Mushroom Poisoning Presenting With Acute Kidney Injury and Elevated Transaminases

Mathilde Beaumier[1,2,3], Jean-Philippe Rioult[4], Marie Georges[5], Isabelle Brocheriou[5], Thierry Lobbedez[1,2,6] and Antoine Lanot[1,2,3]

[1]Néphrologie, Normandie University, UNICAEN, CHU de Caen Normandie, Caen, France; [2]UFR de Médecine, Normandie Université, Unicaen, Caen Cedex, France; [3]"ANTICIPE" U1086 INSERM-UCN, Centre François Baclesse, Caen, France; [4]Normandie Université, UNICAEN, ABTE EA 4651, Centre François Baclesse, Caen, France; [5]Pathology Unit, AP-HP, Pitie-Salpetriere Hospital, Paris, France; and [6]Registre de Dialyse Péritonéale en Langue Française (RDPLF), Pontoise, France

Correspondence: Antoine Lanot, CUMR - Nephrology, Dialysis and Transplantation, CHU de Caen – CS 30001 – 14033 Caen Cedex 9, France. E-mail: antoine.lanot@gadz.org

Received 15 January 2019; revised and accepted 25 February 2019; published online 4 March 2019

Kidney Int Rep (2019) **4,** 877–881; https://doi.org/10.1016/j.ekir.2019.02.016

INTRODUCTION

It is estimated that out of the 100,000 or more species of mushrooms worldwide, more than 100 are toxic. In the United States, the National Poison Data System reported 133,700 cases of mushroom exposure from 1999 to 2016, and 6136 cases in 2017.[1,2] Identifying the specific mushroom species involved is mandatory because specific treatment exists for some mushroom poisoning. A recent algorithm to group the multiple species and syndromes of mushroom poisoning into 6 presenting syndromes has been proposed by White *et al.*, depending on the clinical presentation.[3] Among severe mushroom intoxications, amatoxin syndrome accounts for 68% to 89% of fatalities.[1] Mushroom poisoning usually causes gastroenteritis prodrome. Hepatotoxicity is rare but is associated with a limited group of mushrooms. Renal failure can be due to severe dehydration or to specific toxin damage. Early syndromes (onset of nausea and vomiting in <6 hours) are usually associated with a good prognosis, whereas delayed syndromes carry risk of organ failure, with the liver and kidney as the key organs of concern.

Herein, we present 2 cases of hepato-nephritis after mushroom ingestion in a married couple, with a review of mushroom poisoning, toxidromes, diagnosis, and treatment.

CASE PRESENTATION

A 61-year-old woman and her 63-year-old husband presented to the emergency department with identical symptoms evolving for several hours. They had gone for walk during October in a French forest in Normandy, where they picked mushrooms that they identified as King bolete *(Boletus edulis* or Cep of Bordeaux). Mushrooms were cooked the day that they were picked, and eaten the next day in the evening.

Past medical history included diabetes, hypertension, and arrythmia for the wife, and hypertension, diabetes, and myocardial infarction for the husband. They described severe diarrhea (10 stools per day), nausea, and vomiting occurring 10 hours after eating the mushrooms that they had picked and cooked. They went to the emergency department because of the severity of the symptoms around 20 hours after the ingestion. Blood pressure was 95/60 mm Hg for the wife, with a conserved diuresis, and 117/71 mm Hg for the husband, associated with anuria. Physical examination was similar in both patients, with a poor skin turgor. The abdomens were soft, without distension, rebound, tenderness, or guarding, and the remainder of the general examination results were normal. Laboratory results are presented in Table 1 for the 2 patients. Both patients presented with acute kidney failure, which was complicated for the husband by metabolic acidosis and hyperkalemia. Rhabdomyolysis was ruled out by normal creatine phosphokinase levels. Urine dipsticks were negative for proteinuria. Renal ultrasound findings were normal. Electrocardiograms showed no conduction abnormality, but peaked T waves for the husband.

In the present cases, renal failure was the prominent feature, which is unusual in mushroom poisoning. The

Table 1. Laboratory results on admission

Test	Wife	Husband	Reference range
Serum creatinine (mg/dl)	2.2	2.2	0.6–1.2
Blood urea nitrogen (mg/dl)	92	46.6	7–20
Potassium (mEq)	4.1	7	3.5–5
Bicarbonates (mEq)	15.5	10	24–30
Hemoglobin (g/dl)	11	13.5	13.5–18
Bilirubin (mg/dl)	8	16	1–10
Aspartate aminotransferase (U/l)	289	173	5–35
Alanine aminotransferase (U/l)	140	150	5–35
Alkaline phosphatase (U/l)	117	64	30–105
γ-Glutamyltransferase (U/l)	649	439	5–55
Prothrombin time (%)	81	56	70–100
Creatine phosphokinase (U/l)	36	133	30–200

onset of symptoms was too early to fit an orellanine syndrome. Clinical presentation fitted an amatoxin syndrome.

Testing for amatoxin was positive in urine and plasma samples in both patients, using the enzyme-linked immunosorbent assay method. The testing confirmed that patients consumed mushroom, mistaken for *Boletus edulis,* containing amatoxin (Figure 1). These findings consolidated our diagnosis of amatoxin syndrome.

Intravenous hydration including saline solution and sodium bicarbonate was first administered. The husband also received insulin and glucose, which normalized kalemia within 12 hours. Intravenous *N*-acetyl-cysteine was started on the first day of hospitalization according to the following protocol: 150 mg/kg in 15 minutes, then 50 mg/kg in 4 hours, then 100 mg/kg in 16 hours, and finally 150 mg/kg per day until normalization of transaminases. Intravenous silymarin was administered according to poison center advice: 5 mg/kg in 2 hours followed by perfusion of 5 mg/kg 4 times a day for 3 days.

The evolution of laboratory results is shown in Figure 2. Renal function continued to decrease during 48 hours (creatinine 4.61 mg/dl for the husband and 2.65 mg/dl for the wife). Transaminase levels first increased until the third day of hospitalization, without hepatocellular insufficiency, and then decreased slowly. Hepatic function was normal 7 days after the ingestion. Partial recovery of renal function was observed in both patients (creatinine 2.97mg/dl for the husband and 1.72 mg/dl for the wife). Eight days after the mushroom ingestion, the husband presented with severe renal deterioration with oliguria. Creatinine rose to 10.6 mg/dl without hyperkalemia. Hemodialysis was required, and, given the absence of renal recovery, a kidney biopsy was performed 1 month after ingestion, showing fibrosis in 70% of parenchyma and acute tubular necrosis (Figure 3). Because of the unusual evolution in the case of the husband, we suspected a co-intoxication with *Cortinarius* leading to an orellanine syndrome. Tests were performed on a urine sample collected on the first day of hospitalization to assess for the presence of orellanine toxins, but unfortunately, because of technical difficulties in isolating the toxin, results were not conclusive. The wife recovered baseline renal function, whereas the husband presented with chronic end-stage kidney failure requiring chronic dialysis.

DISCUSSION

Four toxidromes due to mushroom poisoning include kidney failure (Table 2).[3,4] Amatoxin syndrome is the most usual intoxication. Toxicity is due to 2 cyclopeptides: phallotoxin, which is not absorbed by the intestine and causes gastrointestinal symptoms; and amatoxin, which inhibits RNA polymerase II, resulting in deficient protein synthesis and cell death. Cells with a high metabolism are mainly affected: hepatocytes, cells of the proximal tubules of the kidneys, and intestinal mucosa. Amatoxins are thermostable, so cooking or freezing does not alter their toxicity. Clinical presentation starts 6 to 12 hours after mushroom ingestion. The first stage includes a cholera-like diarrhea, vomiting, and abdominal pain. Thereafter, patients show clinical improvement. However, cytolytic hepatitis occurs

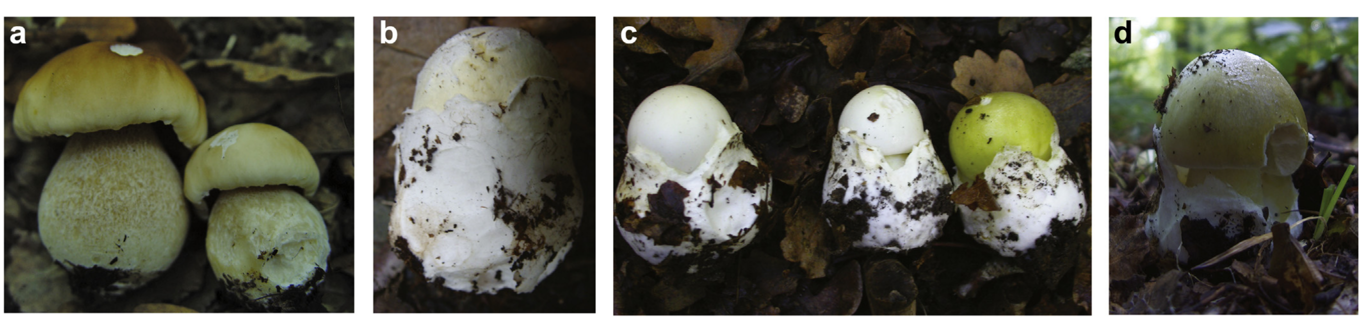

Figure 1. Photographs of the 2 mushroom species suspected to have been mingled by our patients. (a) Edible *Boletus edulis*. (b–d) Young *Amanita phalloides var. alba* at 5 different steps of its growth.

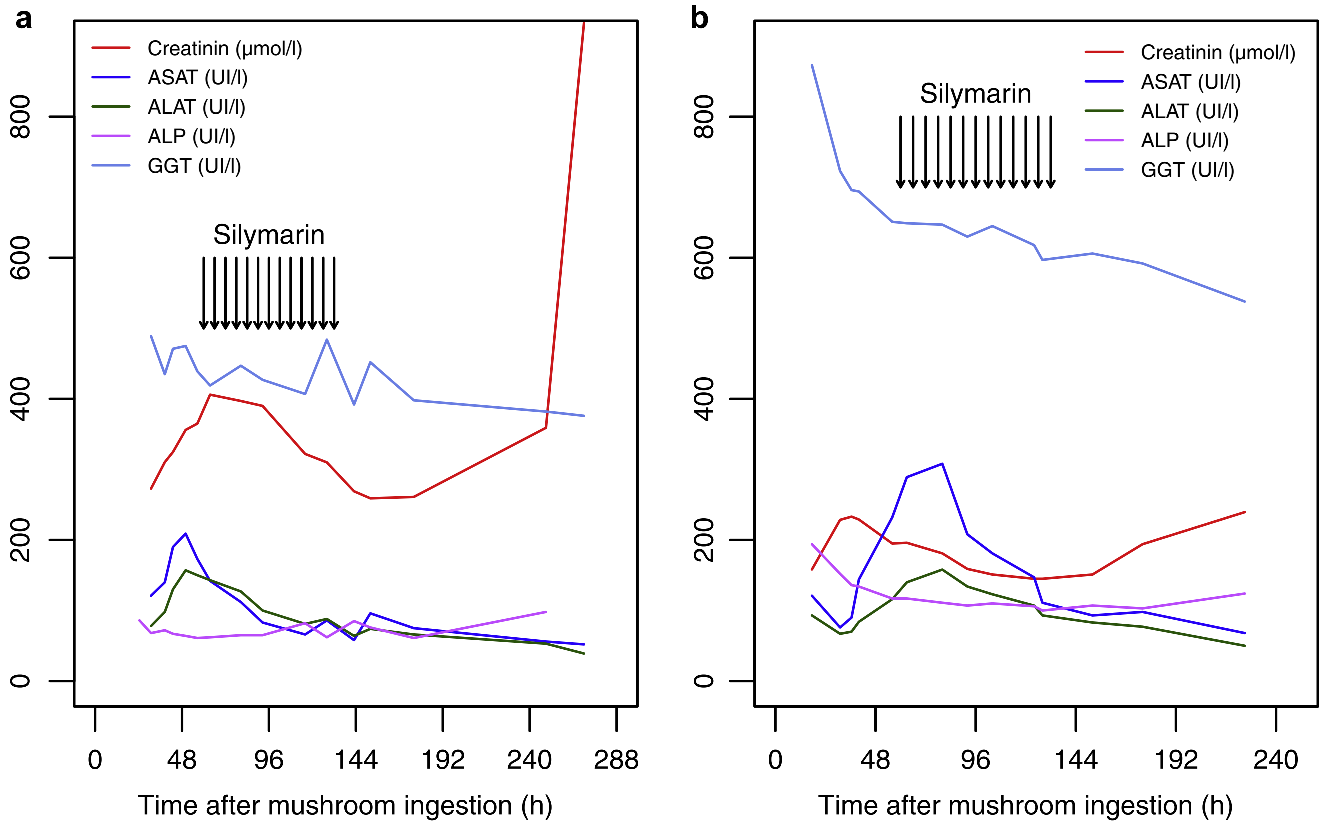

Figure 2. Evolution of laboratory results. (a) Husband. (b) Wife. ALAT, alanine aminotransferase; ALP, alkaline phosphatase; ASAT, aspartate aminotransferase; GGT, γ-glutamyltransferase.

silently. Forty-eight hours or more after the ingestion, the third phase begins, with severe hepatic failure and kidney failure. Ultimately, the pancreas and nervous central system may be affected.[5,6] Orellanine syndrome is due to *Cortinarius*, mushrooms found in Europe, Australia, and Japan. Orellanine inhibits protein synthesis and generates free oxygen radicals, leading to tubulo-interstitial nephritis. Clinical presentation starts with digestive symptoms (nausea, vomiting, and diarrhea) and headache, anorexia, and chills within 24−36 hours after the mushroom ingestion. Oliguric acute kidney failure appears 2 to 20 days afterward, evolving toward terminal chronic kidney disease in 40% to 60% of patients.[4]

In the present cases, renal failure is the prominent feature, which is unusual in mushroom poisoning. The onset of symptoms was too early to fit an orellanine syndrome, and rhabdomyolysis was excluded because creatine phosphokinase levels were within the normal range. The usual mushrooms responsible for an early-onset renal syndrome, from the norleucine group, are not found in the North of France.

Patients with kidney failure secondary to fungal toxin ingestion can present with leukocyturia (50%), hematuria (45.2%), and proteinuria (30.6%). Kidney biopsy shows tubulo-interstitial nephritis with tubular necrosis, interstitial edema with inflammatory infiltrates, and interstitial fibrosis.[7] Diagnosis is confirmed by finding the toxin in body fluids or tissues. Amatoxins can be found in urine until 4 days after ingestion, in plasma in the first 36 hours, and also in gastrointestinal fluids, feces, and tissues (liver and kidney).[8] Orellanine can be found in plasma and urine, but confirmation of orellanine intoxication is difficult because of the latency of the symptoms. At the time that the diagnosis is suspected, toxins are often undetectable in fluids. Nevertheless, toxins persist several months in renal parenchyma. It has to be noted that the amatoxin concentration does not correlate with the severity of poisoning.[9]

Recently, White *et al*. proposed a new classification of mushroom poisoning. It is divided into 6 groups, depending on the predominant clinical symptoms. Nevertheless, diagnosis is often difficult because of atypical clinical presentation and frequent co-ingestion of several types of mushrooms. In an American study, 86% of mushroom exposure was of unknown varieties.[1] The easier way to identify the mushroom is to obtain a photograph of the picked mushrooms and to

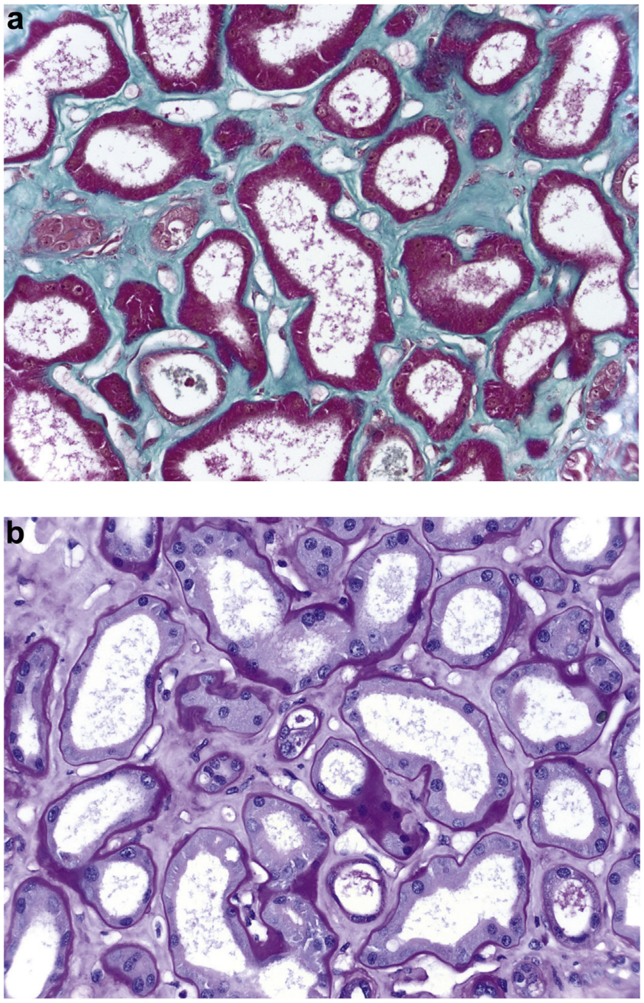

Figure 3. Kidney biopsy specimens from biopsy performed in the husband. (a) Masson's trichrome showing severe interstitial fibrosis, tubules with flattened epithelial cells, and degenerated epithelial cells in the tubular lumen. (b) Periodic acid–Schiff stain with dilated tubular lumen, and loss of brush border of flattened epithelial cells.

show it to a skillful mycologist, but it is rarely available. That is why careful questioning is important. The physician should try to find out where the mushroom was picked and under which kind of tree, for how long and how it was stored, and how it was cooked. Then, the delay and determination of the toxidrome should guide the clinician. White *et al*. propose an algorithm divided into 6 sequential steps to help the physician.[3] In the case of our patients, considering first the gastrointestinal symptoms would lead us to the suspected diagnosis of amatoxin syndrome, whereas the diagnosis remains "uncertain" when starting with the symptom abnormal renal function.[3]

There is no uniformly accepted treatment protocol for mushroom poisoning. Use of activated charcoal is controversial, as poisoned patients are usually asymptomatic several hours after mushroom ingestion, and activated charcoal usually is useful only in the first 6 hours after ingestion. However, due to enterohepatic circulation of fungal toxins, most authors recommend the administration of multiple-dose activated charcoal during the first 3 days after ingestion. Supportive care includes rehydration and correction of electrolytic abnormalities. Vomiting and diarrhea must be tolerated because they allow the elimination of toxins.

No specific amatoxin antidote is available, but some therapeutic agents are useful. Silymarin, a natural extract from milk thistle, contains silibinin, which inhibits amatoxin uptake into the hepatocyte if given in the first 3 days after ingestion. Silymarin should be administered with an i.v. loading dose of 5 mg/kg over 1 hour, followed by a continuous i.v. infusion of 20 mg/kg per day for 3 to 6 days according to

Table 2. Characteristics of toxidromes associated with renal failure after mushroom poisoning

Toxidrome	Amatoxin syndrome Group 1A	Early-onset renal failure Group 1B	Orellanine syndrome Group 1C	Rhabdomyolysis syndrome Group 3A and 3B
Symptoms	Gastroenteritis Hepatic failure Acute renal failure	Gastroenteritis Acute renal failure	Gastroenteritis Acute renal failure	Gastroenteritis Muscle pain Acute renal failure
Onset of symptoms	Late onset toxicity (within 6–24 h)	Early-onset gastrointestinal toxicity (30 min–1 h) Late-onset renal toxicity (within 12–24 h)	Delayed-onset toxicity (within 3–20 days)	Rapid-onset myotoxicity (within 2 h) or delayed-onset toxicity (within 24–72 h)
Mechanism of renal toxicity	Inactivation of RNA polymerase II and inhibition of protein synthesis	Unknown	Interruption of production of adenosine triphosphate at proximal tubular brush border	Rhabdomyolysis
Mycotoxin	Cyclopeptides: - Amatoxin - Phallotoxin	Allenic norleucine	Orellanine Cortinarin A and B	Cycloprop-2-ene carboxylic acid Saponaceolide B and M
Species	*Amanita phalloides* *Amanita verna* *Amanita virosa* *Lepiota helveola* *Galerina marginata* *Galerina autumnalis*	*Amanita smithiana* *Amanita pseudoporphyria* *Amanita proxima* *Amanita gracilior* *Amanita echinocephala*	*Cortinarius orellanus* *Cortinarius speciosissinus*	*Tricholoma equestre* *Tricholoma terreum* *Russula subnigricans Leccinum* spp. *Boletus* spp.

Adapted by permission from White J, Weinstein SA, De Haro L, et al. Mushroom poisoning: a proposed new clinical classification. *Toxicon.* 2019;157:53–65[3] and Springer Nature, *Toxicological Reviews,* New syndromes in mushroom poisoning, Saviuc P, Danel V. Volume 25, pages 199–209. Copyright © 2006.[4]

Table 3. Teaching points

- Early syndromes (<6 h) are usually associated with a good prognosis, whereas delayed syndromes have poorer outcomes.
- Four toxidromes due to mushroom poisoning include kidney failure: early-onset renal failure, amatoxin syndrome, orellanine syndrome, and rhabdomyolysis syndrome.
- Finding the specific mushroom species involved is mandatory, using careful questioning and photographs, because specific treatment exists for some mushroom poisoning.
- Amatoxins can be found in urine until 4 days after ingestion, in plasma in the first 36 h, and also in gastrointestinal fluids, feces, and tissues (liver and kidney).
- Combined use of silymarin and *N*-acetyl-cysteine (NAC) seems to be the most effective therapy in amanita poisoning and should be started as soon as possible.

transaminase level normalization. *N*-acetylcysteine, a glutathione precursor, has a hepatoprotective effect. Other treatments such as i.v. benzylpenicillin, vitamin C, and cimetidine have been used with less success in amanita poisoning. Recently, a new treatment, polymixin B, showed promising results among animals by preventing hepatic and renal damage and by increasing survival.[10] If the results are confirmed among patients, it might be an antidote for amatoxin poisoning. Nowadays, the association of silymarin and *N*-acetylcysteine seems to be the most effective therapy in amanita poisoning. Treatment should be started as soon as possible. Fulminant hepatic failure sometimes requires liver transplantation.[9]

No antidote is available for orellanine or allenic norleucine, and then treatment is only supportive.[4] Renal prognosis is frequently poor, evolving toward end-stage renal disease requiring chronic dialysis or kidney transplantation.

Hemodialysis is not effective to eliminate mycotoxins and is indicated only in the case of severe acute kidney injury. Plasma exchanges and hemoperfusion have been used, with a lack of efficacy, probably because mycotoxins quickly disappear from plasma.[7] The initial evolution of our 2 patients' cases after treatment with NAC and silymarin was positive, making us think that these treatments had been beneficial. Unfortunately, kidney function worsened in a second step in the husband's case. Renal injury was severe, as assessed by histological analysis, with 70% of fibrosis in the renal parenchyma.

In conclusion, we expose here the cases of 2 married patients presenting with acute tubular necrosis due to amatoxin poisoning, after ingestion of young *Amanita phalloides* mistaken for *Boletus edulis*. These cases underline the difficulties in making the diagnosis of mushroom poisoning and determining the exact species of mushroom concerned (Table 3). Nephrologists should be aware of the main features of these life-threatening poisonings, especially since an antidote is available and effective in certain cases, depending on the responsible mushroom species.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Brandenburg WE, Ward KJ. Mushroom poisoning epidemiology in the United States. *Mycologia*. 2018;110: 637–641.
2. Gummin DD, Mowry JB, Spyker DA, et al. 2017 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th annual report. *Clin Toxicol*. 2018;56(12):1213–1415.
3. White J, Weinstein SA, De Haro L, et al. Mushroom poisoning: a proposed new clinical classification. *Toxicon*. 2019;157:53–65.
4. Saviuc P, Danel V. New syndromes in mushroom poisoning. *Toxicol Rev*. 2006;25:199–209.
5. Diaz JH. Syndromic diagnosis and management of confirmed mushroom poisonings. *Crit Care Med*. 2005;33:427–436.
6. Broussard CN, Aggarwal A, Lacey SR, et al. Mushroom poisoning—from diarrhea to liver transplantation. *Am J Gastroenterol*. 2001;96:3195–3198.
7. Danel VC, Saviuc PF, Garon D. Main features of Cortinarius spp. poisoning: a literature review. *Toxicon*. 2001;39:1053–1060.
8. Jaeger A, Jehl F, Flesch F, et al. Kinetics of amatoxins in human poisoning: therapeutic implications. *J Toxicol Clin Toxicol*. 1993;31:63–80.
9. Enjalbert F, Rapior S, Nouguier-Soulé J, et al. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol*. 2002;40:715–757.
10. Garcia J, Costa VM, Carvalho AT, et al. A breakthrough on *Amanita phalloides* poisoning: an effective antidotal effect from polymyxin B. *Arch Toxicol*. 2015;89:2305–2323.