

Amatoxin Mushroom Poisoning in North America 2015-2016

By Michael W. Beug PhD

Chair NAMA Toxicology Committee

Assessing the degree of amatoxin mushroom poisoning in North America is very challenging. Understanding the potential for various treatment practices is even more daunting. Although I have been studying mushroom poisoning for 45 years now, my own views on potential best treatment practices are still evolving. While my training in enzyme kinetics helps me understand the literature about amatoxin poisoning treatments, my lack of medical training limits me. Fortunately, critical comments from six different medical doctors have been incorporated in this article. All six, each concerned about different aspects in early drafts, returned me to the peer reviewed scientific literature for additional reading.

There remains no known specific antidote for amatoxin poisoning. There have not been any gold standard double-blind placebo controlled studies. There never can be. When dealing with a potentially deadly poisoning (where in many non-western countries the amatoxin fatality rate exceeds 50%) treating of half of all poisoning patients with a placebo would be unethical. Using amatoxins on large animals to test new treatments (theoretically a great alternative) has ethical constraints on the experimental design that would most likely obscure the answers researchers sought. We must thus make our best judgement based on analysis of past cases. Although that number is now large enough that we can make some good assumptions, differences of interpretation will continue. Nonetheless, we may be on the cusp of reaching some agreement. Towards that end, I have contacted several Poison Centers and NAMA will be working with the Center for Disease Control (CDC). Dr. Denis Benjamin is taking the lead for NAMA in this endeavor.

Even though I am aware of more than 20 human amatoxin poisonings in 2016, we have not received a single complete report filed for a human poisoning from amatoxin and only a few reports for dogs. Nevertheless, we have gathered some useful information from the scientific literature, the press, NAMA toxicology identifiers, and medical professionals experienced in treatment of amatoxin poisoning.

Currently, we eagerly await the results of the open clinical trial "Intravenous Milk Thistle (Silibinin-Legalón) for Hepatic Failure Induced by Amatoxin/Amanita Mushroom Poisoning." The trial, supervised by Dr. Todd Mitchell, involves use of Legalón-SIL[®], an injectable form of milk thistle extract, *Silybum marianum* (L.) Gaertn. As best I can determine, Legalón-SIL[®] contains a complex of silibinin and the disodium salt of succinic acid. The trial was approved in June 2009, with the first recruited patient treated that October. Although initially scheduled to end by December 2016, the trial is still recruiting patients. The original estimated enrollment was for 50 patients, which number has, by my tracking, now surpassed 90. With the enrollment of 15 new participants in 2016, the trial appears to be gaining momentum. I recommend that the trial be contacted immediately about any new case in order to enroll the patient quickly by calling 1-866-520-4412 or using the websites legalonsil.com or <http://www.clinicaltrials.gov/ct2/show/study/NCT00915681>

Of cause for concern, Legalón-SIL[®] has been purchased by Mylan, recently famous for Epipen[®] and rapidly raising drug prices.

Historically silibinin (also called silybin) and various other treatment options have been used for amatoxin poisoning. Silibinin is both the main bioactive component of milk thistle seeds and by far the most bioactive component, thus my focus on this one compound.

Of greatest interest is death from mushrooms. Over 40 years of NAMA records indicate 1-2 deaths per year from amatoxin poisoning. In the majority of the North American cases, the cause of death has been consumption of *Amanita* species in section *Phalloideae*. Species involved have included *Amanita phalloides*, *A. bisporigera*, *A. ocreata*, and other white “Destroying Angels”. The principal North American *Amanita* researcher, Dr. Rodham E. Tulloss (pers. comm.), reported four eastern North American incidents since August 2008 involving two as yet undescribed species, *Amanita sturgeonii* Tulloss et al. nom. prov. and *Amanita amerivirosa* Tulloss et al. nom. prov. Amatoxins are not confined to *Amanita* section *Phalloideae* but also occur in species of *Galerina* (most notably *G. marginata* = *G. autumnalis* = *G. venenata*), *Lepiota* (most notably *L. subincarnata* = *L. josserandii*) and *Conocybe filaris*. In a disproportionate number of cases relative to the total population, the mushroom poisoning victim is an immigrant. News reports frequently attribute this to the presence of mushrooms in the United States and Canada that are not present where the immigrant is from. However, *Amanita* species in section *Phalloideae*, deadly *Galerina* species, and deadly *Lepiota* species are present worldwide and annually kill people on every inhabited continent. Indeed, elsewhere the incidence of cases and annual mortality from amatoxin is far higher than it is in North America.

The only human death in our 2015–2016 database is the 2016 autumn death of a young child on Vancouver Island, B.C. after consumption of *Amanita phalloides*. Young children (under age 10) and seniors appear to be more likely to die from amatoxin poisoning than healthy individuals 10 to 60 years of age. In the fall/winter of 2016, there was a rash of *Amanita phalloides* cases including one poisoning from Washington State and several incidents in December involving 14 people in California followed by one additional California case in January of 2017. Most were treated using what newspapers now describe as the “Santa Cruz Protocol” developed by Dr. Todd Mitchell. Because no full reports have been received by NAMA for any of these cases, we have only a partial understanding of the components of the Santa Cruz Protocol. However, NAMA toxicologists in California have been in contact with Dr. Todd Mitchell, and news articles provide additional insight. All of the California victims survived, although three (including a 19-month old child and the child’s aunt) required liver transplants. There were other cases of poisoning from the consumption of species in *Amanita* sect. *Phalloideae* in the Midwest and East Coast, but we have no data on those cases. From sketchy news accounts, we understand that most or all of the U.S. patients treated were enrolled in the clinical trial and therefore received intravenous Legalon®SIL as part of the Santa Cruz Protocol.

In over 2,000 retrospectively reviewed amatoxin cases from western Europe, the United States and Canada, the average mortality was 11.58%.¹ The mortality was 10.60% in those cases treated by some form of chemotherapy.¹ From Dr. Denis Benjamin’s book, *Mushrooms Poisons and Panaceas*, my own literature search, and discussions with Dr. Todd Mitchell, I have concluded that the most important single therapy is sustained aggressive IV hydration sufficient to maintain strong urine output (amatoxin is primarily excreted in the urine). This fluid therapy involves careful correction of water, glucose, electrolyte imbalances, and acid-base status.² Correction of altered coagulation factors may also be needed (e.g. administration of vitamin K₁ in patients with INR > 2.1).² The retrospective multidimensional multivariate statistical analysis of 2,110 amatoxin poisoning clinical cases published in 2001 indicated that the drugs silibinin, N-acetylcysteine, and putatively ceftazidime (used with silibinin) may be associated with higher rates of patient survival.¹ The multivariate analysis revealed little or no efficacy for Penicillin G, the most frequently utilized chemotherapy, and no benefit was found for thioctic acid or steroids.³ A retrospective study of 367 patients who were treated using silibinin alone or in combination with penicillin found a 5.1% death rate in the 118 patients treated with silibinin

monotherapy and a 8.8% death rate in 249 patients treated with both silibinin and penicillin (deemed not statistically significant due to the small sample size).⁴

Milk thistle extracts have a long history of use as liver protective agents. A (quick) literature search using the Ebscohost[®] academic search engine returned a list of over 5,000 peer reviewed silymarin (= silibinin) articles. Narrowing the search to “silymarin + amatoxin” still returned 64 peer reviewed articles. From these, I found that “the evidence is limited, but given the lack of alternative treatments in patients with suspected amatoxin-containing mushroom poisoning and the relatively few adverse effects, (intravenous) silibinin should be considered in some patients.”⁵ Silibinin is purified from an extract of milk thistle seeds. The fact that Legalon-SIL[®] is an injectable form of silibinin is important because oral absorption of silibinin is poor, making oral ingestion of milk thistle extract of limited utility. However, one potential route to improving oral absorption is complexing silibinin with phosphatidylcholine (lecithin).⁶ Like silibinin, phosphatidylcholine is extensively researched (I found over 14,000 peer reviewed articles) and very safe. The complex, known as silipide is well researched (I found 76 peer-reviewed articles) and commercially available under the trade name Siliphos[®]. This inexpensive, over-the-counter food supplement (produced by Indena[®] in Italy) is readily available (as Siliphos[®]) from many different vitamin companies throughout the U.S. and Canada. Silipide is readily absorbed orally and exhibits high bioactivity (unlike oral silibinin which is absorbed but has only 1/4 to 1/10 the bioactivity of silipide).³ Both the phosphatidylcholine and the silibinin components have liver protective effects. Indeed, the complexation with phosphatidylcholine improves the targeting of silibinin to the liver and to inflammatory cells.⁶ Despite its intriguing potential, silipide has not been tested against amatoxin, and animal tests should come first.

A 2007 review summarizes a long list of findings regarding silymarin’s hepatoprotective effects:⁷

Antioxidation

Inhibition of lipid peroxidation

Stimulation of ribosomal RNA polymerase and subsequent protein synthesis, leading to enhanced hepatocyte regeneration

Enhanced liver detoxification via inhibition of phase I detoxification

Enhanced glucuronidation and protection from glutathione depletion

Anti-inflammatory effects, including inhibition of leukotrienes and prostaglandin synthesis, Kupffer cell inhibition, mast cell stabilization, and inhibition of neutrophil migration

Slowing or even reversing of fibrosis by reduction of the conversion of hepatic stellate cells into myofibroblasts

Anticarcinogenesis by inhibition of cyclin-dependent kinases and arrest of cancer cell growth

Silymarin is also found to have immunomodulatory effects on the diseased liver

Silymarin (=silibinin) exerts both important pharmacodynamic and pharmacokinetic effects in the treatment of amatoxin poisoning.^{1,8} “Silymarin blocks the interaction of α -amanitin...with cellular components, including basolateral transport systems (thus preventing uptake) and its nuclear receptors (thus preventing inhibition of polymerase II and the concomitant blockade of protein synthesis in the later stages of an amatoxin poisoning).”⁹ Consequently, silibinin will have a role throughout the treatment of an amatoxin poisoning and not just during the first 12–24 hours. Pharmacodynamically it

acts as an antioxidant preventing liver glutathione depletion. It inhibits production of advanced glycation end products. It promotes membrane stabilization and prevents cell death. It is anti-inflammatory.¹ It exhibits DNA dependent RNA polymerase I stimulation promoting liver regeneration. Pharmacokinetically silymarin not only competes with amatoxins for cell entry (thus reducing uptake) but inhibits P-glycoprotein induced cellular efflux, thus reducing amatoxin recirculation.¹

Use of activated charcoal has only been associated with improved outcomes when used in the first hour after mushroom ingestion while mushroom material remains in the digestive tract. There is no clinical evidence for improved outcomes from using activated charcoal later in amatoxin poisoning cases.¹ Dr. Denis Benjamin (pers. comm.) notes, “the one theoretical reason to continue with activated charcoal is that it will absorb the toxin that recirculates from the biliary system back into the GI tract. On the other hand, many physicians might rather prefer to rest the damaged GI tract or stimulating bile flow by avoiding oral intake. There is also no evidence that cathartics provide any significant benefit and could complicate fluid management.” A study of 45 French patients suffering *Amanita phalloides* poisoning found low levels of amatoxin in the GI tract over time. This finding sharply limits any potential benefit from serial dosing with activated charcoal.¹⁰

A number of extracorporeal purifications have been attempted and discarded as ineffective.³ The most recent entry into this field is the Molecular Adsorbent Recirculating System (MARS).¹¹ Most researchers have concluded that for these treatments to be useful, they must be started early.¹² None of these extracorporeal treatments have gained traction in North America. Consistent with pharmacokinetic data, there is broad agreement that by the time any extracorporeal treatments could be initiated, serum levels of amatoxin are already very low.¹⁰

In a small number of cases, attempts have been made to drain the bile directly, thus removing any retained amatoxin from the biliary tract. Dr. Kent Olson, MD cautions, “We do not support the use of biliary drainage. It is invasive and the scattered reports of success are anecdotal. By the time the patient presents for treatment, it is likely that the amatoxin has already been excreted. We had a recent case where biliary drainage did not prevent the need for a liver transplant.” In a study of four pigs receiving α -amanitin (two at 0.35mg/kg and two at 0.15mg/kg), researchers found that α -amanitin almost completely disappeared from systemic and enterohepatic circulation within 24 hours.¹³ The authors concluded that since pig and human amatoxin responses are similar, biliary drainage would be ineffective more than 24 hours post ingestion.

A tantalizing discovery that substantial amounts of amatoxin can remain in the gall bladder more than 72 hours post ingestion comes from one 2006 Missouri case.¹⁴ Three 18-year-old boys consumed varying amounts of *Amanita bisporigera*. One boy consumed 11 raw mushrooms between 6 PM and midnight, awaking at 5 AM with severe nausea, vomiting, and abdominal pain. Within 72 hours, he had developed severe liver dysfunction. He was listed for liver transplantation and aggressive treatment was initiated. Treatment included nasobiliary drainage. Over a 3-day period, 240 mL of bile containing 4 mg of amatoxin was collected. He survived without needing a liver transplant. To put this survival story in perspective, consider that consumption of just one *Amanita bisporigera* is widely considered lethal in an adult human.

I am only aware of one other publication describing biliary drainage. The publication is in German, but an English translation is available.¹⁵ Three males (29, 43, and 50 years) consumed 300 g of *Amanita phalloides* they had collected. Ten to twelve hours later they began to suffer abdominal cramping and diarrhea, presenting at the hospital 26 hours post ingestion. At 48 hours post ingestion,

acute liver injury is evident and all three receive percutaneous drainage of the gall bladder, IV hydration and IV silibinin (for 5 days) during which no food was given by mouth. Recovery of amanitin from the gall bladder was 0.5 mg in patient one, 0.237 mg in patient number two and 0.135 mg in patient number three. All survived.

In a personal communication, Dr. Denis Benjamin noted, "The biliary drainage issue is a tricky one to deal with. The easiest is percutaneous drainage, and this would have to be maintained for a number of days with a catheter. It is not without complications." Dr. James Addison adds, "I think the question of biliary drainage is worth considering, although it is not something that is not without potential adverse consequences. Thus, I agree with Dr. Benjamin that it would perhaps best be reserved for patients who seem to have a more serious ingestion. Also, there are many fairly sophisticated centers where this may not be available in a timely way." My own hope is that biliary drainage might be a way to treat patients who do not qualify for a transplant as well as a way to reduce the need for a liver transplant in extreme cases.

Liver transplantation will at times be required in spite of all other efforts. The challenge is to determine when a liver transplant is going to be required and to make that determination early enough that a liver can be located before the patient has died or is so far gone that they will die soon after a transplant. Several authors have proposed criteria for making this decision.^{16,17,18} Factors like the amount of amatoxin in the urine and levels of liver enzymes have little correlation with outcomes. For amatoxin poisoning, an early indicator (50% probability) that a patient may require a liver transplant is diarrhea onset less than eight hours post ingestion.¹⁴ On this matter, Dr. Denis Benjamin (pers. comm.) noted "while it is evident that the early onset of severe diarrhea (less than 8 hours) is most suggestive of severe poisoning, the 50% probability ... of needing a transplant is no better than tossing a coin. It may be prudent ... that physicians notify a transplant center in such cases, just to make them aware - a kind of heads up. However, ... aggressive supportive care and excellent fluid management, together with intravenous silibinin (should be pursued first). The danger is transferring a patient to a liver transplant center too early or too late. This is a very fine line. It requires good clinical judgement and very good communication between the caregivers and cannot be reduced to any simple rubric."

Dogs may succumb to amatoxins more rapidly than humans may and so treatments employed without any delay are critical. As with humans, use of IV fluids to maintain a strong urine output is of extreme importance. Drainage of the bile duct also is promising, but mainly anecdotal reports on the efficacy of this procedure exist at this point. Many vets who are experienced in treating amatoxin poisonings already use a range of liver protectants and there is great interest in IV silibinin, which is currently not available for dogs. Potential use of a complex of silibinin with phosphatidyl choline (lecithin) is intriguing, although yet untested in any animal model. The complex, known as silipide, is available under the trade name Siliphos[®]. It has four to ten times better oral bioavailability than pure silibinin, is inexpensive, and can be on the shelf, ready for immediate emergency use. For IV silymarin, the LD₅₀ in beagles was 300mg/kg. The recommended dose of intravenous silibinin for amatoxin poisoning is 20 (up to 50) mg/kg/day. Since Siliphos[®] is untested, no recommendation can be made at this time.

An important question remains. When a patient presents at a hospital complaining of severe diarrhea, how do the physicians determine that they may be dealing with an amatoxin poisoning? If it is known or suspected that a mushroom ingestion has occurred (and even if mushrooms are not mentioned), a critical question then becomes how long has it been since a meal was consumed? If the

delay between the last meal and diarrhea is 6 hours or more, it is highly likely that amatoxins are involved. In poisoning cases, NAMA stands ready to assist in mushroom identification. We have a team of over [150 identifiers in North America](#). They can usually (though not always) identify the species through examination of the mushrooms involved (or less ideally identification from photos) or examination of food remains for telltale spores. We offer the same services for animal poisonings. The NAMA website also has descriptions (with photos) of the major [mushroom poisoning syndromes](#). Additional pages are devoted to animal poisonings. Patients (or pet owners) can review the photos, looking for similarities to mushrooms thought to be involved. Physicians and veterinarians can review the syndromes and see how the suite of symptoms for known syndromes compare to the suite of symptoms in their case. The amatoxin poisoning syndrome is very distinctive. Most doctors dealing with an amatoxin poisoning see only one case in their life.

Physicians should not wait for confirmation that they indeed have an amatoxin case before beginning treatment. In all cases of severe diarrhea, fluid loss can damage the kidneys (and liver) and IV fluids are called for. In response to my comments in an early draft of this article, Dr. Kent Olson replied, "I do agree that some deaths result from inadequate fluid resuscitation, as most treating doctors do not appreciate how many liters of fluid the victim has lost". Blood work to check liver enzyme levels is also important. If liver enzyme levels are elevated OR if amatoxin poison is suspected, the IV silibinin clinical study should be contacted immediately. A repeat of the blood work the next day is an important step. If the liver enzyme levels have remained normal, it is a false positive and the patient can be considered for discharge.

In conclusion, with good hospital supportive care alone the majority (80-90%) of human amatoxin poisoning spontaneously resolve. Use of IV-silibinin is strongly associated with improved (up to 94%) survival. Only the most severe cases currently require a liver transplant. Indeed, I believe that emphasis on IV fluid therapies, elimination of use of Penicillin and other treatments where efficacy has not been demonstrated, use of IV silibinin, and possibly in some extreme cases use of nasobiliary drainage, hospitals will be able to reduce the need for transplantation in amatoxin poisoning cases. If for some reason IV-silibinin does not remain available, the use of oral silipide may be promising. The challenge is that in the absence of experimental data, it would be very difficult to prove whether use of silipide makes any difference in survival.

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