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### ► To cite this version:

Jeremy Lecot, Morgane Cellier, Arnaud Courtois, Dominique Vodovar, Gaël Le Roux, et al.. Cyclopeptide mushroom poisoning: A retrospective series of 204 patients. *Basic and Clinical Pharmacology and Toxicology*, 2023, 132 (6), pp.528-537. 10.1111/bcpt.13858 . hal-04059044

**HAL Id: hal-04059044**

**<https://hal.science/hal-04059044>**

Submitted on 15 May 2023

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## Cyclopeptide mushroom poisoning: a retrospective series of 204 patients

Cyclopeptide mushroom poisoning series

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**Keywords:** Mushroom poisoning, cyclopeptide mushroom, Poison control centers, Amatoxins, *Amanita phalloides* poisoning, acute liver failure, severity factor

### Abstract

Cyclopeptide mushroom poisoning is responsible for 90-95% of deaths from macrofungi ingestion. The main objectives of this study are to describe cases of cyclopeptide mushroom poisoning and to determine risk factors that may influence the severity/mortality of poisoned patients.

We included all cases of amatoxin toxicity reported to two french Poison Centers from 2013 through 2019. We compared the severity with the Poison Severity Score (PSS) and the outcomes of patients using simple logistic regression and multinomial logistic regression.

We included 204 cases of amatoxin toxicity. More than three-quarters developed an increase in AST and/or ALT (78.1%) and over half developed a decrease in prothrombin ratio (<70%: 53%) and/or Factor V (<70%: 54%). One third developed an acute renal injury (AKI). Twelve patients (5.9%) developed post-poisoning sequelae (persistent kidney injury more than one month after ingestion and liver transplant). Five patients (2.5%) received a liver transplant and 9 died (4.4%).

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/bcpt.13858

The mean time to onset of digestive disorders was shorter in PSS2 and PSS3-4 patients ( $10.9 \pm 3.9$  /  $11.3 \pm 6.3$  hours) than in PSS1 patients ( $14 \pm 6.5$  hours;  $p < 0.05$ ). Patients who died or developed post-poisoning sequelae had more frequently cardiovascular comorbidities compared with recovered patients (60.0% versus 29.5%;  $p < 0.01$ ).

## Introduction

Wild mushroom picking is a traditional and popular activity in many countries. Despite the warnings from health authorities and mycological societies, ingestion of picked poisonous mushrooms is still common and associated with morbidity and mortality. It is estimated that 100 to 200 deaths occur each year in Europe and the United States due to the ingestion of poisonous mushrooms [1]. In France, 10,625 cases of mushroom poisoning were reported to French Poison Control Centers (PCCs) between 2010 and 2017. The number of severe poisoning and death ranged from 11 to 44 per years and from 0 to 5, respectively [2].

Among the poisonous mushrooms, cyclopeptide mushrooms (group I) are involved in 90-95% of deaths from macrofungal ingestion [3,4]. They are found on the five continents [5] and the three genera most often involved in poisonings are *Amanita*, *Galerina* and *Lepiota* [3,6,7]. Three groups of toxins have been identified as being responsible for their toxicity : amatoxins, phallotoxins and virotoxins [8]. Among them, amatoxins are the only toxins found in common amongst the three genera and would be responsible for organ damages [3]. The main molecular mechanism involved in amatoxin-induced toxicity is their irreversible binding to DNA-dependent RNA polymerase II in eukaryotic cells, causing a progressive decrease in mRNA leading to a decrease in protein synthesis and to cell death [3,6,9].

The clinical presentation of cyclopeptide mushroom poisoning, also called phalloidian syndrome, is typically divided into three phases [10]. After a latency period of 6 to 12 hours (sometimes even of 24 hours) [5,10] severe gastrointestinal symptoms, including profuse diarrhea and vomiting associated with abdominal pain, appear (Phase I). They can be responsible for severe dehydration and its consequences (acute kidney injury, electrolyte and acid-base imbalance, and even hypovolemic shock). The Phase II occurs within 24 to 48 hours after ingestion, when the patient's clinical condition improves after rehydration, but hepatic cytolysis appears, most often asymptomatic. In severe cases, phase II progresses progressively to phase III of hepatic failure and acute renal injury which can lead to death despite supportive care [10,11]. In addition to supportive care, fluid/electrolyte resuscitation, and even liver transplantation in the most severe cases, the management of cyclopeptide mushroom poisoning relies on the administration of antidotes (penicillin G and silibinin, alone or in combination) whose exact effectiveness on prognosis remains to be demonstrated. N-acetyl cysteine (NAC) is also frequently administered not as an antidote but for its hepatoprotective effects [3].

Only few case series of cyclopeptide mushroom poisoning have been published. Most of them are single-center studies, with few patients, and do not describe in detail the clinical/biological course and management. For mushroom exposures/poisonings it is likely that poison control centers (PCCs) are contacted more frequently than for other exposures/poisonings, especially for severe intoxications, because of the need to identify the mushrooms involved and the requirement of specific treatments.

We carried out a retrospective study of the cases of mushroom cyclopeptide poisoning recorded at the Angers and Bordeaux PCCs, which cover the territories where mushroom picking is most

traditional in France (rural and forest areas of western France). The main objectives of this study are to describe and analyze the cases of cyclopeptide mushroom poisoning over seven years and to determine the risk factors that may influence the severity/mortality of patients.

## **Materials and methods**

### Data source:

In France, eight PCCs answer questions 24/7 about toxic exposures from the public, caregivers and health authorities. For each case, real-time data collected within the French National Database of Poisonings (FNDP, French Ministry of Health) includes patient characteristics (age, weight, medical history), exposure circumstances (dose, route, context, time of exposure, symptoms), management, and outcome. The FNDP is registered and approved by the French National Commission on Informatics and Liberty. PCCs anonymously register exposure cases in the FNDP and informed consent of the patients is waived in agreement with French law [12]. The study protocol was approved by the Ethics Committee of Angers University Hospital and was registered under the number 2022-026.

### Data selection:

We conducted a bicentric retrospective study and extracted from the FNDP all cases of cyclopeptide mushroom poisoning reported to the PCCs of Angers and Bordeaux University Hospitals between 1 January 2013 and 31 December 2019. The diagnosis of cyclopeptide mushroom poisoning was based on the history and the identification of the ingested mushroom, lab test abnormalities, clinical symptoms and their time to onset, and the assay of amanitins. Cases of poisoning with a calculation of zero causality, not attributable/not applicable and not ruled out/doubtful causality were not included. When the contaminating meal was shared by several people, each person represented an individual case.

For each poisoning case, the data collected included the patient (age, gender, previous medical history), poisoning (circumstance of exposure, formal identification of the mushroom by a mycologist or positive (>1 ng/mL) amanitin urine detection using the BÜHLMANN Amanitin ELISA kit<sup>®</sup> when available, clinical symptoms and biological findings as well as the delay between mushroom ingestion and their onset), management (including the use of antidote) and the outcome (length of hospital stay, liver transplantation and death). We used the Poisoning Severity Score (PSS) [13] to grade severity: 1 for low severity, 2 for moderate severity, 3 for severe severity, 4 for deaths. Each case was reviewed by a toxicologist to limit the classification bias.

### Statistical analysis:

We expressed results as median [minimum; maximum] and means (standard deviation) for continuous variables and as number (percentage) for non-continuous variables. We compared the means of the maximum values of liver enzymes (AST and ALT) with a Wilcoxon rank sum test with continuity correction. We compared severity using simple multinomial logistic regression and multivariate multinomial logistic regression. We stratified the severity defined by the PSS into 3 strata: PSS 1; PSS 2 and PSS 3-4. We then compared each stratum to the reference stratum PSS=1. We also compared the outcomes of the patients using a simple logistic regression and multivariate logistic regression (recovery versus sequelae and death). Laboratory values returned as "< 10%" were adjusted to 9.99%. Missing data were not attributed. The significance level was  $p < 0.05$ . Analyses were performed with RStudio<sup>®</sup> version 1.3.1093 for Windows<sup>®</sup> (version R 4.0.3) and SAS V9.4 (SAS Inc., Cary, NC USA<sup>®</sup>).

## **Results**

During the study period, 204 cases of cyclopeptide mushroom poisoning were reported to the Angers and Bordeaux PCCs. The mean number per year was  $29 \pm 15.49$  (range from 6 to 47) ([Figure 1A](#)). Most of poisonings occurred in autumn, especially in October ([Figure 1B](#)).

#### Patients' characteristics and severity:

The sex ratio was 1.08 and the mean age was  $54.4 \pm 18.9$  years (range from 1 to 94 years,  $n=202$ ). Sixty-one (61/187 32.6%) patients had a history of cardiovascular disease, 13 (13/189 6.9%) had a history of alcohol use disorder ( $n=13$ ), 7 (7/189 3.7%) had a history of liver disease and 7 (7/189 3.7%) had a history of kidney disease. According to the PSS, 44 patients (21.6%) were PSS1, 56 (27.5%) were PSS2, 95 (46.6%) were PSS3 and 9 (4.4%) were PSS4.

#### Poisoning characteristics:

Except for one case in which the mushroom(s) was(were) ingested voluntarily with the intention of committing suicide, all cases were accidental ingestion of mushroom(s) during a meal. A mycologist formally identified the mushroom(s) in 79 (38.7%) cases. Five species were identified: *Amanita phalloides* ( $n=57$ , 73.1%), *Amanita virosa* ( $n=3$ , 3.8%), *Amanita verna* ( $n=9$ , 11.5%), *Galerina marginata* ( $n=2$ , 2.6%) and *Lepiota brunneoincarnata* ( $n=8$ , 10.3%). Urine detection of amanitin was performed within  $54.4 \pm 33.7$  hours after ingestion in 151 (74.0%) patients. It was negative in 34 (22.5%) and positive in 117 (77.5%) of them. Finally, the cyclopeptide mushroom poisoning was actually documented in 156 (76.5%) patients.

#### Cyclopeptide poisoning associated complications:

All the patients presented gastrointestinal symptoms. Nine (9/198 – 4.6%) patients developed encephalopathy. More than three-quarters of patients developed a hepatic cytolysis (157/201; 78.1%). Peak transaminases were reached within two to three days of ingestion with a similar increase in ALT and AST ( $p=0.058$  - ALT  $n=156$  and AST  $n=154$ ) and more than half had biological and clinical findings compatible with liver failure. Few patients also developed elevated creatinine, thrombocytopenia, hyperbilirubinemia and hyperammonia ([Table 1](#)). Sixty five patient (32.7%) presented an acute renal injury (serum creatinine  $> 1.5$  times baseline) and 33 (50.8%) of them stage 3 (serum creatinine  $> 3.0$  times baseline) according to the staging of KDIGO Clinical Practice Guideline for Acute Kidney Injury [14].

#### Cyclopeptide poisoning management:

Average time from ingestion to emergency room presentation was  $42.2 \pm 31.0$  hours ( $n=188$ ). One-hundred and ninety-four patients (95.0%) were hospitalized after emergency room presentation during  $6.8 \pm 8.2$  days ( $n=194$ ). More than half of the patients (55.2%;  $n=111$ ) were admitted to an intensive care unit and were hospitalized during  $4.8 \pm 4.0$  days ( $n=111$ ). Antidotes were administered in 176 (86.3%) patients, 14 (6.9%) patients required dialysis and 5 (2.5%) received liver transplant ([Table 2](#)).

#### Cyclopeptide poisoning outcome:

One-hundred and eighty-one (89.2%) patients recovered. 12 (5.9%) were considered to have post-poisoning sequelae (persistent kidney injury more than one month after ingestion and liver transplant) and nine (4.4%) died (PSS=4).

#### Identification of risk factors of severe amatoxin severity:

Using univariate analysis, only the presence of at least one comorbidity was significantly higher in the PSS3-4 severity groups compared with the PSS1 severity group ( $p < 0,05$  – [Table 3](#)). Using univariate analysis, only age and the time to onset of gastrointestinal symptoms were significantly higher in the PSS2 and PSS3-4 severity groups compared with the PSS1 severity group ( $p < 0,05$  – [Table 3](#)). After adjusting for sex, the presence of at least one comorbidity and age, the time to onset of digestive disorders was statistically associated with moderate severity (PSS2). After adjusting for sex and age, the presence of at least one comorbidity and the time to onset of digestive disorders were statistically associated with severe severity (PSS3-4) ([Table 3](#)).

#### Identification of risk factors of poor outcome (sequelae and death) after amatoxin poisoning:

Using univariate analysis, patients with poor outcome had a significantly higher age and more frequently had a previous medical history, particularly a previous cardiovascular history, compared with patients who recovered (Table 4). In the group "Death + sequelae", the intoxications severity is distributed as follows: PSS 2: 0; PSS 3: 8 and PSS 4 : 9 cases.

After adjusting for sex, age and time to onset of disorders, poor outcome was significantly higher when the patient had at least one comorbidity (Table 4).

## **Discussion**

#### Poisoning characteristics:

Like most mycological poisonings, amatoxin poisonings are usually autumnal. In fact, autumn is the preferential period of development of the offending mushrooms and thus of their consumption. The annual distribution of poisonings is highly variable. *Amanita phalloides* is the species responsible for most poisonings. The determination of urinary amanitins was not investigated in this study but served only as a diagnostic tool. The documentation rate of poisoning in our study (via formal identification of the ingested fungus or with a positive urinary amanitins assay) is high (76%), which supports our patients selection and decreases the bias for data analysis.

#### Cyclopeptide poisoning associated complication and severity:

Digestive disorders are systematic and are the first clinical symptoms to appear and partly enable the diagnostic hypothesis of cyclopeptide mushroom poisoning to be established. They appeared in this series of cases at a mean of 11.8 +/- 5.9 hours, which is well beyond the 6-hour limit that distinguishes short-latency from long-latency mycotoxic syndromes. The mean time to onset of digestive disorders is comparable to that of other case series found in the literature [15–18]. It should be noted that some patients had symptoms before 6 hours post-meal in our series (minimum 2 hours after ingestion), which is exclusively explained in our series by concurrent ingestions of mushrooms that cause resinoid syndrome, masking the late onset of cyclopeptide mushroom poisoning, and may wrongly rule out its diagnosis. It is therefore essential to be vigilant, even in cases of short-latency syndrome, and to not rule out the possibility of an overlying long-latency syndrome. Finally, late presentations (maximum at 36 hours) are also found in our series but also in other published case series [8,18].

In 78% of cases, patients presented with hepatitis and liver injury. It was observed on average after 60 hours, with a nearly synchronous increase in AST and ALT. This delay is similar to those found in other case series [16,17]. This delay is probably overestimated because hepatitis is only detected when the patient comes to the hospital or when the general practitioner prescribes a liver panel at the local laboratory. In most cases, the hepatitis that is found had already started at home. This delay in the detection of hepatitis is different from the delay in the onset of hepatitis. Its duration could only be found in 35 cases, i.e. only 22% of patients with hepatitis. The average duration of hepatitis was 10 days for the 35 documented cases. It is largely underestimated because the only cases in which the duration of hepatitis could be documented were those for which it was relatively short. After their return home, it is difficult to obtain the results of the patients' assessments, leading to closure of the file. To our knowledge, this duration has never been studied in recent case series.

Patients present in more than half of cases with liver failure, and with decreased PR and Factor V. The time to presentation of liver failure is about 70 hours. This time is close to that found in the series of Roberts et al. [15], Giannini et al. [17] and Escudié et al. [16]. The PR takes 4 to 5 days to normalize; the recovery of Factor V is faster and a little more than 2 days. In fact, Factor V is the most sensitive marker for monitoring liver failure since it is the factor synthesized by the liver with the shortest half-life (around 15 to 24 hours) without being vitamin K- dependent [19]. In addition, Factor V is not modified by the implementation of NAC therapy, unlike PR. In fact, NAC lowers PR by

reducing the activity of certain coagulation factors (vitamin K-dependent Factors II, VII and X, but not Factor V)[20]. An increase in serum creatinine is frequent (38.7%), and it is related to significant fluid losses due to vomiting and prolonged diarrhea. It often resolves quickly with the correction of dehydration.

#### Cyclopeptide poisoning management:

The average time to care in a hospital department was 42 hours, which is close to those found in other European series (29 and 34 hours [16];  $37.6 \pm 2.5$  hours [17]). Patients went to emergency departments due to the persistence of gastrointestinal symptoms. This average time makes it difficult to manage patients very early and to start detoxification treatment. For the implementation of treatments, more than 85% of patients received NAC and nearly 80% of patients received silibinin. Most authors agree that NAC and silibinin are the drugs of choice for the treatment of cyclopeptide mushroom poisoning [1,3,6,11,21]. The two active ingredients, silibinin and NAC, have demonstrated a more pronounced clinical benefit in terms of patient survival compared with other treatments [22] (antibiotics: gentamycin, neomycin, streptomycin, vancomycin, clindamycin, benzylpenicillin; cimetidine; thioctic acid; antiseptics; vitamin C; vitamin E; insulin, glucagon; human growth hormone; steroids; ceftazidime). NAC and silibinin were used for an average of 3 days, which corresponds to the recommended duration of use of silibinin, although there is no consensus. The average time to initiate these two treatments was 44 to 46 hours, which is very close to the time until management of patients in the hospital. It can therefore be concluded that both of these treatments are started very early, from the beginning of the patient's hospital management. Only less than 9% of patients received penicillin G. In fact, the clinical results concerning benzylpenicillin are controversial. Many authors consider that silibinin alone should be used as the first option instead of benzylpenicillin [3,6,22,23]. Indeed, treatment with high dose penicillin does not provide significant improvement in mortality, and its clinical use is no longer recommended because of possible iatrogenic effects (allergic reactions, neurotoxicity, disturbance in patients' electrolyte balance) [24].

This study did not demonstrate a significant difference in the treatments used on the patient outcomes.

#### Cyclopeptide poisoning outcome:

The PSS is a comprehensive severity score that considers the clinical and biological (according to their values) symptoms and is therefore related to, in particular, the severity of the kidney and liver failure. The overall severity, evaluated in the form of the PSS, shows that a little less than 50% of the cases are severity 3, i.e. high severity, which is a reminder that cyclopeptide mushroom poisoning remains a serious poisoning. The overall mortality between 1919 and 1980 was on average between 22 and 30% [25,26]. The mortality in our series is 4.4%, which is in accordance with the most recent data in the literature, indicating a mortality of less than 10% [17,27,28]. According to the retrospective analysis of Enjalbert et al. [3] over 20 years including over 2,000 amatoxin victims, the mortality varies from 1.4 to 16.9% in patients treated with antidotes. A very recent retrospective study on mortality due to cyclopeptide mushroom poisoning in the United States over 11 years (2008 to 2018), found a mortality of 8.8% [28].

Most patients in our series (approximately 90%) recovered without sequelae. However, 5.9% of patients had sequelae. There are two types: we have considered patients who had liver transplants and who will have a considerably altered quality of life following their poisoning, and persistent kidney failure one month after ingestion. The latter account for 3.4% of total patients. Acute kidney injury may be due to hepatorenal syndrome [3,11,29,30] (vasoconstriction of the renal arteries following the drop in blood pressure downstream from the liver, blood accumulating in the portal system, with this renal vasoconstriction resulting in kidney failure [31]). This syndrome is described in cyclopeptide mushroom poisonings [1,3,11]. Acute kidney injury may also be due to renal toxicity from amatoxins because of direct toxic damage leading to acute tubular necrosis [3,5,11]. These

results are interesting for the management of patients. Early monitoring of creatinine and its clearance is important for managing dehydration and functional AKI, but it is also important in the days that follow, especially in case of severe fulminant hepatitis. To our knowledge, these sequelae are not found or described in other case series that have studied patient outcomes in which no hepatic or renal sequelae are found [15,17]. Further studies are needed to investigate more precisely this long-term kidney damage.

#### Identification of risk factors:

Statistical analysis of the data showed that the mean time to onset of digestive disorders was shorter in PSS2 and PSS3-4 patients than in PSS1 patients. This is also found in the literature. Escudie et al. [16] have already demonstrated that the earlier the onset of digestive disorders, the more severe the cases. Thus, for these authors, as soon as diarrhea appears within 8 hours, a liver transplant can be considered. This was confirmed for the transplanted patients in this study, with a mean time to onset of digestive disorders of 8 hours (standard deviation: 2.8 hours). Based on these data and the literature, time to onset of symptoms seems to be predictive of severity. However, this is not the case for mortality. In fact, we could not show a significant difference in the time to onset of digestive disorders on mortality or the appearance of sequelae.

Finally, patients who died or had sequelae had more comorbidities, particularly cardiovascular, than patients who recovered. Also, the presence of at least one comorbidity was associated with greater severity and the occurrence of death or sequelae. To make a better quantification of the risk factors related with this toxicity, we could have used the Charlson comorbidity index[32] of the patients to analyze the outcomes. However, this score requires relatively complete data compared to the retrospective data that we were able to recover.

#### Strength and limitation:

With 204 cases of cyclopeptide mushroom poisoning studied, our series is a large one and is based on real life data from two poison control centers. The main limitation of this study is the retrospective data collection method and therefore the many missing data for some variables. The data for our study were extracted from the national database of poison control centers. The information was sometimes collected in a non-exhaustive manner during calls to patients and physicians, making it impossible to recover missing data remotely. These were considered completely random missing data and were therefore not attributed. Use of a prospective cohort could therefore have overcome this limitation.

#### **Conclusions**

Our study appears to suggest that sequelae, particularly renal, could persist following amatoxin toxicity. The results of this study show that the rapidity of onset of digestive disorders is associated with more severe amatoxin toxicity. Similarly, the presence of cardiovascular history and comorbidity favors the risk of death and sequelae.

**Conflict of interest:** The authors have no conflict of interest to declare.



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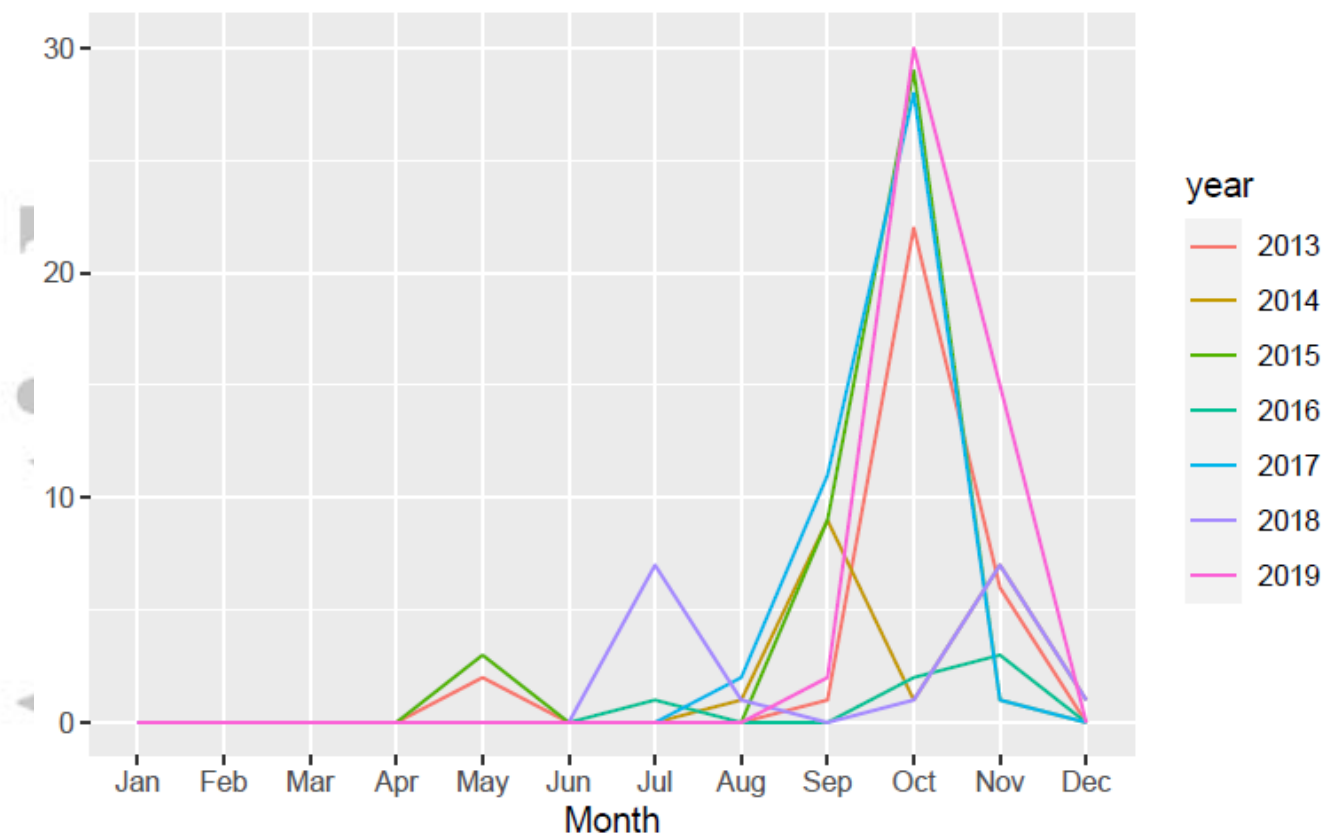


Figure 1

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**Table 1.** Description of clinical-biological disturbances in the case series (n=204)

Main characteristics	n/tot (%)	Average (standard deviation)	Median (min; max)
AST > 35 IU/L	157/201 (78.1)		
AST max (N :normal value=35 UI/L)	n=154	90 (106)	53 (1;566)
1-5N	31/154 (20.1)	3 (1)	2 (1;5)
6-50N	43/154 (27.9)	26 (13)	24 (8;48)
>50N	80/154 (51.9)	158 (110)	126 (52;566)
Time to onset (hours)	n=151	60.0 (25.40)	59 (10;218)
ALT > 45 IU/L	157/201 (78.1)		
ALT max (N: normal value=45UI/L)	n=156	84 (86)	59 (1; 508)
1-5N	26/156 (16.7)	2 (1)	2 (1;5)
6-50N	44/156 (28.2)	25 (12)	26 (6;43)
>50N	86/156 (55.1)	140 (81)	115 (50;508)
Time to onset (hours)	n=151	64.1 (25.18)	61 (10; 218)
Duration of hepatic cytolysis (days)	n=35/82	10.4 (10.97)	7 (1; 48)
PR <70%	103/194 (53.1)		
PR min (%)	n=102	39.7 (19.30)	43.5 (6; 69)
51-70%	35/102 (34.3)	61.1 (5.39)	62.0 (51;69)
25-50%	40/102 (39.2)	38.1 (8.13)	40.1 (25;50)
<25%	27/102 (26.5)	14.4 (5.24)	12.0 (6;23)
Time to onset (hours)	n=91	73.1 (29.05)	66 (37; 215)
Duration (days)	n=65	4.8 (6.83)	4 (1; 55)
FV <70%	87/160 (54.4)		
FV min (%)	n=85	31.6 (19.52)	25 (2;68)
51-70%	17/85 (20)	60.1 (5.90)	63.0 (51;68)
25-50%	27/85 (31.8)	39.0 (8.48)	40.0 (25;50)
<25%	41/85 (48.2)	14.6 (6.41)	14.0 (2;24)
Time to onset (hours)	n=79	67.0 (32.65)	60 (23;244)
Duration (days)	n=44	2.5 (1.42)	2 (1;6)
Creatinine max (µmol/L)	n=75	328.3 (280.70)	188 (112;1592)
Acute Kidney injury (AKI)*	65/199 (32.7)		
Stage 1	15/65 (23.1)		
Stage 2	17/65 (26.2)		
Stage 3	33/65 (50.8)		
Thrombocytopenia < 150 G/L	36/170 (17.7)		
Platelets min (G/L)	n=36	95.9 (43.99)	104 (9;148)
Hyperbilirubinemia > 17 mmol/L	112/170 (65.9)		
Bilirubin max (mmol/L)	n=112	56.8 (60.34)	40 (18;559)
Hyperammonemia > 40 µmol/L	26/75 (34.7)		
Ammonemia max (mmol/L)	n=26	107.8 (76.21)	77 (44;400)
Digestive disorders	204/204 (100)		
Time to onset (hours)	n=198	11.8 (5.89)	11 (2;36)
Encephalopathy**	9/198 (4.6)		
Stage 1	1/7 (14.3)		
Stage 2	1/7 (14.3)		
Stage 3	1/7 (14.3)		
Stage 4	4/7 (57.1)		
Time to onset (days)	n=9	4.3 (1.32)	4 (3;7)

(tot: total number ; min: minimum; max: maximum; \*Staging of AKI based on KDIGO Clinical Practice Guideline for Acute Kidney Injury of the International Society of Nephrology [14] ; \*\* Staging of encephalopathy based on Blei AT, Cordoba J, The Practice Parameters Committee of the American College of Gastroenterology. Hepatic Encephalopathy. 2001;96:9. [33])

Table 2. Description of treatments (n=204)

Main characteristics	n/tot (%)	Average (standard deviation)	Median (min; max)
NAC	175/204 (85.8)		
Implementation time (hour)	n=109	44.2 (29.71)	3.2 (1; 95)
Duration of treatment (days)	n=136	3.2 (1.95)	3 (1; 10)
Silibinin	161/203 (79.3)		
Implementation time (hour)	n=91	45.9 (31.84)	36 (13; 218)
Duration of treatment (days)	n=138	3.1 (1.81)	3 (1; 10)
Penicillin G	18/204 (8.8)		
Implementation time (hour)	n=7	53.9 (29.53)	60 (13; 95)
Duration of treatment (days)	n=10	2.2 (1.14)	2 (1; 4)
Liver clearance	6/204 (2.9)		
Implementation time (days)	n=5	3.4 (0.55)	3 (3; 4)
Duration of treatment (days)	n=5	1.8 (0.84)	2 (1; 3)
Dialysis	14/204 (6.9)		
Implementation time (days)	n=14	9.8 (12.01)	6.5 (2; 49)
Duration of treatment (days)	n=2	8 (9.51)	3 (1; 22)
Plasma exchange / plasmapheresis	6/204 (2.9)		
Implementation time (days)	n=6	4.2 (0.98)	4 (3; 6)
Duration of treatment (days)	n=5	2.2 (0.84)	2 (1; 3)
Transplant	5/204 (2.5)		
Implementation time (days)	n=5	4.4 (0.55)	4 (4; 5)

(tot: total number; min: minimum; max: maximum)

**TABLE 3** Analysis of severity of cyclopeptide mushroom poisoning cases.

Categorical variables	PSS = 1 (reference)		PSS = 2		PSS = 3 + 4					
	n/tot (%)		n/tot (%)	Univ p-value	Multiv p-value	n/tot (%)	Univ p-value	Multiv p-value		
Sex										
Male	28/44 (63.6)		27/56 (48.2)	-	-	51/104 (49.0)	-	-		
Female	16/44 (36.4)		29/56 (51.8)	NS	NS	53/104 (51.0)	NS	NS		
Mushroom involved										
<i>Amanita phalloides</i>	14/28 (50.0)		10/15 (66.7)	-	-	33/36 (91.7)	-	-		
<i>Amanita virosa</i>	0/28 (0)		0/15 (0)	NS	NS	3/36 (8.3)	NS	NS		
<i>Amanita verna</i>	7/28 (25.0)		2/15 (13.3)	NS	NS	0/36 (0)	NS	NS		
<i>Galerina marginata</i>	2/28 (7.1)		0/15 (0)	NS	NS	0/36 (0)	NS	NS		
<i>Lepiota brunneoincarnata</i>	5/28 (17.9)		3/15 (20.0)	NS	NS	0/36 (0)	NS	NS		
At least one comorbidity	15/44 (34.1)		28/56 (50.0)	NS	NS	63/104 (60.6)	0.0038	0.0418		
Continuous variables	n	Mean (+SD)	n	Mean (+SD)	Univ p-value	Multiv p-value	n	Mean (+SD)	Univ p-value	Multiv p-value
Age	42	47.1 (+21.89)	56	57.2 (+18.28)	0.0116	NS	104	55.8 (+17.27)	0.0151	NS
Time to onset of digestive disorders (hour)	44	14.2 (+6.48)	53	10.9 (+3.87)	0.0145	0.037	101	11.3 (+6.25)	0.0114	0.0399

Abbreviations: multiv, multivariate analysis; n, number; NS, non-significant; SD, standard deviation; tot, total number; univ, univariate analysis.

Table 4. Analysis of the outcomes of amatoxin poisonings

Categorical variables	Recovery (reference)		Death + sequelae		univ p-value	multiv p-value
	n/tot (%)		n/tot (%)			
Sex					NS	NS
Male	97/183 (53.0)		8/20 (40.0)		-	-
Female	86/183 (47.0)		12/20 (60.0)		NS	NS
Comorbidities						
Alcoholism	10/168 (6.0)		3/20 (15.0)		NS	
Hepatic	7/168 (4.2)		0/20 (0)		NS	
Cardiovascular	49/166 (29.5)		12/20 (60.0)		0.0088	
Renal	5/168 (3.0)		2/20 (10.0)		NS	
Other	61/168 (36.3)		18/20 (90.0)		0.0003	
At least one comorbidity	87/183 (47.5)		18/20 (90.0)		0.0025	0.0129
Treatments					NS	
No treatment	26/183 (14.2)		1/20 (5.0)		-	
NAC	14/183 (7.7)		1/20 (5.0)		NS	
NAC + Silibinin	128/183 (69.9)		14/20 (70.0)		NS	
NAC + Silibinin + penicillin G	14/183 (7.7)		4/20 (20.0)		NS	
Without Silibinin	39/182 (21.4)		2/20 (10.0)		-	
With Silibinin	143/182 (78.6)		18/20 (90.0)		NS	
Continuous variables	n	Mean ( $\pm$ SD)	n	Mean ( $\pm$ SD)	univ p-value	multiv p-value
Age	182	53.2 ( $\pm$ 19.00)	17	65.2 ( $\pm$ 12.41)	0.0085	NS
Time to onset of digestive disorders	177	11.9 ( $\pm$ 5.64)	20	10.2 ( $\pm$ 6.91)	NS	NS
Time to hospital care	170	41.4 ( $\pm$ 28.73)	18	49.9 ( $\pm$ 48.73)	NS	

(n: number; tot: total number; SD: standard deviation; NS: non-significant; univ: univariate analysis; multiv: multivariate analysis)

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Table 1. Description of clinical-biological disturbances in the case series (n=204)

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6-50N	43/154 (27.9)	26 (13)	24 (8;48)
>50N	80/154 (51.9)	158 (110)	126 (52;566)
Time to onset (hours)	n=151	60.0 (25.40)	59 (10;218)
ALT > 45 IU/L	157/201 (78.1)		
ALT max (N: normal value=45UI/L)	n=156	84 (86)	59 (1; 508)
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>50N	86/156 (55.1)	140 (81)	115 (50;508)
Time to onset (hours)	n=151	64.1 (25.18)	61 (10; 218)
Duration of hepatic cytolysis (days)	n=35/82	10.4 (10.97)	7 (1; 48)
PR <70%	103/194 (53.1)		
PR min (%)	n=102	39.7 (19.30)	43.5 (6; 69)
51-70%	35/102 (34.3)	61.1 (5.39)	62.0 (51;69)
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<25%	27/102 (26.5)	14.4 (5.24)	12.0 (6;23)
Time to onset (hours)	n=91	73.1 (29.05)	66 (37; 215)
Duration (days)	n=65	4.8 (6.83)	4 (1; 55)
FV <70%	87/160 (54.4)		
FV min (%)	n=85	31.6 (19.52)	25 (2;68)
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<25%	41/85 (48.2)	14.6 (6.41)	14.0 (2;24)
Time to onset (hours)	n=79	67.0 (32.65)	60 (23;244)
Duration (days)	n=44	2.5 (1.42)	2 (1;6)
Creatinine max (µmol/L)	n=75	328.3 (280.70)	188 (112;1592)
Acute Kidney injury (AKI)*	65/199 (32.7)		
Stage 1	15/65 (23.1)		
Stage 2	17/65 (26.2)		
Stage 3	33/65 (50.8)		
Thrombocytopenia < 150 G/L	36/170 (17.7)		
Platelets min (G/L)	n=36	95.9 (43.99)	104 (9;148)
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Encephalopathy**	9/198 (4.6)		
Stage 1	1/7 (14.3)		
Stage 2	1/7 (14.3)		
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Stage 4	4/7 (57.1)		
Time to onset (days)	n=9	4.3 (1.32)	4 (3;7)

(tot: total number ; min: minimum; max: maximum; \*Staging of AKI based on KDIGO Clinical Practice Guideline for Acute Kidney Injury of the International Society of Nephrology [14] ; \*\* Staging of encephalopathy based on Blei AT, Cordoba J, The Practice Parameters Committee of the American College of Gastroenterology. Hepatic Encephalopathy. 2001;96:9. [33])

Table 2. Description of treatments (n=204)

Main characteristics	n/tot (%)	Average (standard deviation)	Median (min; max)
NAC	175/204 (85.8)		
Implementation time (hour)	n=109	44.2 (29.71)	3.2 (1; 95)
Duration of treatment (days)	n=136	3.2 (1.95)	3 (1; 10)
Silibinin	161/203 (79.3)		
Implementation time (hour)	n=91	45.9 (31.84)	36 (13; 218)
Duration of treatment (days)	n=138	3.1 (1.81)	3 (1; 10)
Penicillin G	18/204 (8.8)		
Implementation time (hour)	n=7	53.9 (29.53)	60 (13; 95)
Duration of treatment (days)	n=10	2.2 (1.14)	2 (1; 4)
Liver clearance	6/204 (2.9)		
Implementation time (days)	n=5	3.4 (0.55)	3 (3; 4)
Duration of treatment (days)	n=5	1.8 (0.84)	2 (1; 3)
Dialysis	14/204 (6.9)		
Implementation time (days)	n=14	9.8 (12.01)	6.5 (2; 49)
Duration of treatment (days)	n=2	8 (9.51)	3 (1; 22)
Plasma exchange / plasmapheresis	6/204 (2.9)		
Implementation time (days)	n=6	4.2 (0.98)	4 (3; 6)
Duration of treatment (days)	n=5	2.2 (0.84)	2 (1; 3)
Transplant	5/204 (2.5)		
Implementation time (days)	n=5	4.4 (0.55)	4 (4; 5)

(tot: total number; min: minimum; max: maximum)

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Table 3. Analysis of severity of cyclopeptide mushroom poisoning cases

Categorical variables	PSS = 1 (reference)		PSS = 2		PSS = 3 + 4					
	n/tot (%)		n/tot (%)	univ p-value	multiv p-value	n/tot (%)	univ p-value	multiv p-value		
Sex										
Male	28/44 (63.6)		27/56 (48.2)	-	-	51/104 (49.0)	-	-		
Female	16/44 (36.4)		29/56 (51.8)	NS	NS	53/104 (51.0)	NS	NS		
Mushroom involved										
<i>Amanita phalloides</i>	14/28 (50.0)		10/15 (66.7)	-	-	33/36 (91.7)	-	-		
<i>Amanita virosa</i>	0/28 (0)		0/15 (0)	NS	NS	3/36 (8.3)	NS	NS		
<i>Amanita verna</i>	7/28 (25.0)		2/15 (13.3)	NS	NS	0/36 (0)	NS	NS		
<i>Galerina marginata</i>	2/28 (7.1)		0/15 (0)	NS	NS	0/36 (0)	NS	NS		
<i>Lepiota brunneoincarnata</i>	5/28 (17.9)		3/15 (20.0)	NS	NS	0/36 (0)	NS	NS		
At least one comorbidity	15/44 (34.1)		28/56 (50.0)	NS	NS	63/104 (60.6)	0.0038	0.0418		
Continuous variables	n	Mean (±SD)	n	Mean (±SD)	univ p-value	multiv p-value	n	Mean (±SD)	univ p-value	multiv p-value
Age	42	47.1 (±21.89)	56	57.2 (±18.28)	0.0116	NS	104	55.8 (±17.27)	0.0151	NS
Time to onset of digestive disorders (hour)	44	14.2 (±6.48)	53	10.9 (±3.87)	0.0145	0.037	101	11.3 (±6.25)	0.0114	0.0399

(n: number; tot: total number; SD: standard deviation; NS: non-significant; univ: univariate analysis; multiv: multivariate analysis)

Table 4. Analysis of the outcomes of amatoxin poisonings

Categorical variables	Recovery (reference)		Death + sequelae		univ p-value	multiv p-value
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Male	97/183 (53.0)		8/20 (40.0)		-	-
Female	86/183 (47.0)		12/20 (60.0)		NS	NS
Comorbidities						
Alcoholism	10/168 (6.0)		3/20 (15.0)		NS	
Hepatic	7/168 (4.2)		0/20 (0)		NS	
Cardiovascular	49/166 (29.5)		12/20 (60.0)		0.0088	
Renal	5/168 (3.0)		2/20 (10.0)		NS	
Other	61/168 (36.3)		18/20 (90.0)		0.0003	
At least one comorbidity	87/183 (47.5)		18/20 (90.0)		0.0025	0.0129
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NAC	14/183 (7.7)		1/20 (5.0)		NS	
NAC + Silibinin	128/183 (69.9)		14/20 (70.0)		NS	
NAC + Silibinin + penicillin G	14/183 (7.7)		4/20 (20.0)		NS	
Without Silibinin	39/182 (21.4)		2/20 (10.0)		-	
With Silibinin	143/182 (78.6)		18/20 (90.0)		NS	
Continuous variables	n	Mean ( $\pm$ SD)	n	Mean ( $\pm$ SD)	univ p-value	multiv p-value
Age	182	53.2 ( $\pm$ 19.00)	17	65.2 ( $\pm$ 12.41)	0.0085	NS
Time to onset of digestive disorders	177	11.9 ( $\pm$ 5.64)	20	10.2 ( $\pm$ 6.91)	NS	NS
Time to hospital care	170	41.4 ( $\pm$ 28.73)	18	49.9 ( $\pm$ 48.73)	NS	

(n: number; tot: total number; SD: standard deviation; NS: non-significant; univ: univariate analysis; multiv: multivariate analysis)

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