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Epidemiology, Diagnosis, and Treatment of Nephrotoxic Mushroom Poisonings Running Title: Nephrotoxic Mushroom Poisonings

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Abstract

Introduction: Since mushroom poisonings are increasing worldwide today as young adults mistake poisonous mushrooms for psychedelic ones and recent immigrants mistake poisonous mushrooms for edible ones at home, the objectives of this descriptive analysis were to identify nephrotoxic mushroom species, to present a toxidromic approach to earlier diagnoses based on the onset of gastrointestinal manifestations and renal failure, and to compare the efficacies and outcomes of renal replacement management strategies.

Methods: Several internet search engines were queried with the key words in order to identify peer-reviewed scientific articles on nephrotoxic mushroom poisonings and their treatments during the search period, 1957-present.

Results: Although the hepatotoxic amatoxin-containing mushrooms cause most mushroom poisonings and fatalities, nephrotoxic mushrooms, most commonly Cortinarius species can cause renal insufficiency and kidney failure. Recently, several new species of nephrotoxic mushrooms have been identified in Asia, Europe, the United States, and Canada. Renal replacement therapies including temporary hemodialysis and renal transplantation are often indicated in the management of nephrotoxic mushroom poisonings.

Conclusions: Unlike the outcomes of amatoxic mushroom poisonings, which are often fatal without liver transplantation, nephrotoxic mushroom poisonings that are diagnosed early and managed with temporary renal replacement therapies usually have good outcomes with full recovery of pre-existing renal function unless irreversible renal failure ensues.

INTRODUCTION

Mushroom poisonings are increasing worldwide today as young adult's mistake poisonous mushrooms for hallucinogenic ones and immigrants mistake poisonous mushrooms for edible ones in their native countries [1]. In many cases, the causative mycotoxins have not been conclusively identified. There are no specific antidotes for mushroom poisonings. Treatment is supportive and aimed at halting end organ damage to the liver and kidneys. Liver or kidney transplantation may be indicated when supportive measures fail.

Most fatal mushroom poisonings are caused by amatoxin-containing hepatotoxic mushrooms, such as *Amanita phalloides* [2]. In addition to hepatotoxic mushrooms, mushroom poisonings are also caused by nephrotoxic mushrooms, most commonly by *Cortinarius* species mushrooms [2]. Recently, several new species of nephrotoxic mushrooms have been identified including *Amanita proxima* and the formerly considered edible, *Tricholoma equestre*, in Europe; *Amanita smithiana* in Canada and the United States (US); *Amanita pseudoporphyria* in Japan, and the formerly considered edible, *Amanita punctata* in Korea [3-8].

METHODS

To meet the objectives of this review, Internet search engines including PubMed, Medline, Ovid, Google®, Google Scholar® and Cochrane were queried with the key words as medical subject headings in order to identify peer-reviewed scientific articles on nephrotoxic mushroom poisonings and their treatments during the search period, 1957-present. The key words included mushrooms, poisonous, nephrotoxic; *Amanita*, poisonous, nephrotoxic; *Cortinarius*, poisonous, nephrotoxic; *Orellanus* syndrome, and orellanine.

The articles selected in order to identify all currently known nephrotoxic mushroom species included case reports, case series, and descriptive reviews of nephrotoxic mushroom poisonings.

The articles selected to identify a toxidromic approach to earlier diagnoses and to compare the efficacies and outcomes of renal replacement treatment strategies included observational studies, descriptive epidemiological studies, and toxicological investigations. The articles excluded from review included expert opinions and panel discussions. As a descriptive analysis of prior publications, this article was exempted from Institutional Review Board approval.

RESULTS

Identifying the Nephrotoxic Mushroom Species

Table 1 lists all of the known mushroom species that produce nephrotoxins [9]. Many other mushrooms, especially *Cortinarius* species, are suspected, but unconfirmed, as being nephrotoxic on ingestion.

The Descriptive Epidemiology of Nephrotoxic Mushroom Poisonings

The nephrotoxicity of *Cortinarius* species mushrooms was initially described in Poland by Stanislaw Grzymala [10] who reported a series of 102 cases of acute renal failure with 11 fatalities in patients who had consumed cooked *Cortinarius orellanus* mushrooms (Figure 1) [10]. Later, Grzymala [11] isolated a crude extract from *C. orellanus* which he named orellanine and which caused renal toxicity when administered to experimental animals [11].

Bouget and coinvestigators [12] in France reported a case series of 26 healthy young men who developed acute renal failure after ingesting mushroom soup made with *Cortinarius orellanus* [12]. All patients were hospitalized within two weeks with 12 patients presenting with acute tubulointerstitial nephritis on renal biopsies [12]. Of these 12 patients, 8 required hemodialysis and recovered rapidly; and the remaining 4 developed chronic renal failure lasting for months [12]. The remaining 14 of the 26 initially poisoned patients were reassessed by Bouget et al [12]. Among them, 12 developed leukocyturia, and all 14 had normal renal function at one-year follow-up [12].

Duvic and coinvestigators [13] later followed 12 of the 26 men who had developed renal failure in the Bouget et al [12] case series for a period of 13 years after ingesting the *C. orellanus* mushroom soup [13]. Of these 12 patients, 7 recovered normal renal function, 4 had kidney transplants, and one patient on hemodialysis died in a car accident [13].

Table 1: Nephrotoxic Mushroom Species [9]

Cortinarius species*	*Amanita* species	*Tricholoma* species	*Russula* species
Cortinarius bruneofulvus *C. brunneoincarnata* *C. henrici* *C. orellanoides* *C. orellanus* *C. ranierensis* *C. speciosissimus*	*Amanita boudieri* *A. echinocephala* *A. gracilor* *A. pseudophoria* *A. proxima* *A. punctata* *A. smithiana*	*Tricholoma equestre*	*Russula subnigricans*

*Many other *Cortinarius* species mushrooms are suspected of being nephrotoxic poisons in humans. As a result, many experts recommend avoiding consumption of *Cortinarius* species mushrooms.

Although most *Cortinarius* poisonings have been reported from Poland and France, *Cortinarius* species mushrooms are widely distributed in the coniferous forests of the Scandinavian countries, Britain, North America, Canada, and Australia [14]. Holmdahl and Blohme [15] reported a case series of 22 patients who were poisoned after consuming cooked *Cortinarius speciosissimus* mushrooms in Sweden (Figure 2) [15]. Nine patients developed chronic renal failure, and five patients required kidney transplants [15]. Three of these patients were transplanted after up to six months of hemodialysis [15]. Two patients who did regain some renal function had to be restarted on hemodialysis 24 and 30 months later and also received kidney transplants [15]. This case series was the first to utilize kidney transplantation in the management of end-stage renal disease following ingestion of *Cortinarius* species mushrooms [15].

By 1997, several other *Cortinarius* species were laboratory-confirmed to contain orellanine including *C. henrici*, C. *orellanoides*, and *C. ranierensis* in North America [15]. Other *Cortinarius* species were also suspected of containing orellanine. As a result, all *Cortinarius* mushrooms are now considered potentially nephrotoxic, and none are recommended for consumption in any form: raw, boiled, cooked, dried, or frozen (Table 1) [14,16].

The mechanisms of orellanine's toxicity are unknown, but may be the result of an unidentified nephrotoxic metabolite [16,17]. Oubrahim and coinvestigators [17] have demonstrated that oxidated orellanine can generate orthosemiquinone anion radicals *in vitro* that produce oxygen free radicals and deplete glutathione. The investigators proposed 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 [17].

Leray and coinvestigators [18] in Montpellier, France, were the first to report five cases of acute renal insufficiency following consumption of cooked *Amanita proxima* mushrooms (Figure 3) [18]. Temporary hemodialysis was required in four of the five cases, and all patients recovered quickly with normal renal and hepatic function restored by three weeks [18].

By the late 1990s, cases of renal insufficiency and failure were initially reported from the North American Pacific Northwest following the consumption cooked *Amanita smithiana* mushrooms [5,6]. Leathem and coinvestigators [5] in British Columbia reported four cases of renal failure in patients who had consumed cooked *Amanita smithiana* mushrooms and developed gastrointestinal symptoms 5-8 hours following ingestion (Figure 4) [5]. One of the patients, an elderly diabetic, presented to an emergency department with renal failure the day after a mushroom meal and required hemodialysis [5]. The remaining three patients presented to local emergency departments 5-6 days after mushroom ingestions and also received supportive

Figure 1 *Cortinarius orellanus*, also known as the fool's webcap, is similar in appearance to *Cortinarius speciosissimus* (synonym *C. rubellus*) with large orange to rusty brown caps with gills underneath connected to thick stems without rings. Like *C. speciosissimus*, *C. orellanus* also contains highly nephrotoxic orellanin compounds. Source: Wikimedia commons (public domain) Photographer: Michael 1.

Figure 2 *Cortinarius speciosissimus* (synonym *C. rubellus*), also known as the deadly webcap, is one of eight or more nephrotoxic species of *Cortinarius* mushrooms with large flat orange to rusty brown caps with gills connected to thick stems without rings. The top of the cap may have a darker umbo or protuberance. The mushroom has a slight radish smell and has been mistaken for edible chanterelle mushrooms. Source: Wikimedia commons (public domain). Photographer: Eric Steinert.

Figure 3 *Amanita proxima* is one of seven or more nephrotoxic *Amanita* species of mushrooms and has most often been confused with an edible *Amanita* mushroom, *A. ovoidae*. *A. proxima* has a large white cap that flattens out with age with free gills unattached to thick stems with membranous rings. Most poisonings have been reported from France and have caused acute renal failure requiring temporary hemodialysis within a few days of ingestion with good outcomes. Source: Wikimedia commons (public domain). Photographer: James Baker.

Figure 4 *Amanita smithiana*, or Smith's *Amanita*, 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 plano-convex cap with unattached free gills and a thick, shaggy white stem with a torn or absent ring or annulus. Although gastrointestinal toxicity occurs 5-8 hours after ingestion, delayed acute renal failure typically requiring hemodialysis will occur 5-6 days after ingestion. Source: Wikimedia commons (public domain). Photographer: Sava Krstic.

care with hemodialysis [5]. All patients subsequently regained normal renal function [5].

Warden and Benjamin [6] in Portland, Oregon, reported four additional cases of acute renal failure following the consumption of cooked *Amanita smithiana* mushrooms in patients mistaking *A. smithiana* for matsutake mushrooms (Figure 4) [6]. All patients presented with gastrointestinal symptoms from 20 minutes to 12 hours following mushroom consumption [6]. All patients subsequently developed acute renal failure 4-6 days post-ingestion, and all received temporary hemodialysis for several weeks before regaining normal renal function [6].

In addition to *A. proxima* in Europe and *A. smithiana* in North America, a delayed onset of acute renal failure was reported from Asia following the consumption of other species of *Amanita* mushrooms, specifically *A. pseudoporphyria* in Japan (2003) and *A. punctata* in Korea (2015) (Figure 5) [7,8].

Kirchmair and coinvestigators [19] in Lisbon, Portugal, used thin layer chromatography and *Amanita smithiana* toxin to test several other *Amanita* species for the suspected nephrotoxin. The *Amanita smithiana* nephrotoxin, now known as allenic norleucine, was detected in samples of *A. boudieri*, *A. gracilor*, and *A. echinocephala* [19]. The mechanisms of allenic norleucine's toxicity are unknown, but it is a suspected direct nephrotoxin [20]. It causes renal epithelial cell necrosis when cultured with renal tubular epithelium *in vitro* and does not deplete glutathione like orellanine [20].

Lastly, there are two species of myotoxic mushrooms, (1) *Tricholoma equestre*, first reported as poisonous in France in 2001, and (2) *Russula subnigricans*, first reported as poisonous in China in 2015, that can cause potentially fatal rhabdomyolysis resulting in acute renal failure following consumption (Figure 6) [4,21]. *Tricholoma equestre*, the yellow knight mushroom, was formerly considered edible and its toxicity was dose-related and associated with an increasing number of mushroom meals [4]. *Russula subnigricans* was commonly mistaken for a less poisonous species that shared the same coniferous forest habitat in China, *Russula nigricans*; but its myotoxicity was not dose-related [21].

Bedry and coinvestigators [4] reported 12 cases of delayed rhabdomyolysis with three fatalities in patients who had consumed consecutive meals of the edible wild mushroom, *Tricholoma equestre* [4]. Following a prodrome of afebrile fatigue and myalgia 24-72 hours after the last mushroom meal, most (n = 8) patients described a worsening weakness and stiffness of their legs accompanied by facial erythema, mild nausea without vomiting, profuse sweating, and darkening urine color over 3-4 days [4]. Rhabdomyolysis was later confirmed by significantly elevated creatine kinase (CK) levels without any laboratory evidence of cardiac or hepatic injury [4]. Muscle biopsies in 6 patients demonstrated histopathological evidence of acute myopathy [4]. In all but three of the patients, the serum CK levels normalized and most symptoms resolved, but muscular weakness persisted for weeks [4].

In the three fatal cases, the serum CK levels continued to rise and all patients developed hyperthermia up to 42° C, cardiac arrhythmias, renal dysfunction (elevated serum creatinine, BUN, and potassium), and cardiovascular collapse [4]. Autopsies demonstrated myocardial lesions identical to the muscle biopsy lesions in one patient, renal lesions in one patient, and no histopathological evidence of hepatic damage in all cases [4]. The causative mushroom mycotoxin remains unidentified.

Lin and coinvestigators [21] reported 7 cases of delayed rhabdomyolysis with one fatality in a family (age range 18-

Figure 5 *Amanita pseudoporphyria*, also known as Hongo's false death cap, was originally described in Japan and prefers the high altitude, coniferous forest undergrowth in Japan, China, Northern India, and Nepal. Although *A. pseudoporphyria* is sold as an edible mushroom in farmers' markets in these areas, it has caused delayed acute renal failure requiring hemodialysis following ingestion. Nephrotoxicity appears to be dose-related as with other *Amanita* species, such as *A. proxima*. Source: Wikimedia commons (public domain). Photographer: Forestwander.

Figure 6 *Tricholoma equestre* (synonym *T. flavovirens*), is also known as the man on horseback or the yellow knight, and was formerly thought to be edible. *T. equestre* has caused delayed and fatal rhabdomyolysis with acute renal failure after ingestion of large amounts of several meals of cooked mushrooms. The mushroom is yellow with a large flat cap and gills connected to a long thick stem without an annulus or ring. Source: Wikimedia commons (public domain). Photographer: Matthias Renner.

58 years) who had consumed one meal of cooked *Russula subnigricans* mushrooms harvested from the forests of Guizhou Province in southern China [21]. Twenty hours later, all 7 family members were hospitalized with nausea, vomiting, diarrhea, dizziness, fatigue, and muscle weakness [21]. Five patients complained of myalgias in the upper legs [21]. Although the serum creatinine and coagulation tests were normal in all patients, serum CK levels were elevated in 6 patients; and all 7 patients had moderate elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [21]. In 4 of the 6 patients with elevated serum CK levels, the CK continued to rise, weakness worsened, and the urine color darkened consistent with myoglobinuria from rhabdomyolysis [21]. 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 [21].

In the single fatal case in a 50-year-old male, weakness and myalgia with dark urine worsened during the first 12 hours after admission; hemodialysis was instituted on the second day after

admission; and hyperthermia up to 40° C developed on the third day after admission [21]. Cardiac arrhythmias with QRS widening and cardiovascular collapse ensued as the serum CK levels rose to a maximum of 228,750 U/L (laboratory normal range = 38-174 U/L), and the patient expired 4 days after admission [21].

In summary, descriptive epidemiological and toxicological analyses have now confirmed that nephrotoxic mushrooms can cause both reversible and irreversible immediate and delayed acute renal failure; and a few species can cause potentially fatal rhabdomyolysis with its associated risks of acute renal failure. Patients with any potential for mushroom nephrotoxin-induced acute renal injury should be referred to medical centers equipped and staffed for immediate hemodialysis and kidney transplantation in the event that conservative supportive care measures fail and irreversible renal failure ensues.

The Diagnosis of Nephrotoxic Mushroom Poisonings

Today, heat-stable nephrotoxins such as orellanine (a tetrahydroxylated-N-oxide bipyridine) in *Cortinarius* species mushrooms and allenic norleucine (2-amino-4,5-hexadienoic acid) in *Amanita smithiana* can be most accurately measured directly in the serum and urine of poisoned patients using immunological and chromatographic techniques, such as enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, thin-layer chromatography, high-performance liquid chromatography, and gas chromatography-mass spectrometry. Visual and microscopic identification of poisonous mushrooms by experts may offer a more rapid means of identifying mushrooms as potentially nephrotoxic than immunological and chromatographic techniques, which are not universally available.

Mushrooms can now be tentatively identified as potentially nephrotoxic in the field using digital telephone images transmitted directly to expert mycologists [22]. If the mushrooms can be presumed to be poisonous, then valuable on-scene observations can be utilized to justify immediate hospital admission for aggressive, supportive therapy before renal failure ensues [22].

Cortinarius Species and the *Cortinarius* Toxidrome

The family Cortinariaceae is the largest family of mushrooms with over 2,000 species, at least 8 of which are known to be nephrotoxic. *Cortinarius* mushrooms prefer a habitat of needle litter in the damp understories of coniferous forests with chalky, limestone-containing soils. *Cortinarius* mushrooms are typically large with rusty orange to brown caps and underlying gills connected to stems without rings as depicted in the images of *C. orellanus* (Figure 1) and *C. speciosissimus* (Figure 2). As noted, all *Cortinarius* mushrooms are considered potentially nephrotoxic today, and none are recommended for human consumption in any form.

The toxidrome that follows the consumption of nephrotoxic *Cortinarius* mushrooms is characterized by an often overlooked prodrome of mild gastrointestinal symptoms within hours of the mushroom meal with nausea and vomiting and, less often, with abdominal pain and diarrhea. The symptoms and laboratory evidence of renal failure are delayed for days, typically less than 7 days (2-4 days); but occasionally up to 14 days. Patients will usually present for urgent care more than 2 days post-ingestion with abdominal and flank pain, polyphagia, polydipsia, either polyuria or oliguria, and rising serum levels of BUN and creatinine. Other general constitutional symptoms may include fever, chills, headache, anorexia, and fatigue [15]. The differential diagnosis includes pyelonephritis, glomerulonephritis, appendicitis, and pelvic inflammatory disease. There are no antidotes, and recovery is slow. Renal biopsies are characterized by a tubulointerstitial nephritis with later progressive interstitial fibrosis. Acute renal insufficiency will require intermittent hemodialysis. Up to 40% of patients will progress to chronic renal failure and require more frequent hemodialysis or a renal transplant [14]. Renal transplantation should not be offered too early as complete recovery has ensued even after months of intermittent hemodialysis [15].

Amanita Species and the *Amanita* Toxidrome

The family Amanitaceae contains about 600 species of mushrooms including some edible species, the hepatotoxic amanitin-containing species, such as *A. phalloides* and *A. virosa,* and at least 8 nephrotoxic species. *Amanita* mushrooms prefer a habitat of deciduous leaves, coniferous needles, and decaying wood in the damp understories of coniferous and oak woodlands with chalky soils. *Amanita* mushrooms are typically large with ivory to dull white caps with free-hanging gills under the caps and thick often shaggy stems and delicate rings as depicted in the images of *A. proxima* (Figure 3) and *A. smithiana* (Figure 4).

The toxidrome that follows the consumption of nephrotoxic *Amanita* mushrooms is characterized by the early onset of gastrointestinal symptoms including nausea, vomiting, abdominal pain, and diarrhea within 12-15 minutes to 12 hours after the mushroom meal that persists for several days usually without fever. Patients will typically present in acute renal failure 2-6 days (typically 4-5 days) post-ingestion with anuria to oliguria, abdominal and flank pain, and rising levels of serum hepatic transaminases, BUN, and creatinine. There are no antidotes, and recovery is relatively rapid within weeks. Renal biopsies are characterized by tubulointerstitial lesions and minor glomerular abnormalities. Acute renal insufficiency will require intermittent hemodialysis in 25%-50% of cases [3,5-8]. Outcomes are typically favorable with complete recovery of normal renal and hepatic function [3]. Up to 40% of patients will progress to chronic renal failure and require more frequent hemodialysis or a renal transplant [3,8]. Renal transplantation should not be offered too early as partial to complete recovery has ensued even after months of hemodialysis [3,8].

The *Rhabdomyolysis*-Associated *Toxidromes*

The rhabdomyolysis-associated toxidromes are very similar following ingestions of cooked meals of either *Tricholoma equestre* or *Russula subnigricans* [4,21]. Among the differentiating

features, *Tricholoma equestre* was formerly considered edible and its toxicity was dose-related and associated with an increasing number of mushroom meals consumed [4].

Tricholoma equestre is a very distinctive mushroom that is bright yellow in color with a large flat yellow to yellow-green cap with gills connected to a long, thick and smooth stem of even caliber without an annulus or ring (Figure 6). *Tricholoma equestre* mushrooms prefer a habitat of leaf litter in deciduous oak woodlands of mountainous regions.

Tricholoma equestre toxidromes are characterized by prodromes of afebrile fatigue and myalgia 24-72 hours after the last mushroom meal, worsening weakness and stiffness of the lower extremities accompanied by facial edema with erythema, mild nausea without vomiting, profuse sweating, and darkening urine color over 3-4 days. In fatal cases, the serum CK levels will continue to rise and patients will develop hyperthermia, cardiac arrhythmias, worsening renal dysfunction, and cardiovascular collapse.

Russula subnigricans mushrooms are native to Asia and poisonings have been reported from China, Taiwan, and Japan where they have been mistaken for the less poisonous, but apparently edible after parboiling, *Russula nigricans* [21]. The mushrooms have large dull creamy white caps that flatten out from convex in juveniles to an everted umbrella shape with age. The gills hanging beneath the caps are attached to thick stems without rings.

In the cases of delayed rhabdomyolysis following the consumption of cooked *Russula subnigricans* mushrooms, patients typically present with nausea, vomiting, diarrhea, dizziness, fatigue, and muscle weakness within 24 hours of the mushroom meal [21]. Most patients experience myalgias in the upper legs and remain afebrile [21]. Although the serum creatinine and coagulation tests remain normal in patients, the serum CK levels will be significantly elevated in all patients; and all patients will have mild to moderate elevations in serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) levels [21]. In fulminant cases, weakness and myalgia with darkening urine will worsen during the first 12 hours after hospitalization necessitating early hemodialysis [21]. In these cases, hyperthermia will develop within days [21]. Cardiac arrhythmias with QRS widening and cardiovascular collapse may ensue as the serum CK levels rise to values in the hundreds of thousands [21].

Rhabdomyolysis is typically confirmed by significantly elevated creatine kinase (CK) levels with little laboratory evidence of hepatic injury, other than moderate elevations of the serum transaminases. Muscle biopsies usually demonstrate histopathological evidence of acute myopathy. Autopsies may demonstrate myocardial lesions identical to the muscle biopsy lesions and no histopathological evidence of hepatic damage [4].

There are no antidotes for mushroom-induced rhabdomyolysis. The management is entirely supportive with urinary alkalization, correction of electrolyte imbalances, and intravenous fluid loading to support brisk diuresis and with early hemodialysis as indicated for renal insufficiency.

Management of Nephrotoxic Mushroom Poisonings

The general management of mushroom poisonings should include fluid resuscitation and gastric decontamination by initial gastric lavage followed by oral activated charcoal (1 g/kg initially, 0.5 g/kg subsequently) [1]. Any leftover mushroom meals and the initial gastric contents should be submitted for toxicological analyses and spore examination by expert mycologists. 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 creatine kinase (CK) [1]. Hepatic transaminases, coagulation studies, serum bilirubin, serum glucose, serum creatinine, BUN, and CK will serve as baseline comparative laboratory values over time [1]. Liver and renal function tests should be repeated at least every 12-24 hours following toxic mushroom ingestions and followed periodically in order to exclude late onset hepatotoxicity from cyclopeptide-containing mushroom co-ingestions (*Amanita*, *Galerina*, and *Lepiota* species) and delayed onset nephrotoxicity from nephrotoxic *Amanita* mushrooms [1]. Finally, serum CK should be measured every 12-24 hours in the first 5-10 days to every 36 hours for 10-14 days in delayed onset myotoxicity with rhabdomyolysis from *Tricholoma* and *Russula* species ingestions [1].

Since mushroom-poisoned patients often present initially with gastrointestinal findings of nausea, vomiting, and diarrhea, emetics and cathartics are contraindicated [1]. Activated charcoal, 1 gram per kg, may be administered orally in the absence of vomiting, or by nasogastric or orogastric tube; but its efficacy remains unconfirmed. Initial gastrointestinal toxicity may be followed by acute or end-stage renal failure or liver failure and, rarely, pancreatic insufficiency. Any evidence of worsening hepatic or renal function or rhabdomyolysis should alert clinicians to the possibility of potentially fatal toxidromes, and immediate preparations should be made to transfer patients to the closest facilities equipped and staffed for hemodialysis and kidney and liver transplantation.

CONCLUSIONS

Although the hepatotoxic amatoxin-containing mushrooms cause most mushroom poisonings and fatalities worldwide, nephrotoxic mushrooms, most commonly *Cortinarius* species, can cause renal damage and kidney failure. Recently, several new species of nephrotoxic mushrooms have been identified including *Amanita proxima* and *Tricholoma equestre* in Europe, *Amanita smithiana* in the Pacific Northwest of the United States (US) and Canada, *Amanita pseudoporphyria* in Japan, and *Amanita punctata* in Korea. Renal replacement therapies including temporary hemodialysis are often indicated in the management of nephrotoxic mushroom poisonings with renal transplantation reserved for extracorporeal treatment failures. Unlike the

outcomes of amatoxic mushroom poisonings, which can be fatal without liver transplantation, nephrotoxic mushroom poisonings that are diagnosed early and managed with temporary renal replacement usually have good outcomes with full recovery of pre-existing renal function unless irreversible renal failure ensues. Renal transplantation should not be offered too early as partial to complete recovery of pre-existing renal function has ensued even after months of hemodialysis.

Author contributions

Sole author contributed 100% to the manuscript.

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