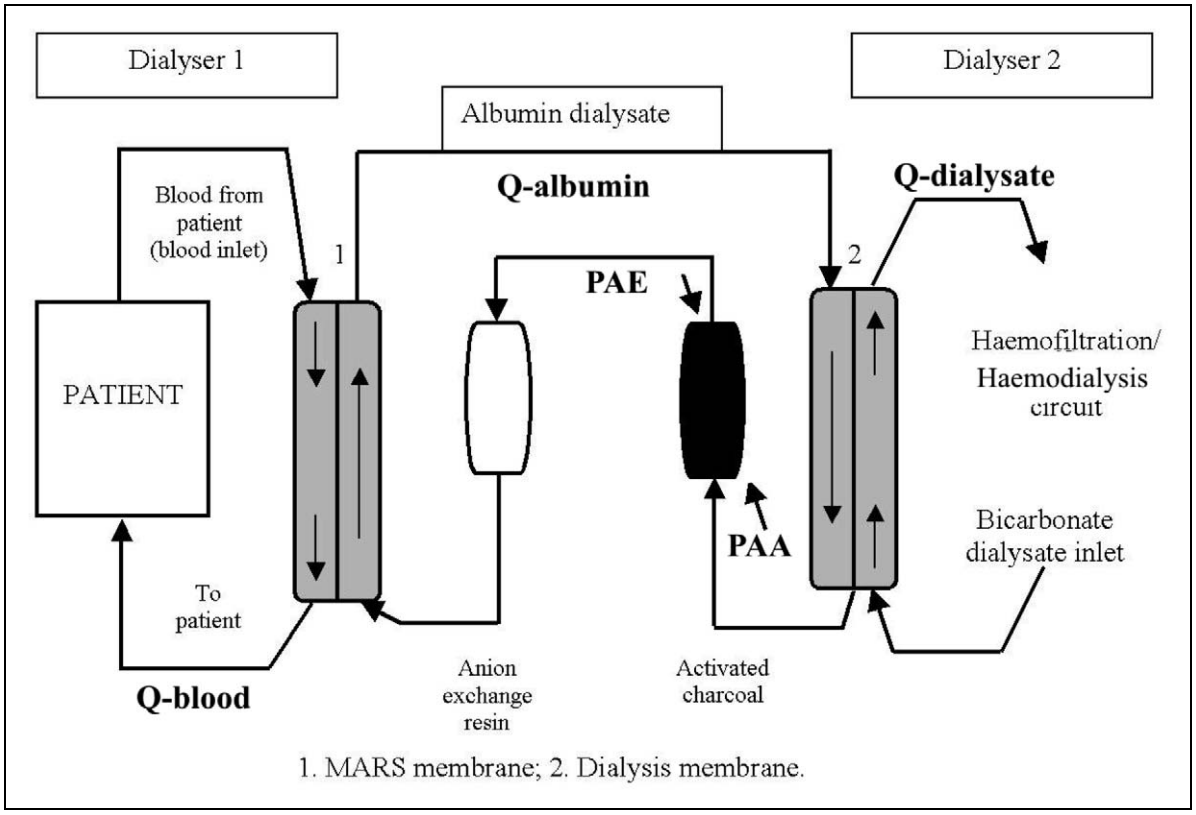

Figure 1. Schematic diagram of the molecular absorbents recirculating system (MARS) circuit showing direction of blood flow and the dialysate. Albumin-bound toxins from the patient's blood pass on to the albumin in the dialysate, which is then cleansed sequentially by a haemodialysis/haemofiltration module (removing water soluble substances) and adsorber columns containing activated charcoal and anion exchange resin (removing most of the albumin-bound substances). The dialysate is thus regenerated, and once more capable of taking up more toxins from the blood. AP = albumin pump; BP = blood pump.

West Haven criteria and Glasgow coma scale.[27] Patients were mechanically ventilated if they became hypoxaemic. Mean arterial pressure, electrocardiogram, heart rate and temperature were monitored continuosly during treatment. Intravascular volume was maintained using crystalloids, colloids or red cells as appropriate to maintain central venous pressure between 8 and 10 cm H_2O. Dopamine was used to maintain mean arterial pressure above 55 mm Hg where necessary. Blood glucose was maintained between 5 and 7 mmol/L.

Results were expressed as the mean $\pm$ standard deviation. Statistical analysis was performed using Student's *t*-test and analysis of variance (ANOVA). $p < .05$ was taken as statistically significant.

Results

We studied six consecutive patients with A.phalloides poisoning and LF. Three patients (aged 38.83 $\pm$ 19.36 years) received OIC, because no hemofiltration/hemodialysis/charcoal hemoperfusion were available at the moment of their admission, and the other three (aged 37.13 $\pm$ 18.37 years) benefited from daily MARS (3 sessions each) and OIC. All three patients were jaundiced and encephalopatic at the time MARS was initiated (Table 1). Their biochemical profiles are given in Table 2.

Patient 3 of MARS group survived and was discharged from the hospital with good liver function, not requiring further hospital admission, 3 months after inclusion into the study. This patient ingested the lowest amount of mushroom meal (50 g, with a ratio between mushroom quantity and BMI of 1.9), as compared with the rest of the patients who ingested larger quantities (150 to 250 g, with higher ratio between quantity ingested and BMI, of 5.49 to 7.55). Even if this was not significantly statistic, we consider that the low amount of mushroom meal ingested contributed in some way to the survival of this patient. The

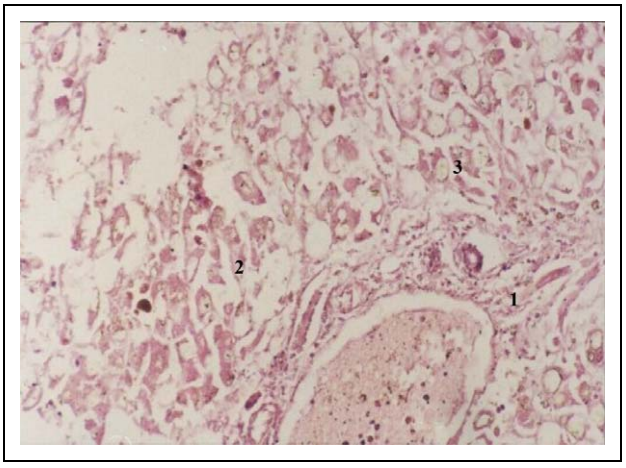

Figure 2. Liver specimen (necroptic examination) of a deceased patient treated with Molecular Absorbents Recirculating System (MARS). A fragment of portobiliary space (1) with massive necrosis of hepatocytes (2), and cholestasis (billiary thrombi) (3). Hematoxylin and eosin stain x20.

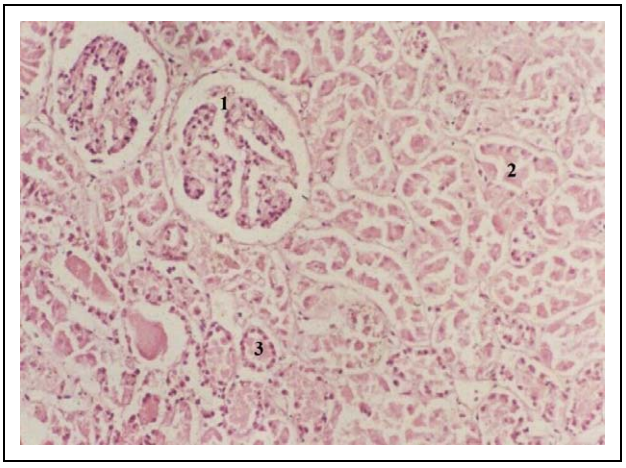

Figure 3. Kidney specimen (necroptic examination) of a deceased patient treated with MARS. Normal glomeruli (1), tubular proximal necrosis (2) are seen in renal cortical. The contour of tubes is kept, but they have necrosis of the epithelium, with epithelial necrotic cells without nucleus detached in lumen. Rare images of tubes with epithelial regeneration (3). Hematoxylin and eosin stain $\times$20.

other two patients died within 9, respectively 8 days after mushroom ingestion (mortality 66.7%). Patients poisoned with A.phalloides receiving only OIC had 100% mortality, within 8 days after mushroom ingestion. Anatomo-pathological examination was performed to all deceased patients, and revealed typical liver and tubular renal lesions (Figures 2 and 3) as well as the Amanita spores present.

The MARS sessions had a similar immediate impact on biochemical parameters (Figure 4): drop in ALT from pre-MARS levels of 12%, 35% and 43%, respectively, and in bilirubin of 15%, 29% and 14%, respectively ($p < .01$). ALT levels 24 hours following MARS-1 were 33% lower and continued to drop by a further 24%, 4% following MARS-2 and MARS-3, respectively. After 9 sessions, ALT decreasing was statistically significant (p value 0.0045). PT was also significantly improved with MARS sessions (p value 0.0044), and normalized in patient 3, after MARS-2. Bilirubin levels were significantly decreased after MARS sessions (p value 0.0015). However, 24 hours following MARS-1 and MARS-2 was a significantly rebound in bilirubin levels (Figure 5) in 2 cases, as follows: case 1 had a rebound of 34.6% and 50%, respectively, and case 2 had 50% and 116%, respectively, rebound of bilirubin level (p 0.048). All three patients were encephalopathic at the time MARS was initiated (Table 1). Patient 3 regained consciousness after two sessions of MARS therapy. Pre-MARS the

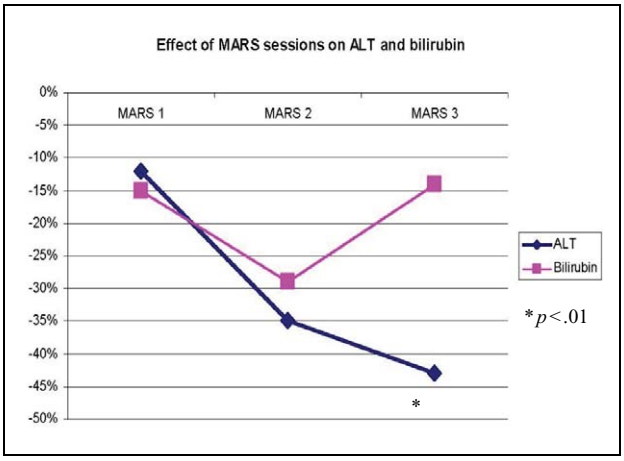

Figure 4. Immediate impact on biochemical parameters of Molecular Absorbents Recirculating System (MARS) sessions.

CTP score was 6.7 $\pm$ 1.2, improved significantly to 4 $\pm$ 1.6 following the three MARS sessions ($p < .05$), and further declined to 3.3 $\pm$ 1.1 at time of discharge/death. Ammonia levels dropped from 219 $\pm$ 69 mg/dL pre-MARS to 59 $\pm$ 7 mg/dL post-MARS (p value 0.011) and further decreased to 44 $\pm$ 16 mg/dL in patient who survived, but increased to 105 $\pm$ 33 mg/dL and 308 $\pm$ 84 mg/dL, respectively, in the other two patients (p value 0.04) who had a bad outcome.

Markers on unfavourable outcome were delayed admission in hospital (4 days after mushroom

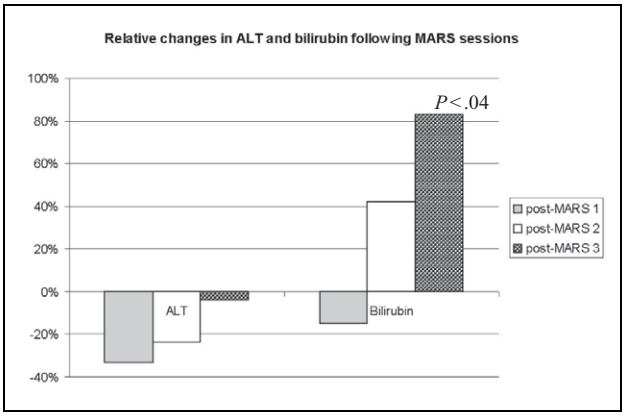

Figure 5. Rebound in bilirubin levels 24 hours following Molecular Absorbents Recirculating System (MARS)-1 and MARS-2.

ingestion in case 1), a lack of complete correction of PT, a continuous rebound and increase in bilirubin levels, even after MARS-3 treatment, delay in MARS therapy initiation (cases 1 and 2) and a lack of improvement in HE scores post MARS-1.

The MARS procedure was completely uneventful and devoited of any incidents or complications. There was an increase in mean arterial pressure immediately after the MARS-1 (case 1) from 74.6 to 80 mm Hg, which was sustained through the treatment period (84 mm Hg at the end of therapy), but the changes were not statistically significant. There was neither decrease in hemoglobin or platelets, nor significant changes in serum electrolytes following MARS treatments.

Patients in OIC group had an unfavourable outcome, with progressive deterioration of hepatic and renal function, and death within 10 days after mushroom ingestion.

Discussion

FLF resulting from different causes (viral hepatitis, paracetamol overdose, toxins from the A.phalloides) remains one of the most critical issues in the discussion of appropriate treatment options. Multiple medical complications and multi-organ failure can result from severe acute LF. These include acute renal failure (ARF) and respiratory failure, severe sepsis, disseminated intravascular coagulation, acute HE and significant haemodinamic derangements.[1,2]

Morbidity and mortality due to mushroom poisoning are common occurrences in Eastern Europe, including Romania.[9] Mushroom poisoning also represents a problem in the United States.[8]

Table 3. Clinical picture of Amanita Phalloides poisoning (adapted from ref. 8 and 9)

Stages	Clinical and biological features
1. Incubation phase – 8–12 h after ingestion	Asymptomatic.
2. Gastrointestinal stage (frequently misdiagnosed as viral gastroenteritis) – 6–40 h after ingestion	Abdominal cramps; Profuse watery diarrhea; Vomiting.
3.Cytotoxic or parenchymatous stage	Jaundice, encephalopaty, oligoanuria; Liver function tests, coagulation studies, and serum creatinine rapidly become abnormal.
4. Comatose stage	Acute tubular necrosis, and subsequent renal failure, followed by respiratory failure, hemorrhage, causes death by days 4–7.

The clinical syndrome associated with A.phalloides poisoning can be characterized by four stages (Table 3). All six patients included in study had typical features of A.phalloides poisoning at the moment of hospital admission (see Table 1).

Amatoxins represent the most important toxins that induce A.phalloides poisoning, because they interfere with DNA transcription by inhibiting RNA polymerase B. Synthesis of messenger RNA and subsequent protein synthesis is interrupted, that is why the gastrointestinal tract, the liver and the kidneys (where exist cells with high rates of protein synthesis) are particularly sensitive to injury.[27] A single mushroom weighing about 50 g (which contains 5–7 mg amatoxin) can produce severe poisoning, the lethal dose of amatoxins being of approximately 0.1 mg/kg.[28,29] All six patients included in study presented typical clinical features of A.phalloides poisonig, they consumed various amounts of mushroom meal (50 to 250 g), but dosage of alpha-amanitin was technically impossible (our laboratory could not perform this assay).

We determined initial levels for PT/PTT, AST/ALT and CBC with platelets, BUN and creatinine, as well as clotting factors, particularly Factor V, because it seemed to have some prognostic significance.[30] Blood glucose and ammonia levels were closely monitored. Active urinary sediment may signal the onset of acute tubular necrosis.[31]

Initial therapy in our patients with A.phalloides poisoning consisted of gastric lavage, intensive

Table 4. King's College Hospital criteria for liver transplantation in patients with non-acetaminophen – induced FLF (adapted from ref. 2)

All patients with:	Patients with any three of the following variables, irrespective of HE grade
Prothrombin time >100 seconds, irrespective of HE grade.	Age <10 or >40 years; Aetiology – non-A, non-B hepatitis, halothane hepatitis, severe idiosyncratic drug reactions, Amanita phalloides poisoning; Duration of jaundice before onset of encephalopathy > 7 days; Prothrombin time >50 seconds; Serum bilirubin > 300 μmol/L.

intravenous fluid resuscitation and multiple doses of activated charcoal with a cathartic to remove all remaining stomach contents and to draw the toxin from the entero-hepatic circulation. We performed continuous nasoduodenal (ND) aspiration with an ND tube as recommended by Scheurlen et al.[11]

A number of drugs have been trialed with varying success in A.phalloides ingestions, such as Penicillin G (for its ability to displace amanitin which exists bound to plasma protein sites and promotes its excretion, for prevention of hepatic uptake of the amatoxin, and its value for inhibiting the toxin's cellular penetration), and Silibinin (competes with amatoxins for transmembrane transport, and inhibits the penetration of amanitin into hepatocytes, thus having direct hepatoprotective effect). Other pharmacological agents used without proven efficacy and various degrees of success have been thioctic acid, steroids, vitamin C, *N*-acetylcysteine and cimetidine.[32] In our patients, we used Penicillin G, Silibinin, thioctic acid and *N*-acetylcysteine in doses recommended in literature. Vitamin K and fresh frozen plasma were given to temporarily supplement clotting factors in severe coagulopathy. Our patients had no improvement in clinical and biochemical evolution, or mortality, despite OIC.

Orthotopic LT should be considered in patients with criteria listed in Table 4. Nevertheless, its use is limited by organ donor shortage, especially in countries like Romania where the supply of livers suitable for transplantation is limited and unpredictable. Only 10% of patients with LF are transplanted because of the limited availability of donor organs. The inability to control cerebral edema and the occurence of multiple organ failure preclude the use of transplantation for the treatment of these patients.[20]

Despite the improvements achieved in the treatment of LF, the mortality rate remains unacceptably high, ranging from 40% to 80%.[33,34] FLF complicated by ARF is associated with almost 100% mortality.[35] Our patients with both LF and ARF had also 100% mortality, in the absence of MARS therapy (cases 4–6).

An integral strategy of management of these patients is to optimize patients' medical condition, either in anticipation of LT in FLF patients or of spontaneous liver recovery. OIC and the use of extracorporeal liver assist devices, which provide acute temporary liver support, remain the cornerstone of medical treatment for such patients.[1]

Stange and Mitzner developed MARS system, a blood detoxification method for protein-bound substances, as well as water-soluble toxins (through the dialysis component).[36-38] Substances removed by MARS include ammonia, bilirubin, free fatty acids and aromatic aminoacids.[39] Improvements in the clinical parameters of cerebral function following MARS treatment may be due to the removal of mediators like ammonia and other protein-bound liver toxins.[40] Case 3 in our study became conscious after 2 MARS sessions.

Other toxins that seemed to be removed during MARS include BUN and creatinine, which is the basis of the de-uraemization effect of MARS in patients with concomitant acute LF and ARF.[20,25,41]

Patients in our MARS group had an immediate improvement in biochemical parameters: drop of ALT, bilirubin and ammonia levels, and significant improvement of PT and creatinine after MARS sessions. The OIC group failed to improve their biochemical tests.

Albumin dialysis with the MARS system has been used clinically as a liver support device in more than 3500 patients with acute LF of various etiologies, hepato-renal syndrome, primary non-function after LT, or an acute decompensation of a chronic LF worldwide until now.[16,20,34,42-46] In LF secondary to mushroom poisoning, we found only 10 reports in PubMed, and only four of these were presentations of case series in adults.

We report the first Romanian case series of MARS technology used in adults with A.phalloides-induced FLF. In our study, MARS sessions were fine tolerated and led to clear-cut clinical improvement in the liver, neurological and general condition in one of three

patients. Patient 1 in MARS group was admitted 4 days after mushroom ingestion, developed cardiopulmonary arrest, with cardiopulmonary resuscitation before MARS could be initiated, and despite OIC and MARS sessions, subject died. Case 2 had a delay in initiation of MARS therapy caused by technical difficulties and developed rebound in bilirubin level after MARS 1 and persistently low PT, which represented negative prognostic markers in our series, as well as in other series of patients treated with MARS.[4]

Case 3 was the only survivor in MARS group, and the small quantity of mushroom meal ingested (50 g) compared with the other patients (150–200 g) could be in favor of this outcome, together with favourable evolution of all biochemical parameters, especially prothrombin time and bilirubin after MARS sessions.

Our study revealed that though there was no significant statistical diferences between the two groups analyzed concerning age, body mass index, approximate amount of mushroom meal ingested, time to hospital admission, vital signs at presentation, initial MELD or Glasgow coma score, or time of death after mushroom ingestion, MARS therapy alone increased significantly hospitalization time in ICU ($p = .01$), improved significantly biochemical parameters (Table 2) and decreased mortality rate. Our results on mortality rate were higher than those reported in other series of cases, probably because of the small number of patients analyzed (three consecutive patients over 3 months), the sex of the patients (feminine gender is a predictive factor for a fatal outcome),[47] delay in MARS initiation from mushroom ingestion (104 ± 16.09 hours) and impossibility of LT. Faybik et al.[48] report six consecutive patients with A.phalloides-induced LF, with an average 76-hour delay to MARS, 16.66% mortality rate, but three patients received also LT. Kantola et al.[49] study present 10 patients analyzed over 7 years, with an average 48-hour delay to MARS, 0% mortality rate, one patient had also LT.

Early initiation of MARS in severe FLF secondary to mushroom poisoning in adults, as well as a longer duration of MARS sessions, could reduce the number of MARS sessions required, prevent irreversible liver deterioration or life-threatening complications and avoid liver transplantation.[48-51] We recommend that the MARS therapy should be used in the treatment of A. phalloides-induced FLF as part of a randomized controlled trial for MARS evaluation in mushroom-induced LF.

In conclusion, MARS is a safe, homeostatic tool and highly effective depurative therapy in adults with A.phalloides-induced LF. Survival is predicted by the initial impact of MARS therapy, amount of mushroom meal ingested and time to MARS initiation. Rebound in bilirubin level after MARS and persistently low PT represent negative prognostic markers in A.phalloides-induced FLF. MARS in association with OIC decreases mortality rates, but does not guarantee survival and recovery in all cases.

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