REUE | Review article

Mushroom poisoning. Update for clinicians

Intoxicaciones por setas. Actualización para clínicos

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Introduction

Mushroom poisonings, also known as mycetisms, have been recognized since ancient times. The existence of toxic and edible species with similar appearance, the persistence of false beliefs regarding mushroom toxicity, and the crossing of cultures that leads individuals without mycological traditions to collect and consume mushrooms without the prudence inherent to mycophilic and mycophagous societies, explain why—even well into the 21st century—numerous cases of this type of poisoning continue to occur every year. In this article, we address various aspects such as epidemiology, clinical presentation, treatment, and mortality, with special emphasis on the most severe forms, particularly those caused by mushrooms that affect the liver, which continue to cause between one and two deaths annually in Spain.

Epidemiology

In poison control centers (PCCs), the possibility of mushroom ingestion or mushroom poisoning is mentioned in 2 to 6 per 1,000 consultations. However, these are not always true mushroom poisonings, since the PCC interviewer routinely asks what the patient has eaten that day. We therefore estimate that these figures represent an incidence approximately ten times higher than the real one, meaning that only about 1 in 10 of these consultations actually corresponds to true mushroom poisoning. Nevertheless, PCC data show that mushrooms are currently present in gastronomy, leisure activities, and the cultural and dietary habits of the population. Consequently, it is logical to expect that if mushrooms are consumed and toxic species exist, cases of mycetism will occur from time to time.

Clinical data from episodes in which affected individuals seek medical assistance or present to the emergency department (ED) after consuming mushrooms and subsequently developing alarming symptoms provide a better estimate of the true incidence of these poisonings. Over a 14-year period, from 2006 to 2019, data were collected on mushroom poisoning episodes using the information sources listed in Table 1.

A total of 296 episodes were identified, in which one or more individuals consumed toxic mushrooms and became ill. This represented an average of 21 episodes per year in Spain, involving 757 people (2.57 patients per episode). Eighteen individuals died (2.37 %), always after consumption of hepatotoxic mushrooms—species capable of causing massive and irreversible hepatocellular necrosis.[1]

GENERAL CONSIDERATIONS AND INITIAL ASSESSMENT

Temporal distribution and characteristics of affected individuals

Due to climatic factors such as rainfall and temperature, these poisonings are typically autumnal; and due to lifestyle habits and customs, they usually occur during weekends. Autumn is the season favorable for mushroom growth, and many individuals take advantage of weekends to collect mushrooms.

Mushroom poisoning is generally a collective intoxication: nearly 8 out of 10 cases involve groups of two or more people—families or friends who gather to eat and share a dish in which toxic mushrooms have been included.[2,3]

In our experience, the proportion of affected individuals is slightly higher among males, and poisoning occurs more frequently in urban environments (three out of four episodes), where the population seems to have forgotten the rules and traditions that are still maintained in rural areas and help prevent such poisonings.

Unlike poisonings caused by plants, berries, and wild fruits—in which 80 % of those affected are children under 6 years of age—mushroom poisoning affects all age groups, to the point that in large case series the age distribution of affected individuals mirrors that of the general population.[4]

Latency period

Mushroom poisonings, like most poisonings in which the route of exposure is oral, follow a logical sequence: after ingestion, and for a period of time, the affected individual(s) remain asymptomatic.

Eventually, clinical signs appear, with symptom onset most often involving the GI tract.

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Key points in mushroom poisoning
– In patients who become acutely ill in autumn, especially after a weekend, mushroom poisoning should be suspected.
– Other possible etiologies must nevertheless be ruled out.
– Mycological identification should never delay the initiation of treatment, but it can be very valuable. If mushroom remnants are available, they should be preserved and an expert determination of the species should be attempted.
– Remember the option of consulting mushroom images via WhatsApp or similar digital platforms.
– Once mushroom poisoning is diagnosed, the presence of severe hepatotoxic poisoning must be confirmed or excluded.
– Consider the use of AmatoxTest when available.
– If hepatotoxic poisoning is confirmed, the appropriate treatment protocol must be initiated immediately.
– At 48–60 hours, the main prognostic parameters for severe hepatotoxic mushroom poisoning should be assessed.
– When indicated, the liver transplantation program should be activated, with transfer to a transplant-capable hospital.
– If cadaveric organ donation is significantly delayed, MARS therapy and N-acetylcysteine (NAC) may be beneficial.

This symptom-free interval, known as the latency period or incubation period, has long been used as a first approach for the clinical classification of mushroom poisonings. Since the early decades of the last century, it was observed that when this period was short (less than 6 hours), the poisoning was usually mild; whereas when the first symptoms appeared after more than 6 hours (sometimes between 8 and 12 hours), the poisoning was typically severe and associated with a worse prognosis.

Thus, mushroom poisonings are classified into two broad groups: short-latency poisonings, generally mild, and long-latency poisonings, often severe and sometimes fatal.

The explanation for this difference in severity lies in the nature of the toxins involved. When the responsible toxins are simple chemical irritants of the GI tract or false neurotransmitters, their effects occur quickly and may manifest within the first hours after ingestion. In contrast, when the toxins are agents that, after ingestion and systemic distribution, penetrate target organ cells and bind to enzymes, blocking synthetic processes and initiating cellular injury, it is possible that by the time symptoms appear, tissue damage is already considerable, resulting in greater severity.

Throughout the last century and into the 21st century, numerous publications and reviews have used the latency period as the basis for classification, and many clinical algorithms still differentiate poisonings according to whether latency is shorter or longer than 6 hours. However, although latency remains one factor to consider in management, its value is relative. There are several situations in which the classic scheme fails. For example, mixed syndromes may occur when ingestion of GI irritant mushrooms is accompanied by ingestion of potentially lethal mushrooms. In general, this mixture can be beneficial, as the former cause a certain "intestinal washout," promoting elimination of the latter: the early onset of vomiting and diarrhea expels mushroom fragments that, had they remained longer in the GI tract, would have affected the liver or kidneys.

Another possible scenario is double ingestion. For instance, when a family eats a dish containing toxic mushrooms at midday and, after the entire afternoon passes without symptoms, eats leftovers again for dinner. Later that night, a striking gastroenteritis develops. This should not be misinterpreted as short latency (from dinner) but rather long latency (from lunch). Typically, the intensity of symptoms will raise alarm, and if the midday meal is not initially mentioned, the possibility of double ingestion should be considered and specifically investigated.

In reality, a cholera-like gastroenteritis with profuse and dehydrating diarrhea preceded hours earlier by mushroom consumption should always raise suspicion of hepatotoxic mushroom poisoning, regardless of the latency period. In this regard, there is one circumstance in which latency truly has prognostic value: in confirmed hepatotoxic mushroom poisoning—either by mycological identification or analytical detection of amatoxins—where a shorter-than-expected latency (< 8 hours) suggests a more severe course.[1,4]

Table 1. Sources of epidemiological information

– Toxicology Information Service (SIT) of the National Institute of Toxicology and Forensic Sciences.
– Hospital clinical services (Emergency Department, Intensive Care, Pediatrics, Gastroenterology, etc.).
– Mycologists or Mycological Societies.
– Primary Care physicians and rural doctors.
– Online mycological forums (Micolist and others).
– Inquiries and notifications to the author by email, telephone, etc.
– News published in the press, both print and online.

Clinical presentation and history taking

Healthcare personnel working in the ED must keep in mind—especially in autumn—the possibility of mushroom poisoning (Table 2).

On some occasions, the allegedly intoxicated person(s), or sometimes a relative or companion, will bring to the ED leftover mushrooms, remains from cleaning the mushrooms taken from the trash bin, or even remnants of the cooked dish containing the mushrooms. We will later discuss what can be done with these "mushrooms," but first it is essential to determine whether this is truly a case of mushroom poisoning and, if so, what type of syndrome is involved. In other words, we must establish both a differential diagnosis and a syndromic diagnosis.

– Differential diagnosis: In journalistic terms, mushrooms are always the "usual suspects." However, they are not always responsible for the clinical picture. We must consider the possibility that another disease or a different toxic agent may be the cause.

– Syndromic diagnosis: The latency period, the type of symptoms, and the study of the mushrooms allow us to

Table 2. The most common clinical scenario
– One or more people, often several.
– Who have ingested mushrooms.
– Who present to the emergency department.
– Who exhibit symptoms (GI or other).
– And who may bring mushroom samples.

establish the toxidrome. In our country, the greatest danger lies in the ingestion of hepatotoxic mushrooms. Faced with a family group who has eaten mushrooms and presents with gastroenteritis, the first step is to formulate a basic syndromic diagnosis, which consists of ruling out or confirming a severe hepatotoxic form. Therefore, the syndromic diagnosis should, at minimum, confirm or exclude this type of intoxication.

– History taking: Family members or the affected individuals must be asked how many people ate the same mushrooms. In some cases, a group of friends or relatives dined together and later separated to different homes. When an intoxication alert appears, all involved individuals must be contacted and advised to attend the hospital.

– Time of symptom onset has relative value, as previously explained. In contrast, the predominant symptom pattern is of great importance because it may orient toward a severe form: a clinical picture in which one or more individuals, after some time following ingestion, develop intense diarrhea affecting the general condition, with nausea, vomiting, and episodes of abdominal pain is, by definition—until proven otherwise—a potentially fatal hepatotoxic mushroom poisoning.

– Study of the mushrooms: Identification of the species ingested (botanical or mycological diagnosis) cannot always be obtained. However, in my experience, a good approximation can be achieved in 90–95 % of cases, often down to the responsible species or at least the genus. Several key aspects that aid this process are summarized in Table 4.

– Classic confusions exist, especially with green-colored mushrooms (the color of *Amanita phalloides*), in relation to other mushrooms such as the "verderol" or "knight's mushroom" *(Tricholoma equestre),* or in the Basque Country the "guibelurdiñas" *(Russula virescens).* Regarding overall appearance, descriptions by non-experts are of limited value, but sometimes they clearly mention a sac at the base of the stem (the volva) and a ring—features characteristic of the genus *Amanita*.

– Knowledge of where the mushrooms were collected or obtained is also helpful. If they were purchased in markets or consumed in restaurants, true mushroom poisoning is unlikely. These cases more likely represent personal idiosyncratic intolerance to mushrooms that manifests during that particular meal.

– Photographs and illustrations of mushrooms can be shown, but individuals unfamiliar with mycology or botany often confuse them easily and may either fail to recognize them or identify every image as the mushroom they consumed.

– Occasionally, individuals bring to the ED leftover mushrooms, remains from cleaning them, or remnants of the dish. These samples may be sent to an expert—either from a local mycological society or a university botany department. It is important to note that if non-consumed mushroom remains are provided and no toxic species are found among them, this does not exclude ingestion of poisonous mushrooms.

Table 3. Medical history
– Number of people who consumed the same mushrooms.
– Time of onset of symptoms (latency period).
– Predominant type of symptoms.
– Species or species of mushrooms ingested (possible mycological diagnosis).

The value of mycological diagnosis

Mycological diagnosis has sometimes been overestimated. Some mycologists claim that thanks to species identification, life-saving treatment could be applied. In reality, the mycologist often confirms what emergency physicians already suspected, and by the time the report is issued, patients have usually already received several hours of appropriate intensive treatment. Moreover, it is unrealistic to expect a member of a mycological society to attend the hospital at 2 or 3 a.m. In practice, clinicians must be accustomed to acting without botanical diagnosis, since mushroom remains are often unavailable and the most important elements are the symptoms and clinical presentation.

Nevertheless, mycological diagnosis has clear value. In addition to occasionally allowing withdrawal of aggressive treatments, improvement of initial protocols, and providing reassurance to patients, families, and physicians, its main motivation lies in its contribution to scientific knowledge of toxic fungal species. Identification of the responsible species expands knowledge in science, medicine, and toxicology. Had clinicians not insisted on collecting mushrooms or their remains, the toxicity of many species now recognized as potentially lethal would still be unknown.

Therefore, when mushroom remains exist, they should be stored refrigerated in plastic containers and later sent to mycological consultants. It must be emphasized that mycological diagnosis—despite its value—must never delay or condition the initiation or type of treatment. Clinical suspicion alone must suffice to activate treatment protocols, especially in suspected severe intoxication. Thus, two principles must always be kept in mind:

1. We treat the patient, not the mushroom.

2. When the patient arrives at the ED, intoxication has already occurred.

Therefore, neither the arrival of a mycological report nor the availability of amatoxin assay results—if ordered—should delay initiation of appropriate treatment for severe

Table 4. Mycological / botanical assessment
– What mushrooms did they believe they were eating?
– What was their appearance?
– Where were they collected or obtained? Meadow, forest, lignicolous habitat, purchased at a market, from a street vendor, or consumed in a restaurant.
– Show photographs and mushroom plates (especially of toxic species).
– Examination of leftover mushrooms, mushroom cleaning residues, cooking remains, or photographs stored on a mobile phone.

hepatotoxic mushroom poisoning, which must begin whenever such intoxication is suspected (one or more individuals who consumed mushrooms and develop intense, dehydrating, cholera-like gastroenteritis hours later). Obviously, treatment can later be discontinued if laboratory testing excludes amatoxins or if, after the second day, no signs of hepatotoxicity appear.

Currently, a rapid point-of-care testing method exists that is particularly valuable: within just 10 minutes it can determine whether a severe hepatotoxic intoxication is present, using either a urine sample or, alternatively, a fragment of the mushroom.

Images of mushrooms in the digital era

To conclude the analysis of the value of the mycological report, it is essential to mention the potential of mushroom images in the digital era. In many cases, mushrooms have been photographed before cooking, and patients bring these photographs with them. In addition, mushroom remains can be photographed in the hospital. With the images obtained, experts can be consulted via email or WhatsApp, allowing mycological opinion to be obtained without requiring the specialist's physical presence at the hospital.

Uncommon conditions potentially explained by prior mushroom poisoning

Regarding clinical presentation, several rare diseases may be attributable to mushroom poisoning in the preceding hours or days and should therefore be considered:

Acute kidney failure may reflect the ingestion of Amanita proxima or *Cortinarius orellanus* in the preceding days.

A clinical picture of erythromelalgia may result from ingestion of the mushroom *Clitocybe amoenolens*. Rhabdomyolysis may be caused by heavy consumption over several days of the "knight's mushroom" *(Tricholoma equestre).*

In patients with chronic kidney disease, cases of encephalitis—occasionally fatal—have been described following consumption of the "angel's wings" *(Pleurocybella porrigens).*

A syndrome of cerebral edema and oliguria has been observed on multiple occasions over the past 50 years in Europe after consumption of *Hapalopilus nidulans*, usually due to confusion with the edible *Fistulina hepatica*.

In Japan, Korea, and some Pacific islands, a syndrome of bone marrow suppression has been described after ingestion of *Podostroma cornudamae*. In spring, a striking but benign cerebellar syndrome may follow consumption of morels *(Morchella spp.).* Finally, a very distinctive form of dermatitis—flagellate dermatitis—may occur after ingestion of raw or insufficiently cooked shiitake mushroom *(Lentinus edodes).*

CLINICAL SYNDROMES OF MYCETISMS

Simple mushroom gastroenteritis

This is the most common form of mushroom poisoning, accounting for nearly 50 % of cases seen in emergency departments. These are generally mild intoxications with GI symptoms (nausea, vomiting, diarrhea), typically self-limited and resolving with symptomatic treatment within 1–2 days.[6] They are frequently caused by *Entoloma lividum* (Figure 1), mistaken for the "pardilla," or by the "striped knight" (*Tricholoma pardinum,* Figure 2), mistaken for the true "negrilla." Currently, mushrooms of the genus *Ramaria* ("coral fungi") are frequently consumed, and some restaurants even include them in their dishes. Confusion may occur with the "poisonous coral fungus" (*Ramaria formosa*, Figure 3). However, it is easily recognized by its characteristic coloration: white flesh at the base, salmon-colored branches, and yellow tips.

Muscarinic (diaphoretic) syndrome

Produced by mushrooms such as *Inocybe fastigiata* (Figure 4), which contain high concentrations of muscarine and cause typical cholinergic intoxication: profuse sweating, hypersalivation, miosis, and blurred vision, appearing 20–90 minutes after ingestion. Mild GI symptoms may accompany the picture. The syndrome is generally mild and self-limited, resolving within hours. Only one fatal case has been described in the medical literature. The only alarm sign warranting atropine administration would be cardiovascular involvement (hypotension and/or bradycardia), which occurs exceptionally.

Coprine or nitritoid syndrome (antabuse-like reaction)

This syndrome occurs after ingestion of alcohol in combination with certain mushrooms such as *Coprinus atramentarius* (Figure 5). Its toxin, coprine, interferes with ethanol metabolism, causing acetaldehyde accumulation when alcohol is consumed hours or days after mushroom ingestion. Symptoms include flushing and warmth of the face, neck, and head, sweating, palpitations, hypotension, and sometimes forceful vomiting. High-dose vitamin C may be used, but symptoms are usually mild and self-limited. Although arrhythmias have occasionally been reported, the only published death was due to esophageal rupture following intense vomiting.[7]

Central neurotoxic syndrome

Also known as "mushroom drunkenness" or mycoatropinic syndrome, it is caused by ingestion of the fly agaric (*Amanita muscaria,* Figure 6), and less commonly *Amanita pantherina* (Figure 7). The toxins are ibotenic acid (excitatory) and muscimol (depressant). Ibotenic acid spontaneously converts into muscimol, explaining the alternating excitatory and depressive symptoms. Symptoms begin about 30 minutes after ingestion and include ataxia, intermittent hallucinations, psychomotor agitation alternating with somnolence, and rarely coma. Treatment is symptomatic; sedatives may be useful. Although generally mild, confirmed *Amanita pantherina* ingestion warrants observation, as severe and even fatal cases have been reported, with rapid neurological depression requiring mechanical ventilation.

Figure 1. *Entoloma lividum*, photograph courtesy of Carlos Rey.

Figure 3. *Ramaria formosa*, photograph courtesy of Plácido Iglesias.

Nephrotoxic syndrome

A) Early nephrotoxicity

Caused by mistaken ingestion of *Amanita proxima* (Figure 8),[8] often confused with the edible Amanita ovoidea. After 10–15 hours, mild GI symptoms may appear. Between days 2–4, more than half of patients develop renal involvement with elevated creatinine and oliguria. One-quarter progress to anuria requiring hemodialysis. Renal recovery usually occurs within 15 days to 2 months.[9,10]

B) Delayed nephrotoxicity: orellanine syndrome

This is a rare form of poisoning: only six cases have been reported in the medical literature of our country over the past 50 years. It is caused by ingestion of mushrooms of the genus *Cortinarius (Cortinarius orellanus*, Figure 10, and *Cortinarius speciosissimus),* whose toxins—orellanins—produce slow, progressive renal injury. After an asymptomatic period of several days (with initial symptoms appearing 3 to 17 days after ingestion), affected individuals develop lumbar pain, general malaise, intense thirst, polyuria, and subsequently progressive loss of renal function that may culminate in anuria. Supportive and symptomatic treatment cannot prevent progression to irreversible renal failure in 10–15 % of cases, in which renal transplantation becomes necessary.[11]

Nephrotoxic *Cortinarius* species have occasionally been confused with a visually similar edible mushroom, the "partridge bed" *(Chroogomphus rutilus).* However, in the edible species the flesh turns a characteristic dark purple upon cooking, a feature not seen in the toxic mushroom.

As reported in the medical literature, one of the cases recorded in Spain involved a young man seeking experiences with "magic mushrooms" who misidentified the species, resulting in renal failure that required kidney transplantation.[5]

Due to its delayed presentation, this tubulointerstitial renal necrosis may not be readily associated with mushroom ingestion that occurred one to two weeks earlier. Therefore, in cases of acute kidney failure of unknown cause—especially during mushroom season—this syndrome should be considered.

Hepatotoxic syndrome

This is the type of intoxication that should concern us the most, and we must know not only how to suspect it,

Figure 2. *Tricholoma pardinum*, photograph courtesy of Jorge Hernan.

Figure 4. *Inocybe fastigiata*, photograph courtesy of Nino Santamaría.

Figure 5. *Coprinus atramentarius*, photograph courtesy of Adolfo Moreno (†).

but also how to diagnose and treat it correctly, because it accounts for most deaths due to toxic mushroom consumption. These mushrooms contain toxins capable of producing acute hepatocellular failure, with fulminant hepatic necrosis that may be irreversible and lead to death. These hepatotoxins are oligopeptides composed of eight amino acids arranged in a double ring (bicyclic oligopeptides). Since their discovery was linked to *Amanita phalloides*, they are known as amanitins or amatoxins. Their toxicity results from inhibition—within the cell nucleus—of RNA polymerase II, to which they bind molecule by molecule. This interrupts protein synthesis and initiates a process of chemical stress and cellular injury that ultimately leads to necrosis.[12,13]

The paradigmatic hepatotoxic mushroom is *Amanita phalloides* (Figure 11).[14] Although various publications (especially mycology books) attribute alleged vernacular names to it ("death cap," "false Caesar's mushroom," "green Caesar's mushroom"), these are in fact neologisms. Numerous deaths have been attributed to this species throughout history, sometimes involving famous figures such as Emperor Claudius or Pope Gregory VII. It is often claimed to be responsible for most fatal cases of mushroom-induced hepatotoxicity. However, very different mushrooms contain the same toxins and can cause the same damage and therefore be lethal, including species of the genus *Galerina*, such as *Galerina marginata* (Figure 12), and species of the genus *Lepiota*, such as *Lepiota brunneoincarnata* (Figure 13).

Figure 7. *Amanita pantherina*, photograph courtesy of Jorge Hernanz.

Methods for detecting amanitins or amatoxins

1) Wieland Test ("Newspaper Paper Test")

Amatoxins have a hydroxyl group on one of their rings that is responsible for a color reaction when it binds to lignin in an acidic medium. This is the basis of the newspaper paper test: after placing a drop of mushroom juice on a fragment of newspaper and letting it dry for a few minutes, a drop of hydrochloric acid is then added. Under these conditions, a characteristic blue coloration appears if the mushroom contains amatoxins. As a control, another drop of acid is placed on a different area of the paper to exclude false positives due to nonspecific color reactions (Figure 14). This is a simple qualitative test whose sensitivity (approximately 20 mg/mL) allows demonstration of amatoxins in mushroom fragments.

Figure 6. *Amanita muscaria*, photograph courtesy of Plácido Iglesias.

Figure 8. *Amanita proxima*, photograph courtesy of Antonio Palazón.

Figure 9. *Amanita ovoidea* and *Amanita proxima* (author's photograph).

Although in an article published in early 1979 the German mycologist Alexander Meixner presented this test as his own personal discovery ("a simple method for detecting amatoxins in mushrooms"),[15] it was in fact first described in 1949 by the German chemist Theodor Wieland in Justus Liebigs Annalen der Chemie.[16] Surprisingly, from 1980 onward, this simple color test has been referred to by most authors in the medical literature as the Meixner Test. Clearly, the correct designation should be the Wieland test.

2) ELISA (Enzyme-Linked Immunosorbent Assay)

In this century, most publications reporting amatoxin determinations have used ELISA (enzyme-linked immunosorbent assay).[17] This immunometric method provides quantitative results within a few hours using urine samples. However, the only hospital toxicology laboratory in our country that performs it is at Hospital Clínic of Barcelona (Bühlmann ELISA test). For logistical reasons and due to geographic distance, it will often be impossible to obtain rapid amatoxin results. In any case, because it is quantitative, it may be useful on the third day when establishing prognosis: values above 50–100 ng/mL in the first urine sample indicate very severe intoxication.

3) LFIA (Lateral Flow Immunoassay)

A research team led by Candace Bever at Carnegie Mellon University in Pittsburgh, Pennsylvania (United States), presented 5 years ago a new analytical method for determining amatoxins in urine or mushroom fragments: the lateral flow immunoassay. We consider this a point-of-care method, since it uses a urine sample directly without pre-treatment, detection is completed within 10 minutes, and results are read with the naked eye without specialized equipment.[18] Alternatively, within the same timeframe, a result can be obtained from a small fragment of leftover mushrooms, including remnants from the cooking pot or vomited material.

With a sensitivity of approximately 5 ng/mL, this method can confirm amatoxin intoxication in 100 % of cases within the first 48 hours after ingestion. This means that a negative urine result, for example at 18–20 hours after mushroom ingestion, virtually rules out the need for aggressive specific treatment for suspected hepatotoxicity.

Figure 10. *Cortinarius orellanus,* photograph courtesy of Jorge Hernanz.

This method is performed using a small plastic cassette similar to rapid COVID tests, with the difference that the result is positive when one colored line appears and negative when two appear (Figure 15). LFIA is a simple, sensitive, selective, portable, rapid, and accurate way to detect amatoxins. It is currently not marketed in Europe, but it can be purchased online through the company AmatoxTest (https://amatoxtest.com).

Having a test like this could be useful, among other circumstances, in the following situations:

1. Any case in which there is doubt about possible ingestion of hepatotoxic mushrooms.
2. Discrepancies between symptom intensity and latency period.
3. Asymptomatic individuals who come to the hospital due to suspicion of hepatotoxic mushroom ingestion.
4. In a confirmed case with mixed-species consumption, other diner(s) who are still asymptomatic.

It could also aid prognosis through a theoretically semi-quantitative procedure: test the urine, and if it is posi-

Figura 11. *Amanita phalloides,* photograph courtesy of Plácido Iglesias.

Figure 12. *Galerina marginata*, photograph courtesy of Plácido Iglesias.

Figure 13. *Lepiota brunneoincarnata*, photograph courtesy of Plácido Iglesias.

tive and the diagnosis is confirmed, then test a 1:10 dilution. If it becomes negative, prognosis is presumably more favorable. If positivity persists, the case may represent a more severe form (Figure 16).[19]

Toxicokinetics of Amatoxins

Once the mushrooms are ingested, they pass through the GI tract and, upon reaching the intestine, toxin absorption begins through intestinal epithelial cells, which very soon will have their nuclear RNA polymerase II blocked and therefore their protein synthesis inhibited (Figure 17). As these are the first cells exposed to amatoxins, the earliest symptoms reflect intestinal epithelial injury, presenting as gastroenteritis that can be very intense, with cholera-like features.

Once absorbed, the toxins reach the liver via the portal venous system and enter functional hepatic cells by crossing the cell membrane through a multispecific transport system, reaching the nucleus where they exert their action. Hepatocyte injury leads to hepatocellular necrosis which, if extensive and severe, becomes irreversible.

The toxins leave the liver through two routes. On the one hand, through biliary elimination into the duodenum, thereby establishing enterohepatic recirculation. On the other hand, by being released into the extracellular space and eliminated by the kidneys through urine. Thus, two potential toxin elimination pathways are available: digestive aspiration and forced diuresis.

Moreover, toxin entry into functional hepatic cells can be antagonized or even blocked by substances that use the same multispecific transport system into the hepatocyte. Drugs such as penicillin or silibinin antagonize this multispecific uptake mechanism. This provides an additional therapeutic target in this intoxication.

Treatment of amatoxin poisoning

With minor variations,[20] the treatment scheme generally used for this intoxication includes:

1. Symptomatic and supportive treatment.
2. Early and intensive rehydration.
3. Continuous digestive aspiration.
4. Drugs that antagonize amatoxin uptake [penicillin and/or silibinin (Legalon Sil®)].
5. Neutral forced diuresis.

1. Symptomatic and supportive treatment is very important in any severe acute condition and, by itself, constitutes a useful measure that contributes to improving prognosis.[19]

2. Early and intensive rehydration in a patient with cholera-like diarrhea and therefore major fluid and electrolyte losses is essential to reverse dehydration and prevent renal failure due to hypoperfusion, which is a poor prognostic factor. It will also help establish facilitated or forced diuresis and, consequently, toxin elimination via the urinary route.[21]

3. Administration of repeated doses of activated charcoal together with a cathartic improves prognosis in these intoxications. However, continuous digestive aspiration is recommended. Ideally, aspiration would be performed using a tube reaching the duodenum so that bile could be aspirated. Nevertheless, as shown in some studies, substantial amounts of amatoxins can also be removed through gastric aspiration. Very high levels of amatoxins have been retrieved even 60 hours after ingestion. Although there is no unanimous agreement, some authors recommend intermittent continuous aspiration alternating with activated charcoal plus a cathartic, interrupting aspiration every 3–4 hours to administer a dose of charcoal and cathartic.

4. Based on the above, the ideal treatment likely consists of early intensive rehydration, forced diuresis, continuous digestive aspiration alternating with activated charcoal and cathartics, and intravenous administration of a drug such as penicillin or silibinin. Controversy also exists regarding these two substances: some authors propose using both together, whereas others argue that it makes little sense because they act through the same mechanism. Some clearly favor penicillin, reserving silibinin only for penicillin allergy. Possibly, silibinin is the best option, as it has demonstrated other beneficial actions in addition to blocking toxin uptake. Currently, thanks to the "Antidote

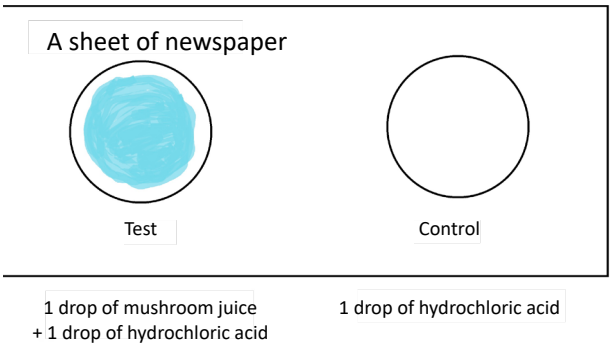

Figure 14. Wieland test.

Network," obtaining silibinin (Legalon Sil®) should not be problematic; thus, penicillin would be used only in cases where there is significant delay or inability to obtain the antidote.[22]

Mortality

Although some older publications from the late 19th century and the first half of the 20th century reported extremely high mortality figures, review of the medical and toxicological literature allows a better understanding of the true mortality of these intoxications. The remarkable advances in medicine during the last century helped improve prognosis and reduce mortality. Thus, while Alder, in a 1961 publication compiling reports in German medical journals from 1919 to 1958, reported a mortality of 30.7 % (86 deaths among 280 patients studied),[22] the Swiss author Floersheim, in a retrospective study published in 1982 compiling intoxications in Germany, Austria, France, Italy, and Switzerland between 1971 and 1980, reported a mortality of 22.4 % (46 deaths among 205 patients studied).[23]

Subsequently, in an article published in 1988, Hruby presented the results of a prospective study collecting data on poisonings occurring in several European countries between 1980 and 1986. Mortality was 10.3 % (26 deaths among a total of 252 patients).[24] Finally, in this century, we presented a study on mushroom poisonings occurring in our country between 2009 and 2017, with a mortality of 12.7 % (16 deaths among 126 patients).[4]

Based on the figures reported in the last two studies, we can conclude that approximately one in every

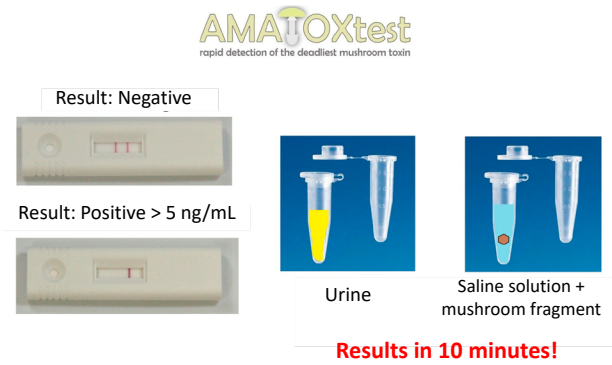

Figure 15. Lateral flow immunoassay (LFIA).

Figure 16. Repeat LFIA in diluted urine.

ten intoxicated patients will die from acute hepatocellular failure. These patients, in whom hepatic necrosis is irreversible, can only recover through liver transplantation.[25]

Liver transplantation in amatoxin poisoning

Only about 1 in 10 intoxicated patients will be candidates for liver transplantation. Many patients, even with high percentages of hepatocellular necrosis, are able to regenerate their liver. Therefore, it is essential to have a set of clinical and analytical parameters with predictive value. Ideally, these parameters should allow early prognostic assessment, since the most severe forms of this intoxication evolve rapidly toward marked clinical deterioration.

Over an 11-year period (2006–2016), analytical, clinical, and outcome data were collected for 15 orthotopic liver transplants performed in Spain as treatment for patients intoxicated by hepatotoxic mushrooms. Of the 15 patients, 4 died in the immediate postoperative period or in the following days. This early mortality of 26.6 % is higher than expected in the 21st century, since normally 90 % of patients survive beyond the first year.[26] It was striking that in all 4 cases transplantation was performed after the fifth day, in patients who at the time of surgery already had severe clinical and laboratory deterioration.[27] In these patients there is a window of time during which transplantation can be successful, but if one waits beyond a "limit point," they deteriorate, develop hepatorenal failure, bleed, and progress to multiorgan failure. Under those cir-

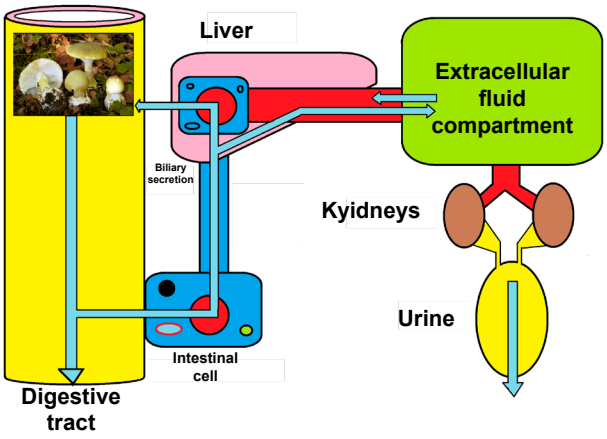

Figure 17. Toxicokinetics of amatoxins.

	Total	Survived	Died
Trasplants before 100 hours	9	9	0
Trasplants after 100 hours	6	2	4
Totals	15	11	4

P < .01*
With Yates* correction: *P* = .0235

Figure 18. Relationship between timing of transplantation and mortality.

cumstances, even with an excellent graft, transplant failure becomes highly likely.

If transplant outcomes are compared according to whether they were performed before 100 hours post-ingestion or after that threshold, all patients transplanted before 100 hours survived, whereas two-thirds of those transplanted after that time died, with statistically significant differences (Figure 18).

This indicates that transplantation should be performed early.[28] However, in the 4 patients who died, transplantation took place after day 5. Why were they not transplanted earlier? This may partly have been due to delay in obtaining a donor organ. But it is more likely that a strict and rigorous attempt was made to follow international guideline criteria for liver transplantation decision-making, such as the King's College criteria[29] or the Clichy–Villejuif criteria,[30] among others. Although some of these criteria are very useful in other conditions, including chronic liver disease such as advanced cirrhosis—where MELD (Model for End-stage Liver Disease) scoring is also useful[31]—they may not be well suited to an acute, rapidly progressive intoxication such as this one. Indeed, some criteria may push decisions beyond the "limit time," for example those based on clinical parameters such as grade 4 coma or analytical thresholds such as INR > 7, which occur when hepatic injury is already extremely severe, or those referring explicitly to intervals of "more than 7 days."

Ultimately, as Drs. Luis Ibáñez-Samaniego and Rafael Bañares stated in a 2016 editorial in *Liver International*,[32] acute liver failure caused by hepatotoxic mushrooms remains a crossroads: what should we do—transplant or wait? We can wait, but we know that beyond day 4 or 5 it may already be too late. (See the management algorithm shown in Figure 19).

Clearly, the availability of clinical and/or analytical parameters with early prognostic predictive value is fundamental. Two phases can be considered in the treatment of these intoxications: a 1st phase in which treatment is primarily toxicological, and a 2nd phase in which treatment is mainly hepatological (Figure 20). Between these phases, during the third day, is the optimal time to establish prognosis. Unfortunately, a rapid liver donation is not always achievable; in some countries, delays of 2–3 days may occur. In such cases, treatment with N-acetylcysteine (NAC) and the application of liver support techniques such as MARS would be indicated. Contrary to the opinion of some authors, I believe it is not advisable to administer NAC earlier, so as not to alter coagulation readings that are highly valuable for prognosis.

Parameters to consider for prognostic assessment

Prognosis should be established at 48–60 hours after ingestion, based on the presence of early renal failure with elevated creatinine, amatoxin levels in the first urine sample, and above all a rapid and early decline in prothrombin time (PT). In patients who died, PT was always below 30 % at 48 hours post-ingestion.[26] Regarding latency, as already noted, a relatively short latency indicates greater severity; currently, a latency of less than 8 hours is agreed upon as a poor prognostic parameter.

The various parameters with prognostic value are summarized in Table 5. Some may occur too late, but if they are already present between the second and third day they indicate greater severity.

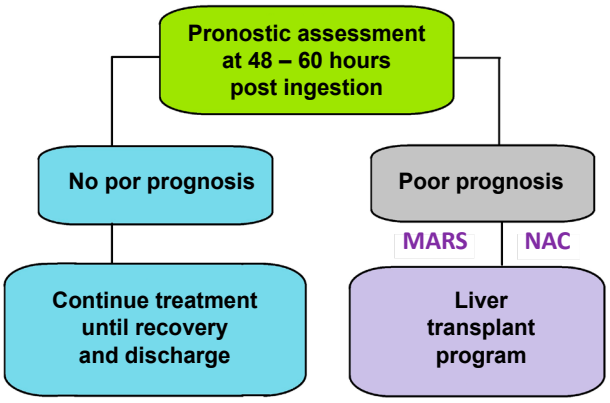

Figure 19. Decision algorithm for prognosis in hepatotoxic mushroom poisoning.

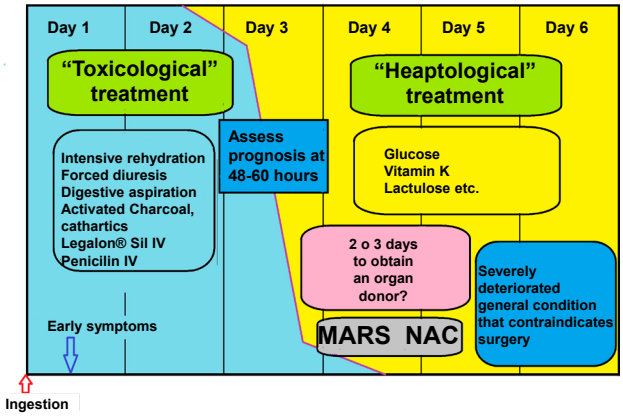

Figure 20. Treatment timeline following ingestion of hepatotoxic mushrooms.

Tabla 5. Parameters with prognostic value
Initial renal failure with increased creatinine.
Amatoxin in first urine greater than 50/100 ng/mL.
Rapid and early drop in PT.
PT less than 30 % at 48 hours post-ingestion.
Latency period of less than 8 hours.
Jaundice, hypoglycemia, and coma.

PT: prothrombin time.

In the 1990s, when Dr. Margarit—pioneer of liver transplantation in Spain—directed the liver transplant program at Hospital Vall d'Hebron in Barcelona, we took advantage of having an in-house Hemostasis Laboratory at a tertiary-level hospital and established an analytical triad that we repeated periodically from day 2 onward and found extremely useful for transplant decision-making. It consisted of three hemostasis parameters: prothrombin time (PT), antithrombin III (ATIII), and factor V activity (FV). The presence of PT < 30 %, ATIII < 30 %, and FV activity < 15 % between 48–72 hours was an indication for liver transplantation.[27]

Regarding liver transplantation, we must answer two simple questions:

– Whom should we transplant? Any patient presenting multiple poor prognostic parameters suggesting an ominous outcome within a few days.

– When should we transplant? As soon as possible once the indication has been established, while continuing to monitor clinical and analytical indicators.[26-28]

In Spain, fortunately, the wait for a deceased-donor liver rarely exceeds 24 hours. Since the rapid and severe deterioration of these patients is largely due to massive hepatic necrosis triggering a cytokine storm and the release of thromboplastic factors—making the "toxic" liver not only nonfunctional but actively harmful—there is the possibility of leaving the patient anhepatic for a few hours to improve transplant success prospects.

In any case, the decision on whether transplantation is needed and the timing should be agreed upon by physicians (toxicologists, emergency physicians, intensivists, hepatologists) and the surgeons performing the procedure.

Conclusions

While every emergency physician should have basic knowledge of mycetisms, it is advisable to contact a clinical toxicology expert in case of doubt when facing a patient with presumed mushroom poisoning.

By way of conclusion, it is important to highlight that:

– Mushroom poisoning is typically a collective intoxication affecting groups of two or more diners, usually occurring in autumn—especially on weekends. The most common pattern is a family group of 2–5 people who eat a mushroom stew on a Sunday night in October or November and seek care overnight or on Monday morning.

– If, after some time following mushroom ingestion, patients develop intense diarrhea with general condition impairment, nausea, vomiting, and intermittent abdominal pain, then—until proven otherwise—we must assume a potentially fatal hepatotoxic mushroom intoxication.

– Different tests exist for amatoxin determination (Wieland test, ELISA, LFIA). With the AMTOX test, a result is obtained in 10 minutes using the patient's urine when severe mushroom intoxication is suspected.

– One in 10 patients intoxicated by amatoxins will require liver transplantation, and prognosis must be established using clinical criteria and analytical parameters (Table 5).

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