REVIEW ARTICLE

Nephrotoxic Mushroom Poisoning: Global Epidemiology, Clinical Manifestations, and Management

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Because mushroom poisonings are increasing worldwide after ingestions of known, newly described, and formerly considered edible species, the objectives of this review are to describe the global epidemiology of nephrotoxic mushroom poisonings, to identify nephrotoxic mushrooms, to present a toxidromic approach to earlier diagnoses of nephrotoxic mushroom poisonings based on the onset of acute renal failure, and to compare the outcomes of renal replacement management strategies. Internet search engines were queried with the keywords to identify scientific articles on nephrotoxic mushroom poisonings and their management during the period of 1957 to the present. Although hepatotoxic, amatoxin-containing mushrooms cause most mushroom poisonings and fatalities, nephrotoxic mushrooms, most commonly *Cortinarius* species, can cause acute renal insufficiency and failure. Several new species of nephrotoxic mushrooms have been identified, including *Amanita proxima* and *Tricholoma equestre* in Europe and *Amanita smithiana* in the United States and Canada. In addition, the edible, hallucinogenic mushroom *Psilocybe cubensis* has been noted recently via mass spectrometry as a rare cause of acute renal insufficiency. Renal replacement therapies including hemodialysis are often indicated in the management of nephrotoxic mushroom poisonings, with renal transplantation reserved for extracorporeal treatment failures.

Keywords: orellanine, orellanus syndrome, allenic norleucine, rhabdomyolysis, mushroom-induced

Introduction

INCREASING MUSHROOM POISONINGS

Mushroom poisonings are increasing worldwide today for many reasons, including novices mistaking poisonous species for edible ones, recent immigrants mistaking poisonous species for edible ones back home, and adolescents mistaking poisonous species for hallucinogenic ones.^{1–6} The American Mycological Association and the US Centers for Disease Control and Prevention have warned clinicians that mushroom intoxications continue to occur among newly arrived migrant groups accustomed to foraging for edible mushrooms in their home countries who are not familiar with local mushroom ecology.^{2,3}

In addition to the risk factors for mushroom poisoning noted among novices and recent immigrants, the

recreational ingestion of hallucinogenic mushrooms has become a popular form of substance abuse among adolescents and young adults that can also result in mistaking poisonous mushrooms for hallucinogenic ones.^{4,5} Among 174 adolescents previously identified as substance abusers, 45 (26%) reported having ingested psilocybin-containing hallucinogenic mushrooms, often in conjunction with alcohol and other drugs.⁴ In a 2012 survey study of 882 randomly selected college students, 30% of the 409 responders reported having ingested hallucinogenic mushrooms (mean number of ingestions 3.4; mode 1) on several occasions.⁵

NEPHROTOXIC MUSHROOM POISONINGS

Recently, several new species of *Amanita* mushrooms have been identified as nephrotoxic, including *A proxima* in Europe, *A smithiana* in Canada and the United States, *A pseudoporphyria* in Japan, and *A punctata* in Korea.^{7–13} Prior case reports have also suggested, without any laboratory confirmation, that acute renal failure could result from the consumption of hallucinogenic *Psilocybe* species mushrooms.^{14,15} In 2019, a case of acute kidney

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injury was reported after consumption of edible, hallucinogenic *Psilocybe cubensis* mushrooms from a psychedelic mushroom “grow kit” purchased online.¹⁶ A sample from the crop of *P. cubensis* mushrooms consumed in this case was noted via mass spectrometry to contain the hallucinogenic toxin psilocin.¹⁶ In addition to directly nephrotoxic mushrooms, newly recognized myotoxic mushrooms can cause rhabdomyolysis with massive myoglobin release that may indirectly cause acute kidney injury, including the formerly considered edible *Tricholoma equestre* in Europe and *Russula subnigricans* in China.^{17–19}

Because mushroom poisonings are increasing worldwide after ingestions of known, newly described, and formerly considered edible species, the objectives of this review are to describe the global epidemiology of nephrotoxic mushroom poisonings, to identify nephrotoxic mushrooms, to present a toxidromic approach to earlier diagnoses of nephrotoxic mushroom poisonings based on the onset of acute renal failure, and to compare the frequencies and outcomes of renal replacement management strategies.

SEARCH STRATEGY

Internet search engines and databases including PubMed, Google Scholar, Google, and Ovid Medline were queried with the keywords as medical subject headings to identify scientific articles on nephrotoxic mushroom poisonings and their treatments and outcomes during the search period, 1957 to present. The keywords included mushrooms, poisonous, nephrotoxic; *Amanita*, poisonous, nephrotoxic; *Cortinarius*, poisonous, nephrotoxic; orellanus syndrome, orellanine; and allenic norleucine.

The articles selected to meet the first objective to identify nephrotoxic mushroom species included case reports, case series, and review articles on nephrotoxic mushroom poisonings. The articles selected to meet the second and third objectives to present a toxidromic approach to earlier diagnoses and to compare the frequencies and outcomes of renal replacement treatment strategies included observational studies, retrospective descriptive and analytical epidemiologic studies, and toxicologic investigations. Articles excluded from review included letters to the editor, dispatches, opinion-editorial articles, clinical-pathological case conferences, and abstracts of posters presented at conferences and scientific meetings. These selection methodologies met all recommended criteria for narrative reviews, including use of several keywords, use of 2 or more Internet search engines, a defined study period, and article inclusion and exclusion criteria.²⁰

Figure 1. *Cortinarius orellanus* has a large orange to rusty brown cap with gills underneath connected to a thick stem without a ring or annulus. It contains highly nephrotoxic orellanine compounds. Source: Wikimedia Commons (public domain). Photographer: Michael 11. Available at <https://en.wikipedia.org/wiki/Orellani#/media/File:Corellanus.jpg>.

THE GLOBAL EPIDEMIOLOGY OF NEPHROTOXIC MUSHROOM POISONINGS AND THE INITIAL IDENTIFICATION OF NEPHROTOXIC MUSHROOMS

Nephrotoxic Cortinarius Mushrooms

Nephrotoxicity and mortality after ingestion of *Cortinarius* species mushrooms was initially described in Poland in 1957 in a series of 102 cases of acute renal failure with 11 fatalities in patients who had consumed cooked *Cortinarius orellanus* mushrooms.²¹ By 1962, Polish investigators had isolated a crude extract from *C. orellanus*, which was named orellanine and which caused renal toxicity when administered orally to experimental animals.²²

In 1990, French investigators reported a case series of 26 healthy young men who developed acute renal failure after ingesting a mushroom soup made with *C. orellanus*.²³ All patients were hospitalized within 10 to 12 d of ingestion, with 12 patients presenting in acute renal failure with acute tubulointerstitial nephritis on renal biopsy.²³ Among these 12 patients, 8 required hemodialysis and recovered rapidly.²³ The remaining 4 patients developed chronic renal failure lasting for months and ultimately required kidney transplants.²³ Of the remaining 14 patients, 12 developed leukocyturia, and all 12 had normal renal function at 1-y follow-up.²³ Another group of investigators later followed 12 of the 26 men who had developed renal failure for a period of 13 y after ingestion of the *C. orellanus* mushroom soup.²⁴ Of these 12 patients, 7 recovered normal renal function, 4 underwent kidney transplant for chronic renal failure, and 1 patient on hemodialysis died in a car accident.²⁴ Investigators estimated the incidence of acute renal failure after *C. orellanus* ingestion to range from 30 to 46% depending on individual sensitivity, pre-existing nephropathy, and the cumulated dose of nephrotoxin ingested.²⁴

Figure 2. *Amanita smithiana* is native to the Pacific Northwest of the United States and Canada, where it has been mistaken for the edible pine or matsutake mushroom, *Tricholoma magnivalere*. It has a large white convex cap with unattached free gills and a thick, shaggy white stem with a torn or absent ring. Source: Wikimedia Commons (public domain). Photographer: Sava Krstic. Available at https://upload.wikimedia.org/wikipedia/commons/8/89/Amanita_smithiana_283102.jpg.

Investigators also noted that renal failure regressed progressively over several months in 60% of cases.²⁴

Although most *Cortinarius* poisonings to date have been reported from Poland and France, *Cortinarius* species mushrooms are widely distributed in the coniferous forests of the Scandinavian countries, Britain, the United States, Canada, and Australia.²⁵ In 1995, Swedish investigators reported a case series of 22 patients who were poisoned after consuming cooked *C speciosissimus* mushrooms during the period of 1979 to 1993 (Figure 1).²⁵ Nine patients developed chronic renal failure, and 5 patients required kidney transplants.²⁵ Three of these patients underwent transplantation after up to 6 mo of hemodialysis.²⁵ Two patients who did regain some renal function restarted hemodialysis 24 and 30 mo later and received kidney transplants.²⁵ The investigators concluded that delayed renal failure could follow partial renal recovery by many years and that renal transplantation could guarantee successful outcomes even years after mushroom poisonings.²⁵

NEPHROTOXIC AMANITA MUSHROOMS

In 1994, French investigators were the first to report 5 cases of acute renal insufficiency after consumption of cooked *A*

proxima mushrooms that were most likely mistaken for the edible *Amanita* species *A ovoidae*, which shares the same habitat.⁷ Temporary hemodialysis was required in 4 of the 5 cases, and all patients recovered quickly, with normal renal and hepatic function restored by 3 wk.⁷

In 1998, Canadian investigators in British Columbia reported 4 cases of renal failure in patients who had consumed cooked *A smithiana* mushrooms and developed gastrointestinal symptoms 5 to 8 h after ingestion (Figure 2).¹⁰ One of the patients, an elderly patient with diabetes, presented to an emergency department with renal failure the day after a mushroom meal and required hemodialysis.¹⁰ The remaining 3 patients presented to local emergency departments 5 to 6 d after mushroom ingestions and also received supportive care with hemodialysis.¹⁰ All patients subsequently regained normal renal function.¹⁰

In 2009, clinicians in Portland, Oregon, reported 4 additional cases of acute renal failure after consumption of cooked *A smithiana* mushrooms in patients who mistook *A smithiana* for edible matsutake (*Tricholoma matsutake*) mushrooms.¹¹ All patients presented with gastrointestinal symptoms from 20 min to 12 h after mushroom consumption.¹¹ All patients subsequently developed acute renal failure 4 to 6 d post-ingestion, and all received temporary hemodialysis for several weeks before regaining normal renal function.¹¹ The laboratory ranges of the presenting serum biomarkers of acute renal failure in these cases included a blood urea nitrogen of 72 to 91 mg·dL⁻¹ and a creatinine level of 12 to 14 mg·dL⁻¹.¹¹ In addition to *A proxima* in Europe and *A smithiana* in North America, delayed onset of acute renal failure was reported from Asia after consumption of other species of *Amanita* mushrooms,

Figure 3. *Psilocybe cubensis* hallucinogenic mushrooms cultivated in a home “grow kit” or “grow box” easily purchased online. Source: Wikimedia Commons (public domain). Photographer: Lord Toran. Available at <https://commons.wikimedia.org/wiki/File:growbox-cubensis.jpg>.

Figure 4. *Tricholoma equestre* (synonym *T. flavovirens*), also known as the yellow knight mushroom, has a large flat yellow cap with gills underneath connected to a long thick stem without a ring. *T. equestre* has caused delayed and fatal rhabdomyolysis with acute renal failure. Source: Wikimedia Commons (public domain). Photographer: Matthias Renner. Available at: https://upload.wikimedia.org/wikipedia/commons/8/82/Tricholoma_equestre.jpg.

specifically *A. pseudoporphyria* in Japan (2003) and *A. punctata* in Korea (2015).^{12,13}

PSILOCYBE CUBENSIS

In 2019, the first case of acute kidney injury was reported in a 15-y-old Canadian male who consumed several hallucinogenic *P. cubensis* mushrooms from a psychedelic mushroom “grow kit” purchased online along with 3 of his friends (Figure 3).¹⁶ The suspect mushrooms were identified morphologically by a mycologist, and the serotonergic hallucinogen psilocin was identified by liquid chromatography-mass spectrometry in a sample of the mushroom meal consumed.¹⁶

Before identification of the ingested mushrooms, the patient’s initial presentation was consistent with orellanine toxicity after ingestion of *Cortinarius* mushrooms.¹⁶ However, orellanine was not detected in the mushroom meal sample, and the 3 other boys who ingested mushrooms from the patient’s mushroom meal remained asymptomatic and had normal renal function.¹⁶ In this case, no other cause of acute renal injury was suspected by history or detected by laboratory analyses, including rhabdomyolysis, which was ruled out by normal serum creatine kinase (CK) levels.¹⁶ Hallucinogenic *P. cubensis* mushrooms are frequently consumed recreationally without adverse effects other than negative sensory experiences.^{4,5,16} Future case reports and toxicologic studies will be required to document the nephrotoxicity of *P. cubensis* mushrooms.

RHABDOMYOLYSIS-CAUSING MUSHROOMS

Finally, there are 2 species of mycotoxic mushrooms: *Tricholoma equestre*, first reported as toxic in France in 2001, and *Russula subnigricans*, first reported as toxic in China in 2015. Both mycotoxins can cause potentially fatal rhabdomyolysis resulting in acute renal failure after consumption.^{17–19}

In 2001, French investigators reported 12 cases of delayed rhabdomyolysis with 3 fatalities in patients who had consumed consecutive meals of the edible wild mushroom *Tricholoma equestre*, harvested from pine forests in coastal southwestern France (Figure 4).¹⁷ After a prodrome of afebrile fatigue and myalgia 24 to 72 h after the last mushroom meal, most (n=8) patients described worsening weakness and stiffness of their legs, accompanied by facial erythema, mild nausea without vomiting, profuse sweating, and darkening urine color over 3 to 4 d.¹⁷ Rhabdomyolysis was later confirmed by significantly elevated CK levels without laboratory evidence of cardiac or hepatic injury.¹⁷ Muscle biopsy in 6 patients demonstrated histopathologic evidence of acute myopathy.¹⁷ In all but 3 of the patients, serum CK levels normalized and most symptoms resolved, but muscular weakness persisted for weeks.¹⁷

In the 3 fatal cases, serum CK levels continued to rise, and all patients developed hyperthermia up to 42°C,

Figure 5. *Russula subnigricans* mushrooms are native to Asia, with poisonings reported from China, Taiwan, and Japan, where they have been mistaken for edible *Russula nigricans* mushrooms. *R. subnigricans* has caused delayed and fatal rhabdomyolysis with acute renal failure. Source: Lin et al.¹⁸

cardiac arrhythmias, renal dysfunction (elevated serum creatinine, blood urea nitrogen, and potassium), and cardiovascular collapse.¹⁷ Autopsy revealed myocardial lesions identical to the muscle biopsy lesions in 1 patient, renal lesions in 1 patient, and no histopathologic evidence of hepatic damage.¹⁷

In 2015, Chinese investigators reported 7 cases of delayed rhabdomyolysis with 1 fatality in a family (age range 18–58 y) who had consumed 1 meal of cooked *Russula subnigricans* mushrooms harvested from the forests of Guizhou Province in southern China (Figure 5).¹⁸ Twenty hours later, all 7 family members were hospitalized with nausea, vomiting, diarrhea, dizziness, fatigue, and muscle weakness.¹⁸ Five patients presented with myalgias in the upper legs.¹⁸ No patient was febrile on admission.¹⁸ Although serum creatinine and coagulation tests were normal in all patients, serum CK levels were elevated in 6 patients, and all 7 had moderate elevations in serum alanine aminotransferase and aspartate aminotransferase.¹⁸ In 4 of the 6 patients with elevated serum CK levels, the CK continued to rise, weakness worsened, and urine color darkened, consistent with rhabdomyolysis.¹⁸ All 4 patients received hemodialysis to prevent acute kidney injury, and their serum CK levels began to decline to normal ranges by the third day of hemodialysis.¹⁸ In the single fatality, a 50-y-old male, weakness and myalgia with dark urine worsened during the first 12 h after admission, hemodialysis was initiated on the second day after admission, and hyperthermia up to 40°C developed on the third day after admission.¹⁸ Cardiac arrhythmias with QRS widening and cardiovascular collapse ensued as the serum CK levels rose to a maximum of 228,750 UL⁻¹ (laboratory normal range 38–174 UL⁻¹), and the patient died 4 d after admission.¹⁸ Autopsy was not performed.¹⁸

In summary, retrospective epidemiologic analyses conducted worldwide have confirmed that nephrotoxic mushrooms can cause both reversible and irreversible acute and delayed-onset renal failure, with some cases progressing to chronic renal failure, and a few species can cause potentially fatal rhabdomyolysis with its indirectly associated risks of renal damage and failure.

CLINICAL MANIFESTATIONS OF NEPHROTOXIC MUSHROOM POISONING

The currently known and suspected nephrotoxic mushroom species stratified by genera are listed in Table 1. The ecologic and morphologic features of nephrotoxic mushrooms and the clinical manifestations of nephrotoxic mushroom poisonings are described in Table 2.

IDENTIFYING NEPHROTOXINS IN MUSHROOMS AND IN POISONED PATIENTS

Today, heat-stable nephrotoxins such as orellanine (a tetrahydroxylated-N-oxide bipyridine) in *Cortinarius* species mushrooms, allenic norleucine (2-amino-4,5-hexadienoic acid) in *Amanita* species mushrooms, and psilocin in *P cubensis* mushrooms can be most accurately measured directly in the serum and urine of poisoned patients using immunologic and chromatographic techniques, such as enzyme-linked immunosorbent assay, radioimmunoassay, thin-layer chromatography, high-performance liquid chromatography, and liquid chromatography-mass spectrometry.^{26,27}

The mechanisms of orellanine's toxicity in *Cortinarius* species mushrooms are unknown but may be the result of an unidentified nephrotoxic metabolite.²⁷ Toxicologists have demonstrated that oxidated orellanine can generate orthosemiquinone anion radicals in vitro that produce oxygen free radicals and deplete glutathione.²⁷ Investigators have postulated that the oxidation of orellanine in the kidneys may result in an accumulation of quinone metabolites that covalently bind to renal tissues and cause cellular damage.²⁷

Portuguese toxicologists used thin-layer chromatography and *A smithiana* toxin to test several other *Amanita* species for a suspected nephrotoxin.⁹ The *A smithiana* nephrotoxin, now known as allenic norleucine, was detected in samples of *A boudieri*, *A gracilor*, and *A echinocephala*.⁹ The investigators concluded that the intoxications produced by these *Amanita* mushrooms would resemble the toxidrome that followed the consumption of *A smithiana*, with a delayed onset of acute, reversible renal failure and mild hepatitis with

Table 1. Nephrotoxic mushroom species

<i>Cortinarius</i>	<i>Amanita</i>	<i>Tricholoma</i>	<i>Russula</i>	<i>Psilocybe</i>
<i>C bruneofulvus</i>	<i>A boudieri</i>	<i>T equestre</i>	<i>R subnigricans</i>	<i>P cubensis</i>
<i>C brunneoincarnata</i>	<i>A echinocephala</i>	(synonym <i>T flavovirens</i>)		
<i>C callisteus</i> (suspected)	<i>A gracilor</i>			
<i>C cinnamomeus</i> (suspected)	<i>A neoovoidea</i>			
<i>C henrici</i>	<i>A pseudo-porphyrina</i>			
<i>C limonium</i> (suspected)	<i>A proxima</i>			
<i>C ranierensis</i>	<i>A punctata</i>			
<i>C sanguineus</i> (suspected)	<i>A smithiana</i>			
<i>C speciosissimus</i> (synonym <i>C rubellus</i>)				
<i>C splendens</i> (suspected)				

Table 2. Ecology and morphology of nephrotoxic mushroom species and clinical manifestations of poisonings

	<i>Amanita mushrooms</i>	<i>Cortinarius mushrooms</i>	<i>Russula subnigricans</i>	<i>Tricholoma equestre</i>	<i>Psilocybe cubensis</i>
Family	Amanitaceae	Cortinariaceae	Russulaceae	Tricholomataceae	Hymenogastraceae
General descriptions	Large off-white mushrooms; about 600 species; at least 7 are nephrotoxic; many are edible	Largest mushroom family with 2000–3000 species; at least 8 are nephrotoxic; none are recommended as edible worldwide; more nephrotoxic species likely exist	A creamy white mushroom native to eastern Asia, where ingestions have resulted in outbreaks of rhabdomyolysis associated with ARF	A yellow mushroom also known as the yellow knight; formerly considered edible; rhabdomyolysis-associated nephrotoxicity may follow several mushroom meals; many <i>Tricholoma</i> species are edible	Frequently cultivated for its hallucinogenic effects shortly after ingestion, caused by its primary active serotonergic compound, psilocybin
Geographic distribution	Worldwide	Worldwide	China, Japan, Korea, Taiwan	Worldwide	Worldwide in a semitropical band above and below the equator
Preferred habitat	Leaf and needle litter and decaying wood of coniferous and oak woodlands with chalky (limestone) soil	Needle litter of coniferous woodlands with chalky (limestone) soil	Leaf litter of deciduous oak woodlands in mountainous regions	Needle litter of pine forests with sandy soil	Moist, sunny, grassy fields and meadows used for cattle grazing; requires meadow habitats containing cow dung
Color (adult)	Large, white caps that can flatten out from convex to plano-convex	Large orange to rusty brown caps that flatten from convex to flat with age	Large dull creamy white caps that flatten from convex to flat to concave with age	Large yellow to yellow-green cap with yellow gills	Golden brown conical to convex cap that flattens with age; gills darken with age
Color (spore)	Rust brown	Brown	White	White	Dark purple brown
Smell	Described as unpleasant	Slight radish smell	Not distinctive	Not distinctive	Distinctive smell of moist cucumber or watermelon rind
Distinctive mycologic features	Cap convex to flat with age; free gills; stem (stipe) is shaggy with an easily torn annulus (ring) and a prominent volva (base)	Large flat orange to rusty brown caps with gills connected to stems without rings; top of the cap may have a darker umbo (protuberance)	Large dull creamy white caps that flatten from convex to flat to an everted umbrella shape with age; gills attached to thick, stems; no annulus	Large yellow to yellow-green cap with yellow gills attached to an even diameter stem without a ring	Small golden brown conical caps that become more convex to flat to slightly everted umbrella shape; dark gills are attached to long, thin stems with a white annulus
Dimensions (adult)	<i>C orellanus</i>	<i>A smithiana</i>	<i>R subnigricans</i>	<i>T equestre</i>	<i>P cubensis</i>
Height, cm	6–12	6–18	4–10	7–10	4–15
Diameter (cap), cm	3–8	5–17	5–18	5–10	2–8
Edible species most commonly mistaken for	<i>A proxima</i> has been mistaken for edible <i>A ovoidae</i> . <i>A smithiana</i> has been mistaken for edible <i>Tricholoma magnivalere</i> .	<i>Cortinarius</i> species mushrooms have been mistaken for edible chanterelles. <i>C speciosissimus</i> (synonym <i>C rubellus</i>) has been mistaken for edible <i>Cratellus tubaeformis</i> and <i>Hygrophorus</i> species.	<i>R subnigricans</i> has been mistaken for <i>R nigricans</i> , a less poisonous species that may be consumed.	<i>T equestre</i> was formerly considered edible. It has been mistaken for other edible <i>Tricholoma</i> species, such as <i>T aestuans</i> , <i>T auratum</i> , and <i>T sulphureum</i> .	Often confused with other <i>Psilocybe</i> species that contain different amounts of psilocybin.
Clinical toxidromes after ingestion	Rapid-onset GI distress in 6–12 h. Lab evidence ARF in <2–4 d.	Rapid-onset GI distress in 6–12 h. Lab evidence of ARF in >2–14 d.	Delayed-onset GI distress in >24–72 h. Delayed lab evidence of rhabdomyolysis in 3–5 d.	Delayed-onset GI distress in >24–72 h. Delayed lab evidence of rhabdomyolysis in 3–5 d.	Hallucinations within 20–30 min with facial flushing, mydriasis, tachycardia. Resolves in 4–6 h.

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Table 2 (continued)

	<i>Amanita</i> mushrooms	<i>Cortinarius</i> mushrooms	<i>Russula subnigricans</i>	<i>Tricholoma equestre</i>	<i>Psilocybe cubensis</i>
Associated presenting clinical features	Fever, chills, headache, anorexia, fatigue, abdominal and flank pain	Fever uncommon, oliguria progressing to anuria, abdominal and flank pain	Fever uncommon, dizziness, fatigue, weakness, myalgias in upper legs, vomiting uncommon, darkening urine	Fever uncommon, weakness and stiffness in lower extremities, facial erythema and edema, profuse sweating, vomiting uncommon, darkening urine	Potential for delayed onset of ARF within 36 h that resolves with supportive therapy
Risk of CRF	40%	40%	20%	20%	NR

ARF, acute renal failure; CFR, case fatality rate; CRF, chronic renal failure; GI distress, gastrointestinal distress (nausea, vomiting, diarrhea); NR, not reported.

transaminitis.⁹ The mechanisms of allenic norleucine's toxicity are unknown, but it is a suspected direct nephrotoxin.⁹ It causes renal epithelial cell necrosis when cultured with renal tubular epithelium in vitro and does not deplete glutathione as does orellanine.⁹

The hallucinogenic nephrotoxin in *P cubensis* is the tryptamine psilocybin, which is dephosphorylated by hepatic alkaline phosphatase to its active metabolite, psilocin.¹⁶ Both psilocybin and psilocin are multiple serotonin receptor agonists, and their agonism at the 5-HT_{2A} serotonin receptor accounts for most of their hallucinogenic properties.¹⁶

French investigators administered boiled extracts of *T equestre* to mice, which developed significant increases in CK levels and postmortem histopathologic evidence of striated muscle damage compared to control mice, which received boiled extracts from another species of mushroom and maintained normal CK levels and muscle biopsies.¹⁷ The investigators concluded that because most patients with toxic rhabdomyolysis survived, a genetic muscular susceptibility may have triggered the fatal dose-related myotoxic effects after an ingestion threshold of mushrooms was exceeded.¹⁷

In 2016, Japanese investigators isolated a unique compound from *R subnigricans* mushrooms, cyclopropylacetyl-(R)-carnitine, which caused elevated CK levels in mice and was suspected to be the human myotoxin.¹⁹

Visual and microscopic identification of poisonous mushrooms and their spores by experts may offer a more rapid means of identifying mushrooms as potentially nephrotoxic in the field than immunologic and chromatographic techniques in the laboratory. In 2012, Boston-based investigators reported 2 cases of hepatotoxic *Amanita* mushroom poisoning in Ukrainian immigrants in the Boston area; the authors attributed their successful supportive management to early identification of the ingested mushrooms as containing amatoxin via an initial cellphone image transmitted to a consulting poison control center mycologist.²⁸ Nevertheless, there are no specific antidotes for nephrotoxic mushroom poisoning, all treatments are

supportive, and precise identification of the causative species is unnecessary in the short term but recommended for epidemiologic and educational purposes in the long term.

MANAGEMENT OF NEPHROTOXIC MUSHROOM POISONINGS

The general management of nephrotoxic mushroom poisonings should include fluid resuscitation and oral activated charcoal (1 g·kg⁻¹) within the first 1 to 4 h after ingestion. A baseline laboratory assessment should include complete blood count; peripheral blood smear; serum glucose and electrolytes, including calcium; liver and renal function tests; and serum CK. Hepatic transaminases, coagulation studies, serum bilirubin, serum glucose, serum creatinine, blood urea nitrogen, and CK will serve as baseline comparative laboratory values over time. Liver and renal function tests should be repeated at least every 12 to 24 h after toxic mushroom ingestion and followed periodically to exclude late-onset hepatotoxicity from cyclopeptide-containing mushroom co-ingestions (*Amanita*, *Galerina*, and *Lepiota* species) and delayed-onset nephrotoxicity from nephrotoxic *A proxima* and *A smithiana* mushrooms. Finally, serum CK should be measured every 12 to 24 h in the first 5 to 10 d and every 36 h for 10 to 14 d in delayed-onset myotoxicity with rhabdomyolysis from *T equestre* or *R subnigricans* ingestion. All patients with any potential for mushroom nephrotoxin-induced acute renal injury should be referred to medical centers equipped and staffed for hemodialysis and kidney transplantation in the event that conservative supportive care measures fail and severe renal failure ensues.

Conclusions

Nephrotoxic mushrooms, most commonly *Cortinarius* species, can cause acute renal damage and kidney failure. Recently, several new species of nephrotoxic mushrooms have been identified, including *A proxima* and *T equestre* in Europe, *A smithiana* in the Pacific Northwest of the

United States and Canada, *A pseudoporphyria* in Japan, and *A punctata* in Korea. In rare cases, consumption of the edible, hallucinogenic mushroom *P cubensis* has caused acute, reversible renal failure. In addition, 2 newly recognized myotoxic mushrooms can cause rhabdomyolysis with massive myoglobin release that indirectly causes acute kidney injury, *T equestre* in Europe and *R subnigricans* in China. The management of nephrotoxic mushroom poisonings often requires renal replacement treatments, with renal transplantation reserved for extracorporeal treatment failures.

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