

Worldwide Mushroom Poisoning, Diagnosis and Treatment: Comments on Some of the Recent Research

Michael W. Beug

I periodically get questioned about what is being published on mushroom toxicology, and so I have spent some time assembling references to some of the recent papers. I have not done an exhaustive review, but have tried to find interesting papers that provide insight into how diagnoses and treatment of mushroom poisoning is being approached around the world as well as the scope and nature mistakes people are making when attempting to pick edible mushrooms for the table. The papers will be presented in approximate order of publication starting with 2005 and proceeding through 2007.

Berger and Guss (2005) “reviews the epidemiology and demographics of mushroom poisoning, the physical characteristics of the most toxic varieties, the classification of toxic species, and an overview of the cyclopeptide-containing mushroom class. Part II, to be published in the next issue of the Journal [*The Journal Emergency Medicine*], will be focused on the presentation of the other classes of toxic mushrooms. . . .” This pair of papers will be of particular interest to individuals interested in mushroom toxicology who do not have a reference like Lincoff and Mitchell (1977), *Toxic and Hallucinogenic Mushroom Poisoning*, or the more recent book by Denis R. Benjamin (1995), *Mushrooms: Poisons and Panaceas*.

Diaz (2005) reviewed 28,018 mushroom poisonings covering the period 1951–2004. He expands the 8–10 major recognized syndromes to 14 major syndromes delineated by timing of onset of symptoms and by target organ systemic toxicity. He uses the standard early onset (<6 hours), late onset (6–24 hours) and delayed onset (> or = 1 day) syndromes. Diaz then recognizes

eight early syndromes: four neurotoxic, two gastrointestinal, and two allergic. He recognizes three late syndromes involving liver damage (hepatotoxic), accelerated kidney damage (accelerated nephrotoxic), and burning pain plus warmth and redness of the extremities (erythromelalgia). Finally, he outlines three delayed syndromes involving delayed kidney damage, delayed neurotoxicity, and breakdown of muscle fibers with release of myoglobin into the blood stream (rhabdomyolysis). Accelerated nephrotoxicity are characteristics of *Amanita smithiana* and *Amanita proxima*. Rhabdomyolysis has been attributed to massive ingestions of *Tricholoma equestre* (= *T. flavovirens*) in France and *Russula subnigricans* in Japan (note: *Russula subnigricans* is also in the southern U.S.). Erythromelalgia is associated with *Clitocybe amoenolens* (in Europe) and *Clitocybe acromelalgia* (in Japan). He reported on delayed neurotoxicity with *Hapalopilus rutilans* (= *Hapalopilus nidulans*). This last case was new to me but could turn up in North America since *Hapalopilus rutilans* is a small fleshy orange-ish polypore found in eastern North America that turns purple or lilac when a drop of KOH is placed on its surface.

Saviuc and Danel (2006) add additional insight into some of the new syndromes that generally occur more than six hours post-ingestion. They point out that the erythromelalgia syndrome was described as early as the 19th century in Japan and South Korea with *Clitocybe acromelalga* and since 1996 in France and later in Italy with *Clitocybe amoenolens*. Erythromelalgia occurs as a result of a maldistribution of blood flow with extremities of the body (typically nose, fingers, and toes), calling for more blood and winding up with so much blood flow through various open vessels that hands and feet and nose receive too much and turn bright red and



Figure 1a. *Clitocybe inversa* (left). Figure 1b. *Clitocybe squamulosa* (right).



Figure 2. *Amanita smithiana* (left).
Figure 3. *Cortinarius rubellus* (right).

warm to the touch. The situation is very painful, and symptoms can last for months. Onset of symptoms is about one week after ingestion of the mushrooms and appears to be caused by acromelic acids, compounds that structurally mimic the neurotransmitter glutamate. Tsutomu et al. (2001) note that *Clitocybe acromelalga* also contains clitidine, “which resembles nicotinic acid mononucleotide, and 4-amino-pyridine-2,3-dicarboxylic acid, which resembles quinolinic acid. Both are important intermediates in the tryptophan-niacin pathway.” They concluded in a rat feeding study that *Clitocybe acromelalga* appeared to increase the conversion of tryptophan to niacin.

I have not yet received any reports of either *Clitocybe acromelalga* or *Clitocybe amoenolens* in North America nor do I have any reports of the erythromelalgia syndrome in North America. However, I do not recommend the consumption of *Clitocybe* species where there is not a long history of edibility. I would especially avoid species like *Clitocybe (Lepista) inversa*, *Clitocybe squamulosa* (Fig. 1), *Clitocybe gibba*, and *Hygrophoropsis aurantiaca* which somewhat resemble *Clitocybe amoenolens*.

Consistent with the poisoning that occurred in Oregon when a man mistakenly consumed *Amanita smithiana* (Fig. 2) thinking he had Matsutake, Saviuc and Daniel (2006) find that the poisoning, probably caused by 2-amino-4,5-hexadienoic acid in *Amanita smithiana*, typically does not have a poor outcome. The *Amanita smithiana* syndrome which has been described since 1992 in North America consists of acute tubulopathy (damage to the tubes in the kidney) appears earlier and does not have the same poor prognosis as the orellanine-induced syndrome. The syndrome has been reported in France, Spain, and Italy with *Amanita proxima* and in Japan with *Amanita pseudoporphyria*. Yang et al. (2006) report on two cases of acute anuric renal failure in Taiwan possibly due to *Amanita smithiana* or a related species. They report a full recovery following hemodialysis and supportive treatment. They note that mushroom poisoning is rarely reported in Taiwan despite an abundance of wild mushrooms.

While we have several cases of the *Amanita smithiana* syndrome from the Pacific Northwest in North America, so far we have only one case of the more dangerous and potentially lethal orellanine-induced syndrome. That poisoning occurred in the summer of 2008 and involved kidney failure in a woman who consumed a *Cortinarius* species found under oaks. Full details have not yet been published, but DNA analysis indicated that the mushroom was closely related to *Cortinarius orellanus* (Ammirati and Matheny, personal communication). We also have one named mushroom in North America known to contain orellanine and that is *Cortinarius rubellus* Cooke (Robertson et al., 2006). This mushroom has long been known as *Cortinarius orellanoides* (from deciduous forests in northeastern North America), *Cortinarius speciosissimus* (from acidic coniferous woods and moorlands in Europe) and *Cortinarius rainierensis* from acidic coniferous woods in the Pacific Northwest. Christie Robertson has provided illustrations of this species (Fig. 3).

Saviuc and Danel (2006) also discuss several cases of massive rhabdomyolysis first reported in France in 1993 and later in Poland in 2001 from ingestions of large amounts of *Tricholoma equestre*. *Tricholoma equestre* (Fig. 4) is common in North America. They report that “these cases of rhabdomyolysis are associated with res-



Figure 4. *Tricholoma equestre*.

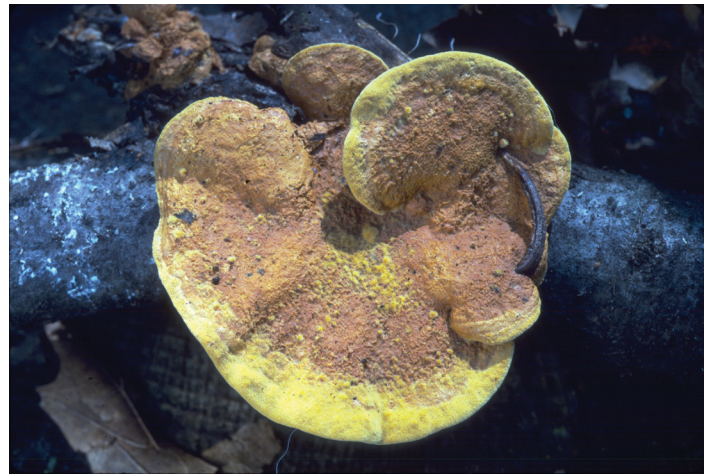


Figure 5a. *Hapalopilus nidulans*, left, and the more yellowish *Hapalopilus croceus*, Figure 5b, right, both courtesy of Bill Roody.

piratory and cardiac (myocarditis) complications leading to death.” Myocarditis is an inflammation of the heart muscle. They note that the rhabdomyolysis observed with *Russula subnigricans* in Japan and Taiwan occurs by a different mechanism than that observed with *Tricholoma equestre*. Saviuc and Danel (2006) conclude with a discussion of encephalopathy observed twice in Germany in 1992 after ingestion of *Hapalopilus rutilans* (= *Hapalopilus nidulans*) (Fig. 5). Encephalopathy is a degenerative brain disorder. They also discuss incidents in Japan in 2004 where ingestion of large amounts of *Pleurocybella porrigens* (Fig. 6) led to an outbreak of convulsive encephalopathy in patients with a history of chronic renal failure resulting in over a dozen deaths.

Unverir et al. (2007) in Turkey provided what they say is the first report of elevation of cardiac enzymes in a patient with *Amanita phalloides* poisoning. The man presented at the hospital 42 hours post ingestion. “Hepatic, renal function tests, amylase and cardiac enzymes (troponin I, creatine kinase [CK], CK-MB isoenzyme and myoglobin) were found elevated in his blood chemistry. The electrocardiogram disclosed sinus tachycardia. Aggressive treatment with fluids, activated charcoal, penicillin G and silibinin were started. The patient was sent to hemodialysis because of anuria.” The patient was eventually discharged following arrangement for dialysis due to chronic renal failure. The authors conclude that, “Elevated cardiac enzyme levels without any acute coronary syndrome are probable in mushroom poisoning cases involving amatoxin ingestion.”

Joshi et al. (2007) reported on a retrospective analysis of mushroom cases at one hospital in Nepal during a two-month period in 2005. Out of 41 admissions, they analyzed the 34 cases where records were available. Fifteen of the cases (44%) were in the pediatric age group. There were 12 mortalities with a median time of 3.5 days after admission with the main causes of death acute liver failure and acute renal failure due to consumption of *Amanita phalloides* (Fig. 7). They felt that they were seeing an increased mortality in alcoholics versus non-alcoholics who had

consumed *Amanita phalloides*. They attribute the high mortality to late presentation at the hospital and only conservative management in all of the cases. Since they do not say how many of the 34 cases were due to ingestion of *Amanita phalloides*, and have no data on an additional seven cases, it is difficult to calculate a mortality rate. We can safely say that the minimum mortality rate observed for *Amanita phalloides* was 12/41 or 30%.

Erguven et al. (2007) analyzed 39 pediatric patient outcomes in Turkey for the period 1994–2004 in order to better understand the clinical picture and prognostic factors in children with α -amanitin and non-amanitin mushroom poisoning. “Conventional therapy, antidote therapy together with hemoperfusion, was carried out in 16 (41%) of the patients. Four of the patients in whose blood amatoxin was detected (50%) and 3 of the patients highly suggestive of amanita poisoning (30%), totally 7 patients died of hepatic coma. The average time of admission to hospital, mean AST, ALT, creatin and PT values at 3rd day were significantly higher in patients who died of hepatic coma.” They conclude that early diagnosis and treatment can be lifesaving. This is consistent with what Joshi et al. observed in Nepal and with we have found in North America where early and aggressive treatment of α -amanitin poisoning has resulted in a mortality rate of less than 10%. The death rate in Turkey was 36.8% of the pediatric patients with suspect or confirmed α -amanitin exposure. Karakayali et al. (2007) examined 12 cases of pediatric liver transplantation in Turkey for liver failure due to a variety of causes, only one of which was *Amanita phalloides* poisoning. What was noteworthy to me is that only 9 of the 12 transplant patients survived for more than 7 months after surgery. This highlights the need to be absolutely certain that transplantation is a necessary procedure. Pawlowska et al. (2006) report on a Polish poisoning of a family of three by *Amanita phalloides*. All three suffered fulminant hepatic failure and underwent liver transplantation. The son and father transplanted at days 5 and 7 survived while the mother operated on at day 9 died in surgery of massive hemorrhage and cardiac arrest. Escudé

et al. (2007), working in France, proposed a reassessment of transplantation criteria for *Amanita phalloides* poisonings. In France 30% of the people who ingest *Amanita phalloides* become so ill that they will die without a liver transplant. The authors conclude that if the interval between ingestion and diarrhea is < 8 hours, liver transplantation is almost certainly going to be required in order to prevent a fatal outcome. They point out that encephalopathy should not be an absolute prerequisite for deciding transplantation since neither encephalopathy nor renal insufficiency were constant in the fatal intoxication group. In contrast, a prothrombin index lower than 10% (approximate INR of 6) from day four after ingestion was 100% accurate in predicting a fatal outcome unless a liver becomes available in time. The prothrombin index and INR are measurements of blood clotting ability. The Polish woman being operated on for a liver transplant cited in Pawlowska (2006) essentially died from the result of α -amanitin acting as an extreme blood thinner so that the surgeons could not control bleeding when they attempted to do a liver transplant.

Bakos et al. (2007) in Budapest reported on their study of three patients with acute incurable liver failure from severe intoxication with paracetamol, potassium permanganate and *Amanita phalloides* respectively who were treated using a relatively new procedure called Prometheus® treatment. "During the procedure the patient's own separated albumin-rich plasma passes through special absorbents making possible the elimination of albumin-bound toxins, while hemodialysis gets rid of water-soluble toxins." Because of organ shortage in liver transplantation leading to a significant number of deaths of patients waiting for a liver transplant, the authors were seeking a way to deal with cases untreatable with conservative therapy while waiting for either spontaneous liver regeneration or the availability of a donor organ. In this study, all three patients in acute liver failure were cured without liver transplantation. The beauty of the human liver is that it is the one human organ that can regenerate after damage.

Madhok (2007) presents a "case report of 7 Minnesota residents who developed symptoms of *Amanita* poisoning after consuming cooked mushrooms picked at a county park." The author also includes a review of the symptoms and management of *Amanita* poisoning from ingestion of α -amanitin. Puschner et al. (2007) discuss how to confirm α -amanitin poisoning in a dog.

Rainone (2005) was one of several authors who examined milk thistle extract as a means of protecting against liver damage from mushrooms containing α -amanitin. He points out that clinical studies are largely heterogeneous and contradictory but that aside from mild gastrointestinal distress and allergic reactions, side effects are rare and when they occur are rarely severe. "In an oral form standardized to contain 70 to 80% silymarin, milk thistle appears to be safe for up to 41 months of use." My understanding, however, is that silymarin is not very available orally. Injectable silymarin, which is heavily used in Germany, has been approved



Figure 6. *Pleurocybella porrigens*.



Figure 7. *Amanita phalloides*.

for experimental use in the U.S. beginning in the summer of 2009. Pradhan and Girish (2006) in India conclude that "as it (silymarin) is having a good safety profile, better patient tolerability, and an effective drug at an affordable price, in near future new derivatives or new combinations of this drug may prove useful." They maintain that the drug is effectively absorbed orally and that it promotes "protein synthesis, helps in regenerating liver tissue, controls inflammation, enhances glucuronidation and protects against glutathione depletion." In laboratory animals it was found to act by "antioxidative, anti-lipid peroxidative, antifibrotic, anti-inflammatory and liver regenerating mechanisms."

Xiao et al. (2007) in China set out to assess the effects of treatment of *Amanita* mushroom poisoning (due to α -amanitin) with a decoction of "Glossy Ganoderma" (*Ganoderma lucidum*). "Twelve patients with acute *Amanita* mushroom poisoning received conventional treatment (penicillin and reduced glutathione) combined with oral administration of GGD (treated group), which was prepared out of 200 g Glossy Ganoderma decocted in water to 600 mL, and 200 mL was given once, three times a day for 7

successive days; while conventional treatment alone was given to the other 11 patients assigned to the control group.” They concluded that they observed a statistically significant reduction in mortality and improvement in recovery rate with the GGD.

Zhao et al. (2006), in Sichuan University, China, studied the pathological effects of injected α -amanitin on BALB/c mice. They found that sensitive markers of damage to the liver and kidneys were sera BUN, Crea, ALT, AST, TBIL and DBIL. Likewise, the expression of 66 genes decreased while 80 increased more than two-fold after 48 hours. Alpha-amanitin influenced not only RNA polymerase II, but also the expression of its associated genes. They proposed a system for use in screening curative drugs to deal with α -amanitin intoxication.

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