CASE REPORT

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Application of single-pass albumin dialysis in the acute phase of amanitin syndrome caused by mushroom poisoning

Primena jednoprotočne albuminske dijalize u akutnoj fazi amanitinskog sindroma uzrokovanog trovanjem pečurkama

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Abstract

Introduction. The frequency of mushroom poisoning is increasing both in the world and in our country. The most poisonous type of mushroom in our region is *Amanita phalloides*, which causes amanitin syndrome in poisoned patients, and it is considered responsible for the majority of deaths of patients intoxicated by mushrooms. The liver is one of the primary target organs of amatoxin toxicity. Clinical symptoms and signs of amatoxin poisoning manifest themselves in different ways and can range from simple gastrointestinal disorders to fatal outcomes. Currently, there is no knowledge in the literature about the existence of a specific antidote that should be used in the acute phase of amanitin syndrome. The basis of therapy is symptomatic and supportive therapy. Albumin dialysis is an extracorporeal, non-biological mechanism of liver function support used in liver failure of various etiologies. **Case report.** The initial treatment of a patient treated with the clinical picture of alimentary intoxication with mushrooms and amanitine syndrome included symptomatic and supportive therapy. Due to elevated values of liver enzymes, as well as ammonia and present oliguria, a multidisciplinary analysis determined that single-pass albumin dialysis (SPAD) should be applied as a treatment measure in this patient to support hepatic and renal function. Following a temporary improvement, the general condition worsened upon continuing the treatment. That was manifested by a worsening of the state of consciousness and, consequently, the respiratory function. Further treatment included mechanical ventilation and repeated SPAD procedure. This eventually led to positive outcomes, including improved consciousness, better respiratory function, and normalization of laboratory indicators of liver and kidney function. **Conclusion.** Considering that liver function is compromised in amanitin syndrome, SPAD is a good choice in the treatment of a patient with a severe clinical picture of mushroom poisoning. The presented patient is the first mushroom-intoxicated patient with this severity of the clinical picture, treated at our institution, in whom no fatal outcome was recorded. Based on further tests or analyses and more clinical experience that will be gained with the further use of SPAD, it is necessary to create a clear protocol for the use of this method during the treatment of patients intoxicated by mushrooms.

Key words:
amanitins; dialysis; hepatic encephalopathy; hepatic insufficiency; mushroom poisoning.

Apstrakt

Uvod. Učestalost trovanja pečurkama je u porastu kako u svetu tako i u našoj zemlji. Najotrovnija vrsta pečuraka na našim prostorima je Zelena pupavka (*Amanita phalloides*), koja prouzrokuje amanitinski sindrom kod otrovanih pacijenata i smatra se odgovornom za većinu smrtnih slučajeva kod pacijenata otrovanih pečurkama. Jetra je jedan od primarnih ciljnih organa toksičnog delovanja amatoksina. Klinički simptomi i znaci trovanja amatoksinom se različito manifestuju, od jednostavnih gastrointestinalnih poremećaja do smrtnog ishoda. Trenutno ne postoje literaturna saznanja o postojanju specifičnog antidota koji bi trebalo da se primenjuje u akutnoj fazi amanitinskog sindroma. Osnovu terapije čine simptomatska i suportivna terapija. Albuminska dijaliza je ekstrakorporalni, nebiološki mehanizam potpore

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funkcije jetre koji se koristi kod insuficijencije jetre različitih etiologija. **Prikaz bolesnika.** Inicijalni tretman pacijenta lečenog pod kliničkom slikom alimentarne intoksikacije pečurkama i amanitinskog sindroma uključio je simptomatsku i suportivnu terapiju. Zbog povišenih vrednosti enzima jetre, kao i amonijaka i prisutne oligurije, multidisciplinarnom analizom donesena je odluka da se u lečenju ovog pacijenta primeni jednoprotočna albuminska dijaliza (JPAD) kao terapijska mera potpore funkcijama jetre i bubrega. Posle prolaznog poboljšanja, u nastavku lečenja, dolazi do pogoršanja opšteg stanja. To se manifestovalo pogoršanjem stanja svesti i, posledično, respiratorne funkcije. Dalje lečenje uključivalo je mehaničku ventilaciju i ponovljene JPAD procedure. Ovo je na kraju dovelo do pozitivnih ishoda, uključujući poboljšanje svesti, bolju respiratornu funkciju i normalizaciju laboratorijskih pokazatelja funkcija jetre i bubrega. **Zaključak.** S obzirom da je funkcija jetre kompromitovana u amanitinskom sindromu, JPAD predstavlja dobar izbor u lečenju pacijenata sa teškom kliničkom slikom trovanja pečurkama. Prikazani pacijent je prvi pacijent otrovan pečurkama sa ovim stepenom težine kliničke slike, lečen u našoj ustanovi, kod koga nije zabeležen smrtni ishod. Na osnovu daljih ispitivanja i analiza i većeg kliničkog iskustva koje će se steći daljom upotrebom JPAD-a, potrebno je napraviti jasan protokol za upotrebu ove metode u toku lečenja pacijenata otrovanih pečurkama.

Ključne reči:
amanitin; dijaliza; hepatička encefalopatija; jetra, insuficijencija; trovanje pečurkama.

Introduction

Mushrooms are certainly an indispensable food item in the varied nutrition of modern humans [1]. With a greater prevalence in human nutrition, the risk of mushroom intoxication is inevitably increased [2].

Toxic substances from fungi cannot yet be reliably identified in a laboratory. Therefore, in practice, analyses that prove the presence of toxins in the organism of the poisoned person are generally not used for the diagnosis of mushroom intoxication. Instead, diagnosis is based on certain symptoms and signs, and patients are clinically classified into specific toxic syndromes.

The most poisonous mushroom species in our region is *Amanita* (*A.*) *phalloides*, which causes amanitin syndrome in humans. This species is considered responsible for most fatal outcomes in mushroom-intoxicated patients [3, 4]. According to data from the National Center for Poison Control, Belgrade, Serbia, three to eight fatal outcomes are recorded every year due to poisoning with this species of mushroom [5].

The most toxic substance found in *A. phalloides* is amatoxin. The mortality rate after ingesting *A. phalloides* ranges from 25% to 50% [6]. The lethal dose of amanita toxin is 0.1 mg/kg of body weight, and, therefore, severe poisoning can occur with only 5 to 7 mg of amanita toxin, which is the dose that can be found in a single mushroom [6]. Amatoxin has high thermal stability; it is very soluble in water, resistant to enzymatic degradation, and as such is very toxic (it cannot be destroyed by boiling or drying) [7]. Moreover, amatoxins are not subject to enzymatic degradation or the action of acids, so they are not inactivated after entering the gastrointestinal tract. Amatoxin is easily absorbed from the gastrointestinal system, does not bind to albumin, is quickly eliminated from the blood, within 48 hrs it is distributed to the liver and kidneys [8]. The liver is the primary target organ of amatoxin toxicity, and the hepatocellular effect is the most severe manifestation of *A. phalloides* poisoning. This toxin is not metabolized in the body and is excreted from the body mainly through urine and a small amount through bile [9]. The mortality rate in these patients is correlated with the degree of liver damage, the ability of the remaining healthy part of the liver to regenerate, as well as the degree of expression of complications that may develop during intoxication. In addition to hepatotoxicity, amatoxin also exhibits nephrotoxicity, probably due to the dominant route of toxin elimination through the kidneys [10].

Clinical symptoms and signs of amatoxin poisoning manifest themselves differently and can range from simple gastroenterological disorders to fatal outcomes. Clinical symptoms are primarily caused by toxic damage to the liver and, to some extent, the kidneys [11].

Currently, there are no clear guidelines in the literature for treating the acute phase of amanitine syndrome caused by mushroom ingestion [12]. Symptomatic and supportive therapy is aimed primarily at complaints related to the gastrointestinal tract, but also at alleviating symptoms and signs resulting from hepatic encephalopathy [12]. It is recommended to use activated charcoal in the first few hrs after ingestion, as well as adequate rehydration, primarily due to large gastrointestinal losses. Due to the reduced synthetic function of the liver, these patients are prone to bleeding, so blood and blood derivatives are often represented in the treatment of these patients [13]. Since the urinary tract is the main route for eliminating these toxins, forced diuresis is recommended (100–200 ml/hr). This approach is especially important because amanitin also damages renal function in affected patients. After applying conservative measures, in case of inadequate response, the possibility of hemodialysis should be considered, especially in patients with uremic encephalopathy, hyperkalemia, acidosis, and fluid overload in the form of pulmonary edema.

Based on previous retrospective studies [13, 14], certain trends can be observed in the survival of patients treated with different substances as potential antidotes. Based on the mortality rate, the authors of these studies concluded that the substance silibinin, alone or in combination with N-acetylcysteine, achieved the best effect in terms of reducing the amatoxin impact. However, further research is underway, which should result in a substance that is a specific antidote for amatoxin.

Intravenous administration of albumin is beneficial in multiple ways for patients with cirrhosis and hepatic insufficiency, achieving its effects through several different mechanisms. Namely, albumin is an essential molecule involved in detoxification by binding different substances, and is therefore very important in various liver diseases. This characteristic of albumin is the basis for the use of albumin as a binding and filtration molecule in albumin-based dialysis devices, which recommends these devices for patients with liver failure [15].

Albumin dialysis is an extracorporeal non-biological mechanism of liver support, and is chosen therapy for patients with liver failure of various etiologies [16]. There are several commercial types of albumin dialysis, such as the molecular adsorbent recycling system, single-pass albumin dialysis (SPAD), or the Prometheus system. SPAD is the simplest form of albumin dialysis and is based on the general principles of hemodialysis and hemofiltration. The SPAD procedure is performed on a standard machine for continuous veno-venous hemodiafiltration, where the patient's blood passes through a standard filter impermeable to albumin and is filtered, but with the use of dialysate containing albumin in a concentration of 2–5%. This removes protein-bound molecules that are small enough to pass through the membrane pores, as well as water-soluble toxins that also pass through the membrane [17].

In the clinical picture of patients with liver failure, due to compromised detoxification, synthetic, metabolic, and regulatory functions of the liver are often present with life-threatening disorders such as acute renal insufficiency due to hepatorenal syndrome, hepatic encephalopathy, cerebral edema, hemorrhage, clinically significant hypotension, and infection progressing to multiorgan dysfunction. One of the primary mechanisms of the origin of these disorders is the accumulation of various toxins that the insufficiently functioning liver is unable to remove. The effects of these substances, such as ammonia, bilirubin, bile acids, nitrogen oxides, various free radicals, and cytokines, lead to the listed life-threatening conditions [16, 18].

Regarding the rapid clearance of amatoxin from the blood, it has been questioned whether extracorporeal purification techniques, such as hemodialysis, albumin dialysis, and plasmapheresis, are useful for patients with amanitin syndrome at all. However, it has been practically proven that the use of albumin dialysis for patients with liver failure caused by mushroom poisoning increases the incidence of survival [15]. The reason for this is that, besides amatoxin, albumin dialysis can also filter out other substances that are in excess in the blood, primarily due to compromised liver function, such as ammonia.

Considering the limited amount of data available in the literature regarding extracorporeal support, particularly SPAD albumin dialysis, in conditions caused by mushroom intoxication, the aim of this case report was to highlight the potential beneficial effects of this procedure on patient survival and treatment outcomes. The result of this case report indicates the potential of albumin dialysis in treating the condition, as well as the importance of a multidisciplinary approach.

Case report

A case of mushroom poisoning of eight people was registered in the vicinity of Šabac, Serbia, at the beginning of October 2022. The onset of the disease was characterized by non-specific symptoms of the gastrointestinal tract in the form of nausea, vomiting, and abdominal pain, and all the poisoned persons reported themselves to the local Healthcare Center for treatment. After it was found out that all eight patients had consumed mushrooms bought at the city market and from the same seller, alimentary intoxication with mushrooms was suspected. After the initial assessment and triage, three patients with the most severe clinical picture were referred to the National Poison Control Center, Clinic for Emergency and Clinical Toxicology of the Military Medical Academy in Belgrade. One female patient, out of the three referred patients, was admitted in hemorrhagic shock. She was quickly subjected to cardiopulmonary resuscitation measures, and after two days, a fatal outcome was recorded. The second patient had less expressed symptoms and signs and was discharged after a few days in good general condition. The third patient, 48 years old, was admitted to the Clinic for Emergency and Clinical Toxicology of the Military Medical Academy, Belgrade, with non-specific gastrointestinal symptoms in the form of nausea, vomiting, abdominal pain, and watery diarrhea.

On admission to the Intensive Care Unit (ICU) of the Clinic for Emergency and Clinical Toxicology, the patient was adynamic, sweaty, subicteric, tachycardic, and hypotensive. He had a painfully sensitive epigastrium, which forced him into a specific position in bed. Despite this, he was breathing spontaneously with good respiratory parameters. The first results of blood analysis and biochemical parameters showed high values of liver enzymes, bilirubin, and ammonia (Figures 1–3).

According to the anamnestic data, clinical picture, and laboratory values of liver enzymes as well as nitrogenous substances, it was concluded that the patient had alimentary intoxication complicated by acute hepatic insufficiency and acute renal insufficiency manifested by oliguria (Figure 4).

The initial treatment of the patient included the application of the standard protocol used in alimentary intoxication with mushrooms, primarily through intensive parenteral infusion therapy and hepatoprotective application of N-acetylcysteine according to a 21-hr protocol with extended application, as well as silibinin from the second day in a dose of 500 mg every 4 hrs. On the second and third day of hospitalization, the patient underwent extracorporeal detoxification by plasmapheresis with albumin exchange. Since the values of liver enzymes as well as ammonia remained high with the presence of oliguria and consequently high values of nitrogenous substances in biochemical analyses, it was decided on the fourth and fifth day to apply albumin dialysis type SPAD for the first time for patients poisoned by mushrooms. The SPAD procedure was performed at the ICU of the Clinic for Anesthesiology and Intensive Therapy, Belgrade. After this treatment, both the patient's general condition and laboratory parameters, especially liver and kidney

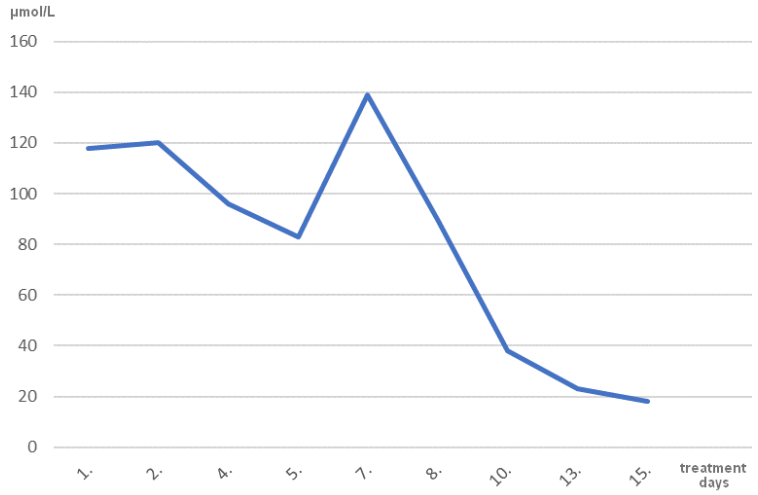

Fig. 1 – Ammonia concentration in blood during treatment.
***Note*: Ammonia reference physiological values are 11-32 µmol/L.**

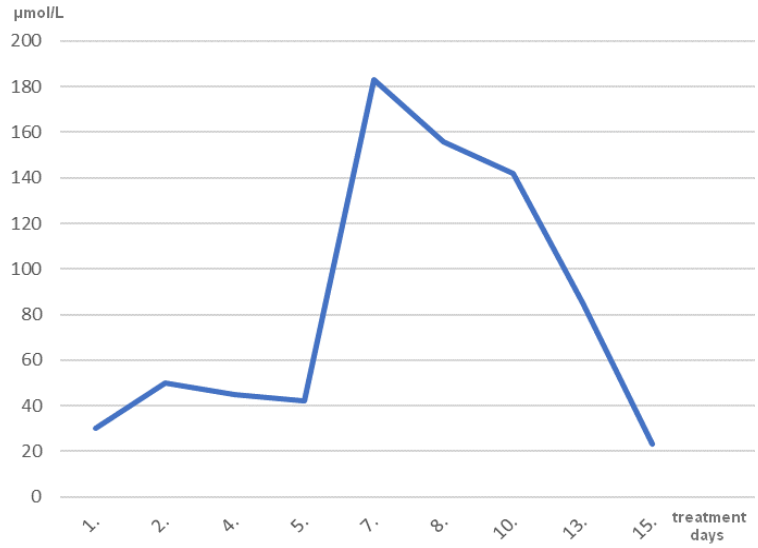

Fig. 2 – Blood bilirubin concentration during treatment.
***Note*: Bilirubin reference physiological values are 0-21 µmol/L.**

Fig. 3 – Concentration of liver enzymes in blood during treatment.
AST – aspartat aminotransferaza; ALT– alanin aminotransferaza; LDH – laktat dehidrogenaza.
***Note*: AST, ALT, and LDH reference physiological values are 0-37 U/L, 10-49 U/L, and 120-246 U/L respectively.**

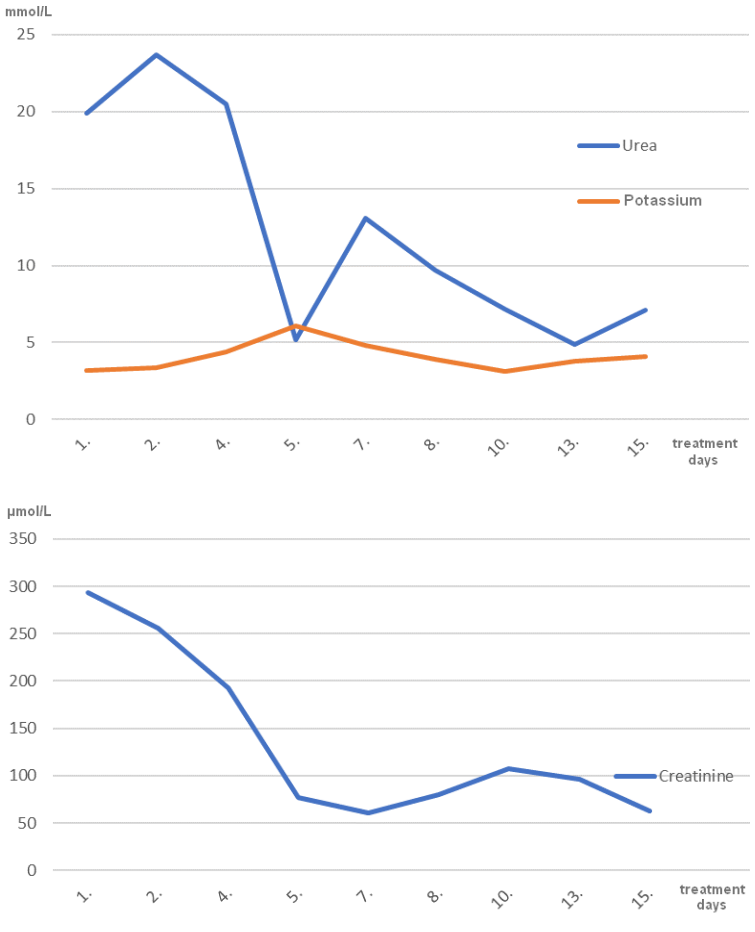

Fig. 4 – Concentration of laboratory parameters of renal functions in blood during treatment: A) urea, kalium, and B) creatinine.
***Note*: Urea, potassium, and creatinine reference physiological values are 2.5-7.5 mmol/L, 3.5-5.1 mmol/L, and 44-88 µmol/L respectively.**

function, were improved. Due to the still present oliguria, renal support in the form of hemodialysis was continued.

Still, the improvement of the condition was only transient. On the seventh day of hospitalization, the patient's general condition worsened again. This was manifested by a deterioration of consciousness, and for the first time, respiratory function disorders appeared, including hyperventilation, decreased partial pressure of oxygen in arterial blood, and reduced blood oxygen saturation. Therefore, on the seventh day of hospitalization, the patient had to be intubated and subjected to mechanical ventilation measures. As expected, in the laboratory biochemical analyses, an increase in the values of hepatic enzymes and ammonia concentration was observed, which is why this deterioration of the state of consciousness can be characterized as a consequence of hepatic encephalopathy. Furthermore, all biochemical parameters, which indicate the quality of the synthetic role of the liver, show a transient drop in values from the seventh day, which remains for the next few days. Due to the deterioration of the condition, it was decided to repeat the SPAD on the eighth, ninth, and tenth day.

Following these procedures, there was an improvement in the general condition, as well as in the values of the monitored biochemical parameters. After eight days, the patient was weaned from mechanical ventilation, with spontaneous breathing, and his respiratory parameters were within physiological limits. Since confusion and disorientation continued occasionally, therapy for hepatic encephalopathy aimed at fixing free ammonia (lactulose, Hepa-Merz®, and Normix®) was continued for the next ten days after consulting a gastroenterologist.

From the second to the fourth day, the patient developed manifest gastrointestinal bleeding, presenting as hematemesis and hematochezia. The condition was treated conservatively with proton pump inhibitors and procoagulant drugs, along with the replacement of blood and blood products. The assumption is that the bleeding has occurred primarily due to a reduced synthetic function of the liver, and due to the risk of invasiveness of the procedure itself and the creation of major bleeding, the endoscopic procedure was not indicated.

In the further course of treatment, the clinical condition stabilized, and the liver and kidney function parameters normalized. Physical therapy was initiated, first with exercises performed in bed, followed by verticalization of the patient.

The entire treatment of this patient, except for the duration of the SPAD procedure, was carried out at the ICU of the Clinic for Emergency and Clinical Toxicology and involved a multidisciplinary approach by doctors of various specialties.

Discussion

Poisoning with amatoxin, the dominant toxin of the mushroom *A. phalloides*, has a high mortality rate, and the primary cause of this is liver lesions, which occur in large numbers of patients poisoned by this toxin [18]. The degree of survival is correlated with the degree of liver damage, the ability of the remaining part of the liver to regenerate, and the degree of expression of complications that may develop during intoxication. As already mentioned, an effective antidote for this toxin has not yet been identified, so the treatment strategy is based on symptomatic and supportive therapy. In the initial phase of treatment, according to existing recommendations, silibinin and N-acetylcysteine were used. However, analyses and studies revealed that these treatments did not yield the expected results, and the mortality rate remained high [19]. Symptomatic and supportive therapy was represented in the treatment, primarily through aggressive hydration and forced diuresis, electrolyte replacement, and, due to gastrointestinal bleeding, the patient received replacement blood and blood derivatives.

Following the existing protocol for the treatment of this type of intoxication, the patient underwent plasmapheresis as a type of extracorporeal blood purification technique [20–22]. Plasmapheresis as a method involves taking venous blood, separating plasma from blood cells (by centrifugation or membrane filtration), and reinfusing blood cells with autologous plasma or an adequate substitute (most often 5% albumin solution or fresh frozen plasma). Although plasmapheresis is often used in various intoxications, clear evidence of the benefit of this procedure in mushroom intoxication is still lacking [22]. Additional difficulties in analyzing the success of the procedure exist because plasmapheresis is rarely used alone in the treatment of intoxication, but is almost always combined with the use of antidotes or some other type of extracorporeal filtration such as hemodialysis. Plasmapheresis reduces the concentration of amatoxin in the blood by removing the toxin bound to the plasma protein. The results obtained in the filtration of toxins by plasmapheresis are best when the toxin does not have a fast metabolism, when it has a high affinity for protein as well as a small volume of distribution. Since amatoxin metabolizes very quickly, the role of plasmapheresis in the treatment of amatoxin intoxication is debatable. Study results are conflicting, with some suggesting an effect on mortality and others finding no impact [23, 24].

For the first time in our institution, and according to the available data from the literature, most likely for the first time in our country, SPAD was applied to this patient in the treatment of conditions caused by amanitin intoxication, i.e., mushroom poisoning.

Based on the laboratory results (elevated ammonia and liver enzyme levels in the blood) and the clinical picture, it was concluded that the patient had developed signs of hepatic insufficiency and encephalopathy. These were manifested by deterioration of consciousness and, consequently, impairment of other vital functions, especially breathing and hemodynamics. Therefore, the decision was made to treat the patient with SPAD as a form of extracorporeal support of liver function. Furthermore, this method supported the function of the kidneys, since the clinical picture was characterized by oliguria. Previous experiences in the application of different types of extracorporeal filtration in liver failure of various etiologies point out that albumin dialysis has given good results in supporting, above all, the detoxification role of the liver [25]. SPAD was applied to the patient on the fourth and fifth day of treatment in our institution, after which there was an improvement in both the clinical picture and the monitored values of biochemical parameters, primarily liver function. The improvement was only temporary. After the patient's condition worsened again—primarily with deterioration of consciousness and respiratory function—biochemical parameters also indicated impaired detoxification and synthetic function of the liver. For this reason, SPAD had to be repeated three more times, on the eighth, ninth, and tenth day of hospitalization. After these treatments, a definite improvement in the patient's condition was observed.

Obviously, it is necessary to have more experience and perform more procedures to reach the correct recommendation on when to include extracorporeal filtration in the treatment of these patients, as well as the extent and type of this procedure that is best for the patient. Besides, this is the first patient who had a severe clinical picture of hepatic encephalopathy with a consequent disturbance of the state of consciousness as well as the need for mechanical ventilation for adequate respiratory exchange, for whom no fatal outcome was recorded in the end. The assumption is that one of the reasons for this is the decision to include the support of hepatic function with extracorporeal circulation in the treatment for the first time. Further experiences will show the credibility of this assumption as well as determine the right place and the right way to include albumin dialysis as an extracorporeal type of liver function support, which is particularly compromised in patients intoxicated by mushrooms.

Conclusion

Based on the available data from the professional literature, it can be noted that the pathophysiology of amanitin syndrome in alimentary intoxication with mushrooms has not yet been sufficiently studied and explained. This fact may also be a partial explanation for the continued absence of an effective antidote in the treatment of amanitin syndrome. Therefore, the treatment of this syndrome is a constant challenge primarily for toxicologists, but also for anesthesiologists-intensivists, nephrologists, and gastroenterologists-hepatologists. In that regard, until a specific and effective antidote for mushroom toxins, especially amanitin, becomes available to modern medicine, albumin dialysis can serve as a useful supportive measure. It is particularly valuable in the advanced stages of intoxication when the clinical picture includes symptoms and signs of hepatic insufficiency, and also for intoxicated patients with renal insufficiency.

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