CHEST

# Survival Following Investigational Treatment of Amanita Mushroom Poisoning

## Thistle or Shamrock?

*Kathryn M. Gores, MD; Tarek S. Hamieh, MD; and Gregory A. Schmidt, MD, FCCP*

We report the first case, to our knowledge, of amatoxin hepatotoxicity in Iowa and explore the ethical and decisional challenges of offering an investigational treatment of a rare disease. Acute liver failure due to ingestion of amatoxin-containing mushrooms is a relatively rare entity. Once amatoxin poisoning is identified, there is no clearly effective treatment, leading to a broad range of theoretically beneficial, anecdotally successful, or investigational options. The evolution of hepatotoxicity led us to offer investigational treatment with silibinin, an extract of Mediterranean milk thistle. We explore the pitfalls in medical decision-making experienced by both the patient and the physician in the face of ambiguity. The patient did well following silibinin infusion, but we are left uncertain as to whether the patient truly responded to treatment or was simply destined to recover. CHEST 2014; 146(4):e126-e129

Mushroom poisoning is a rare but important cause of acute hepatic failure. Amatoxin-containing mushrooms, such as *Amanita phalloides* and *Amanita virosa*, account for approximately 95% of the deaths attributable to mushroom ingestion worldwide.[1] Most Amanita toxicity is seen in Europe and Central America, but cases appear to be on the rise in the United States as well. Toxic species are most prevalent in the Pacific Northwest, but case reports have identified cases in midwestern states, including Minnesota,[2] Missouri,[3] and Ohio.[4] Deadly Amanitas resemble edible mushrooms, accounting for their accidental ingestion. Poisoning produces a wide array of vague symptoms that are often delayed in onset, making this a difficult diagnosis and emphasizing the importance of thorough assessment and laboratory investigation in any suspected poisoning.[5,6]

Amatoxins are taken up by hepatocytes and bind irreversibly with RNA polymerase II to inhibit the elongation step of transcription, suppressing protein synthesis and causing cell death.[1,7] Approximately 60% of the absorbed amatoxin is excreted into the bile and returned to the liver via enterohepatic circulation, serving to prolong the exposure.[8] The dominant toxicity of amatoxins is hepatic injury, but respiratory arrest,[9] renal failure, and rhabdomyolysis have been reported.[10] Encephalopathy and convulsions are common in severe cases.[11]

Amanita mushroom poisoning is rare, and treatment advice is based largely on anecdotal reports and observational series.[12-15]

Manuscript received July 9, 2013; revision accepted April 15, 2014.

**AFFILIATIONS:** From the Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA.

**CORRESPONDENCE TO:** Gregory A. Schmidt, MD, FCCP, 200 Hawkins Dr, Iowa City, IA 52242; e-mail: gregory-a-schmidt@uiowa.edu



**DOI:** 10.1378/chest.13-1573

Because enterohepatic circulation may amplify toxicity (as shown in dogs),[1] multiple-dose activated charcoal is recommended. N-acetylcysteine has also been offered for its antioxidant effects. High-dose penicillin may disrupt hepatocellular uptake of amatoxins,[14,16] and similar properties have been attributed to silibinin, an extract of Mediterranean milk thistle.[13,14,17] Milk thistle and its extracts have been used for centuries as homeopathic remedies for liver and gallbladder problems.[18] Modern research has shown that silibinin may be efficacious in amatoxin poisoning because it competes with amatoxins for transmembrane transport and inhibits penetration into hepatocytes.[19] Currently, physicians have no basis for preferring one treatment over another because there are no randomized, clinical trials. Therefore, the high risk of death may push the physician to offer unproved options.

We present the first case of Amanita mushroom poisoning in Iowa. The patient developed acute hepatic failure, prompting us to offer and administer silibinin as part of an investigational, open-label, treatment trial.[20] The patient recovered, yet we are left to wonder whether the investigational treatment or simple good luck should get the credit. We discuss some of the reasons a physician or a patient may be persuaded to consider an unsupported treatment, and the pitfalls associated with this treatment dilemma.

## Case Report

A 71-year-old man presented with progressive nausea, vomiting, diarrhea, and weakness 48 h after having ingested wild mushrooms while camping in northwestern Iowa. The following day, nausea, vomiting, and profuse, watery diarrhea led him to seek medical attention. Vital signs and physical examination results were normal. Abnormal chemistry levels included elevated aspartate aminotransferase, 2,313 IU/L (normal range, 15-37 IU/L); alanine aminotransferase, 2,730 IU/L (normal range, 12-78 IU/L); total bilirubin, 1.5 mg/dL (normal range, 0.0-1.0 mg/dL); international normalized ratio, 1.3 (normal range, 0.8-1.2); and creatinine, 2.7 mg/dL (normal range, 0.51-1.2 mg/dL) (Fig 1). The regional Poison Control recommended treatment with IV N-acetylcysteine for 48 h and penicillin G, 24 million units daily continuous infusion for 48 h. The following morning the patient became encephalopathic. Given the combination of acute kidney injury, encephalopathy, coagulopathy, and worsening transaminase elevations, he was classified as having stage 4 amatoxin poisoning and was transferred to our liver transplant center.

Transplant evaluation was initiated, and multidose activated charcoal was added via nasogastric tube. Following evaluation, the transplant team concluded that continued supportive measures were indicated. The patient was also granted expedited institutional review board approval for enrollment in phase 2/phase 3 Prevention and Treatment of Amatoxin Induced Hepatic Failure With Intravenous Silibinin (Legalon SIL): an Open Multicenter Clinical Trial.[20] Silibinin was first given about 96 h after ingestion at the clinical trial loading dose of 5 mg/kg over 1 h and was continued for 3 days at 20 mg/kg/d with no apparent adverse drug reaction. Encephalopathy and acute kidney injury resolved by hospital day 3, and the patient was discharged on hospital day 5. Liver enzymes were normal at 1 month (aspartate aminotransferase, 21 IU/L; alanine aminotransferase, 20 IU/L; bilirubin, 0.2 mg/dL). The patient was counseled to avoid ingesting wild mushrooms.

## Discussion

Patients diagnosed early with amatoxin poisoning have the best chance of surviving and generally require symptomatic treatment only. Patients identified later have a much higher probability of death. When faced with severe morbidity or high mortality, physicians and patients often consider nonapproved therapies. When given a bleak prognosis, such patients are often willing to accept the risks associated with experimental treatments in exchange for hope of cure, prolongation of life, or significant palliation of symptoms.

Although patients often come to treatment expecting clear benefit, experienced physicians understand ambiguity; not all patients will benefit from a selected treatment.[21] Shared decision-making, a process in which patients and physicians join together in a partnership to evaluate the alternatives for a particular medical decision,[22-24] can be an effective approach to ambiguity, but both the physician and the patient must recognize the uncertainty of diagnosis and treatment options, as well as the accompanying risks and benefits.

A potential research subject may not understand the differences between the therapeutic and the research aspects of treatment. Ethical principles of research demand that this distinction be elucidated clearly in the informed consent process, but this process is imperfect. A study by Grossman and colleagues[25] showed that only 1% to 6% of consent forms were readable at the eighth grade level, with the mean scores befitting 2 years of college education. In addition, a similar study found that 90% of patients stated that they understood all or most of the information provided to them about a phase 1

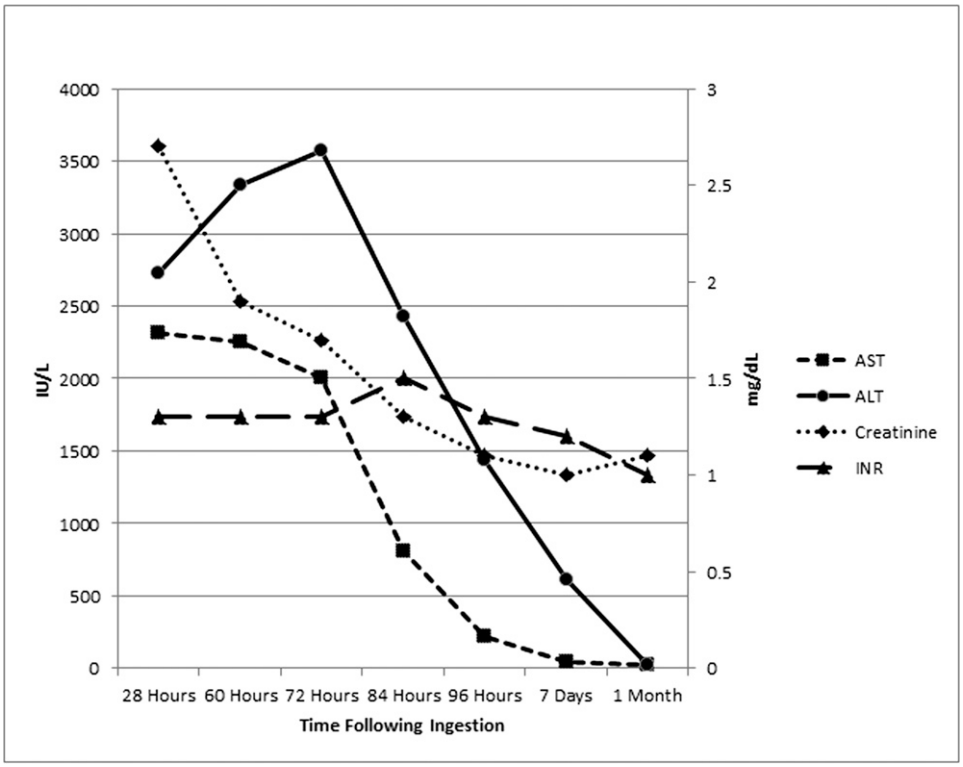


Figure 1 – *Elevation of ALT, AST, creatinine, and INR after admission to the hospital, indicating severe liver injury. ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio.*

clinical trial in which they had agreed to participate,[15] but follow-up studies showed that fewer than one-third of the patients could state the purpose of the trial in which they had agreed to participate.[15,26] Multiple studies have shown that subjects participating in phase 1 trials are motivated by hope of therapeutic benefit.[26,27] In fact, many patients were unable to recall whether alternative pathways, including palliative care or other nonexperimental therapies, were offered to them. For diseases that produce encephalopathy, as is common in hepatic failure, there is even less prospect of the patient participating in shared decision making. Finally, the more life threatening the disease is, the less likely subjects are to refuse experimental treatment.[28] Overall, these studies suggest that many research participants have difficulty understanding consent language, have interpreted the possible outcomes with undue optimism, and lack understanding of treatment alternatives.

The physician's role is similarly laden with pitfalls. From an ethical perspective, physician-researchers have a conflict of interest in their roles as both an individual's physician and a research scientist.[29] The ability of investigators to provide unbiased information regarding participation in clinical trials in a way that enables patients to fully recognize and understand the risks and benefits has been called into question.[30] Principal investigators will often admit that balancing patients', as well as their own, hopes and expectations is a daily challenge.[31]

## Conclusions

We report the successful treatment of the first case of Amanita mushroom toxicity in the state of Iowa. We found ourselves faced with a deteriorating patient, no proven treatment, and the question of whether we should offer an experimental therapy or trust only in our supportive management. The patient recovered after treatment with multiple-dose activated charcoal, N-acetylcysteine, and penicillin, and experimental treatment with silibinin, prompting him and his physicians to believe that the experimental treatment "worked." Moreover, no adverse, short-term, treatment-related toxicity was apparent. But should we attribute his recovery to an extract of thistle or was he blessed by the shamrock, a beneficiary of luck alone? Of course, we will never know in this individual circumstance, as is too often true in medicine.

## Acknowledgments

**Financial/nonfinancial disclosures:** The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

**Other contributions:** *CHEST* worked with the authors to ensure that the Journal policies on patient consent to report information were met.

## References


1. Magdalan J, Ostrowska A, Podhorska-Okołów M, et al. Early morphological and functional alterations in canine hepatocytes due to alpha-amanitin, a major toxin of *Amanita phalloides*. *Arch Toxicol*. 2009;83(1):55-60.
2. Madhok M. Amanita bisporgera. Ingestion and death from mistaken identity. *Minn Med*. 2007;90(9):48-50.
3. Madhok M, Scalzo AJ, Blume CM, Neuschwander-Tetri BA, Weber JA, Thompson MW. Amanita bisporigera ingestion: mistaken identity, dose-related toxicity, and improvement despite severe hepatotoxicity. *Pediatr Emerg Care*. 2006;22(3): 177-180.
4. Broussard CN, Aggarwal A, Lacey SR, et al. Mushroom poisoning-from diarrhea to liver transplantation. *Am J Gastroenterol*. 2001;96(11):3195-3198.
5. Levine M, Brooks DE, Truitt CA, Wolk BJ, Boyer EW, Ruha AM. Toxicology in the ICU: part 1: general overview and approach to treatment. *Chest*. 2011;140(3):795-806.
6. Brooks DE, Levine M, O'Connor AD, French RN, Curry SC. Toxicology in the ICU: part 2: specific toxins. *Chest*. 2011;140(4):1072-1085.
7. Klein AS, Hart J, Brems JJ, Goldstein L, Lewin K, Busuttil RW. Amanita poisoning: treatment and the role of liver transplantation. *Am J Med*. 1989;86(2):187-193.
8. Faulstich H. New aspects of amanita poisoning. *Klin Wochenschr*. 1979;57(21):1143-1152.
9. Brandin AC, Meola SD, Mazzaferro EM. Respiratory arrest following ingestion of wild mushrooms in 3 dogs (2006-2011). *J Vet Emerg Critical Care (San Antonio)*. 2013;23(6):605-609.
10. Mastaglia FL, Needham M. Update on toxic myopathies. *Curr Neurol Neurosci Rep*. 2012;12(1):54-61.
11. Levine M, Ruha AM, Graeme K, Brooks DE, Canning J, Curry SC. Toxicology in the ICU: part 3: natural toxins. *Chest*. 2011;140(5):1357-1370.
12. Enjalbert F, Rapior S, Nouguier-Soulé J, Guillon S, Amouroux N, Cabot C. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol*. 2002;40(6):715-757.
13. Mengs U, Pohl RT, Mitchell T. Legalon® SIL: the antidote of choice in patients with acute hepatotoxicity from amatoxin poisoning. *Curr Pharm Biotechnol*. 2012;13(10):1964-1970.
14. Poucheret P, Fons F, Doré JC, Michelot D, Rapior S. Amatoxin poisoning treatment decision-making: pharmaco-therapeutic clinical strategy assessment using multidimensional multivariate statistic analysis. *Toxicon*. 2010;55(7):1338-1345.
15. Daugherty C, Ratain MJ, Grochowski E, et al. Perceptions of cancer patients and their physicians involved in phase I trials. *J Clin Oncol*. 1995;13(5):1062-1072.
16. Floersheim GL. Experimental basis for the therapy of *Amanita phalloides* poisoning [in German]. *Schweiz Med Wochenschr*. 1978;108(6):185-197.
17. Ward JKK, Kapadia K, Brush E, Salhanick SD. Amatoxin poisoning: case reports and review of current therapies. *J Emerg Med*. 2013;44(1):116-121.
18. Flora K, Hahn M, Rosen H, Benner K. Milk thistle (Silybum marianum) for the therapy of liver disease. *Am J Gastroenterol*. 1998;93(2):139-143.
19. Sorodoc L, Lionte C, Sorodoc V, Petris O, Jaba I. Is MARS system enough for A. phalloides-induced liver failure treatment? *Hum Exp Toxicol*. 2010;29(10):823-832.
20. National Institutes of Health Clinical Center. Intravenous milk thistle (Silibinin-Legalon) for hepatic failure induced by amatoxin/amanita mushroom poisoning. NCT00915681. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2009. http://clinicaltrials.gov/ct2/show/NCT00915681. Updated October 26, 2012.
21. Kaplan RM, Frosch DL. Decision making in medicine and health care. *Annu Rev Clin Psychol*. 2005;1:525-556.
22. Elwyn GEA, Edwards A, Kinnersley P. Shared decision-making in primary care: the neglected second half of the consultation. *Br J Gen Pract*. 1999;49(443):477-482.
23. Frosch DLKR, Kaplan RM. Shared decision making in clinical medicine: past research and future directions. *Am J Prev Med*. 1999;17(4):285-294.
24. Woolf SH. Shared decision-making: the case for letting patients decide which choice is best. *J Fam Pract*. 1997;45(3):205-208.
25. Grossman SAPS, Piantadosi S, Covahey C. Are informed consent forms that describe clinical oncology research protocols readable by most patients and their families? *J Clin Oncol*. 1994;12(10): 2211-2215.
26. Daugherty CK, Kialbasa TA, Siegler M, et al. Informed consent in clinical research: a study of cancer patient understanding of consent forms and alternatives of care in phase I clinical trials. *Proc Am Soc Clin Oncol*. 1997;16:188a.
27. Daugherty CK, Lyman K, Mick R, et al. Differences in perceptions of goals, expectations, and level of informed consent in phase I clinical trials. *Proc Am Soc Clin Oncol*. 1996;15:352a.
28. Gallo CPF, Perrone F, De Placido S, Giusti C. Informed versus randomised consent to clinical trials. *Lancet*. 1995;346(8982):1060-1064.
29. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Belmont Report: Ethical Principles and Guidelines for the protection of Human Subjects of Research*. Washington, DC: Government Printing Office; 1978.
30. Bok S. Shading the truth in informed consent for clinical research. *Kennedy Inst Ethics*. 1995;5(1):1-17.
31. Henderson GEDA, Davis AM, King NM, et al. Uncertain benefit: investigators' views and communications in early phase gene transfer trials. *Mol Ther*. 2004;10(2):225-231.