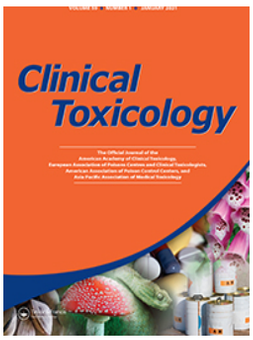

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CLINICAL RESEARCH

Current fatality rate of suspected cyclopeptide mushroom poisoning in the United States

Jonathan De Olano[a], Josh J. Wang[a], Eric Villeneuve[b], Sophie Gosselin[c,d,e], Rana Biary[a], Mark K. Su[a,f] and Robert S. Hoffman[a]

[a]Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, NYU Grossman School of Medicine, New York, NY, USA; [b]Department of Pharmacy, McGill University Health Centre, Montreal, QC, Canada; [c]Department of Emergency Medicine, McGill University, QC, Canada; [d]CISSS Montérégie Centre, Department of Emergency Medicine, Greenfield Park, QC, Canada; [e]Centre antipoison du Québec, QC, Canada; [f]New York City Poison Control Center, New York, NY, USA

ABSTRACT

Objective: This study was designed to determine the fatality rate of suspected cyclopeptide-containing mushroom ingestions reported to the National Poison Data System (NPDS).

Background: Although silibinin reportedly improves survival in suspected cyclopeptide-containing mushroom ingestions, the greater than 20% untreated fatality rate that is often cited is based on decades-old data. An ongoing open-label silibinin trial will likely use historical cases as comparators. A recent single poison control center (PCC) study showed a fatality rate of 8.3%. This study was designed to validate those findings in the NPDS.

Methods: This study was an 11-year (1/1/2008-12/31/2018) retrospective review of suspected cyclopeptide-containing mushroom ingestions reported to NPDS. Inclusion and exclusion criteria were the same as the ongoing silibinin trial: Age >2-years-old; history of eating foraged mushrooms; gastrointestinal symptoms within 48 h of mushroom ingestion; and aminotransferases above the upper limit of normal within 48 h after ingestion. Each original participating PCC confirmed eligibility, diagnosis, treatment, and outcome on included cases.

Results: During the study period, 8,953 mushroom exposures were reported to NPDS, of which 296 met inclusion criteria. The PCC survey response rate was 60% (28/47 PCCs), and the individual case response rate was 59% (174/296). Twenty-six cases were subsequently excluded leaving 148 included cases. The overall mortality rate was 8.8% (13/148). Mortality in silibinin/silymarin-treated vs untreated cases was 9.5% (4/42), vs 8.5% (9/106), respectively. A mycologist identified mushrooms in 16.9% of cases (25/148), of which 80% (20/25) were cyclopeptide-containing. Among these confirmed cases, the mortality rate was 10% (1/10) in both silibinin/silymarin-treated and untreated cases.

Conclusions: The contemporary mortality rate of patients with presumed cyclopeptide-mushroom poisoning is only 8.8%. This likely represents improved supportive care for patients with acute liver injury and should be considered the current standard for historical controls in the United States.

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Mushroom; amatoxin; fatality rate

Introduction

Some mushrooms from the genera *Amanita*, *Lepiota*, *Galerina* and *Conocybe* contain toxic cyclopeptides. These toxins, often collectively called amatoxins, are potent inhibitors of RNA polymerase II [1]. Following ingestion of a toxic dose of amatoxin-containing mushrooms, patients typically present with delayed gastrointestinal symptoms that may progress to fulminant hepatic failure [2]. Reported fatality rates among patients who ingest cyclopeptide-containing mushrooms vary widely. One of the largest single series reported a fatality rate of over 22% in 205 clinical cases [3], and reported fatality rates ranged from 4.8% to 40% in one review [4]. In another review, the fatality rate with supportive care alone was reported at over 47% [2]. We recently reported that the fatality rate in one North American PCC's experience was only 8.3% [5]. Although the exact explanation for this large variability in reported fatality rates is unknown, possible factors include geographic variations in toxicity, improvements in supportive care over time, and the variable use of a wide range of therapies. It is noteworthy that of all the proposed treatments for cyclopeptide mushroom poisoning, not a single one has been the subject of a randomized controlled trial in humans.

Recently in the United States (US) there is a renewed interest in the use of silibinin. The authors of one review claim that silibinin reduces the fatality rate from cyclopeptide mushroom poisoning by 50% [6]. An ongoing industry-sponsored open-label trial of silibinin (www.Clinicaltrials.gov NCT00915681) may be used to seek drug approval by the US Food and Drug Administration (FDA). Because this trial will likely make claims based on historical controls, we designed the present study to determine the

CONTACT Robert S. Hoffman robert.hoffman@nyumc.org 455 First Avenue, Room 123, New York, 10016, NY USA
This article has been corrected with minor changes. These changes do not impact the academic content of the article

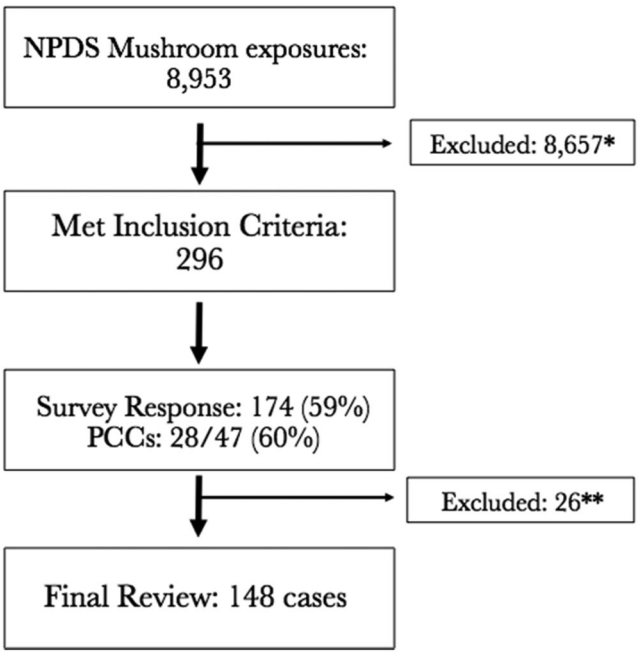

Figure 1. Patient enrollment and exclusion. * = Excluded not meeting initial inclusion criteria; ** = Excluded due to normal aminotransferase values on survey response.

contemporary fatality rate of patients who ingest suspected cyclopeptide-containing mushrooms in North America. Specifically, we designed the present study to validate our local findings in the larger and geographically diverse American Association of Poison Control Center's (AAPCC) National Poison Data System (NPDS).

Methods

The American Association of Poison Control Center's (AAPCC) National Poison Data System (NPDS) prospectively collects data on nearly two million cases of exposures to poisoning each year [7]. Cases are entered by trained poison information specialists using a variety of fixed data fields and a free-text notes section. All data from participating PCCs are merged into a single database with the exception of the free-text notes which are retained locally. This study is an 11-year (1/1/2008-12/31/2018) retrospective review of all suspected cyclopeptide-containing mushroom ingestions reported to NPDS. We elected to use the same inclusion/exclusion criteria as the ongoing silibinin trial in order to provide a direct comparison with those results. The inclusion criteria were: age >2-years-old, history of eating foraged mushrooms, gastrointestinal symptoms (cramping abdominal pain, nausea, vomiting, or watery diarrhea) within 48 h of mushroom ingestion, and aminotransferases (AST or ALT) above the upper limit of normal value for the laboratory reference range within 48 h after mushroom ingestion. As in the ongoing silibinin trial, neither mycological nor chemical confirmation of exposure was required. Cases were excluded only if they failed to meet *all* these criteria regardless of final diagnosis.

The study was approved by the institutional review board for the New York City Department of Health and Mental Hygiene and the Data Access Committee for the AAPCC.

Table 1. Patient demographics.

Parameter	Result ($n = 148$)
Region (*n*)	
North East US	50
South East US	22
West Coast US	46
Mid West US	24
South Central US	6
Identified by a mycologist (*n*)	25
Therapies given (*n*)*	
Biliary drainage	3
H_2 receptor antagonist	9
Multiple dose activated charcoal	35
Single dose activated charcoal	12
N-acetylcysteine	101
Penicillin	42
Renal replacement therapy	12
Silibinin intravenously	30
Silibinin orally	12
Other	64
AST/ALT U/L (*n*)	
>ULN, <100	18
>100 U/L, <1000	52
>1000	78

* = Total therapies exceed 148 because many patients got more than one therapy. UNL: Upper limit of normal laboratory value.

Following approval, the AAPCC provided a spreadsheet of all reported mushroom exposures that had either gastrointestinal symptoms or an abnormal AST or ALT. The spreadsheet was manually searched by two of the authors (JDO and JJW) to find cases that m*et al*l inclusion criteria. For cases that m*et al*l inclusion criteria, individual centers were contacted to confirm that the data entered into NPDS were correct and asked to provide greater detail on diagnosis, treatments, and outcomes. In order to maintain confidentiality, individual centers were asked to provide this information on an electronic survey tool using a non-traceable unique case number for each exposure generated by the NPDS. Only descriptive statistics were used.

Results

During the 11-year study period 8953 mushroom exposures that had either any gastrointestinal symptoms or an abnormal AST or ALT were recorded by the NPDS. The vast majority of these cases were subsequently excluded (Figure 1) because they did not have both gastrointestinal symptoms and an abnormal AST or ALT recorded. This left 296 cases requiring PCCs confirmation The PCC survey response rate was 60% (28/47) and accounted for 59% (174/296) of individual cases. A further 26 cases were excluded based on normal aminotransferases on survey responses, leaving 148 cases in the final data set for analysis.

The patient demographics are presented in Table 1. These cases were geographically distributed across all regions of the US. This population was generally numerically ill with 53% having an AST or ALT greater than 1000 U/L.

The overall mortality rate was 8.8% (13/148). (Table 2) There were two cases that were counted as survivors in whom the mortality was unreported. The first was a patient who had a final diagnosis of a false morel ingestion, with a peak ALT of 80 U/L and who remained asymptomatic at last

Table 2. Case fatality rate.

	Total (*n*)	Died (*n*)	Case Fatality (%)
Overall	148	13	8.8%
Overall treated with silibinin/silymarin	42	4	9.5%
Overall not treated with silibinin/silymarin	106	9	8.5%
Mycologist identified cyclopeptide mushroom treated with silibinin/silymarin	10	1	10%
Mycologist identified cyclopeptide mushroom not treated with Silibinin/silymarin	10	1	10%

Table 3. Mycologist Identified Mushrooms.

Mushroom Species	Cases (*n*)
Agaricus xanthodermus	1
Amanita bisporigera	**7**
Amanita phalloides	**6**
Amanita smithiana	2
***Amanita* unspecified**	**4**
Amanita virosa	**1**
Galerina marginata	**1**
Lepiota josserandi	**1**
Pholiota velaglutinosa	1
Russula species	1
Total	25

Bolded species are cyclopeptide (i.e. amatoxin) -containing mushrooms.

PCC contact. The second patient with an unreported outcome did not bring any mushroom samples to the emergency department and had aminotransferases above the upper limit of the normal reference range but less than 100 U/L. They left the hospital and refused to return on call back.

Silibinin or silymarin was given in 42/148 (28%) of cases. Unfortunately, the dose and regimen was not reported. There were 4 deaths (9.5%) in cases that received silibinin/silymarin, and 9 deaths (8.5%) in cases that did not receive silibinin. All 12 cases that received oral silymarin survived. Among those receiving intravenous silibinin, the mortality rate was 13% (4/30). Of the 25 mushroom ingestions identified by a mycologist, 20 of them were cyclopeptide-containing mushrooms (Table 3). The most commonly identified mushrooms were *A. phalloides* and *A. bisporigera*. There were 2 deaths (10%) in mycologist-identified cyclopeptide- containing mushrooms. The fatality rate for mycologist-identified cyclopeptide-containing mushrooms was 10% (1/10) in both silibinin/silymarin-treated and untreated cases.

Discussion

Determining the fatality rate of patients who ingest suspected cyclopeptide-containing mushrooms is challenging. Although amatoxin exposure can be confirmed through urine or blood analyses, such tests are not widely available. Likewise, while expert mycologists can accurately identify the mushroom, it is uncommon that both uneaten parts of the mushroom and an expert mycologist are available to review suspected clinical cases in real time. Thus for the vast majority of patients, the diagnosis of cyclopeptide mushroom poisoning is based on history, symptoms, and clinical signs. In the present study, 5 of the 25 patients who met clinical criteria were confirmed by mycologists to have consumed non cyclopeptide-containing mushrooms. Additionally, 6 patients who otherwise met clinical criteria (but were not confirmed by mycologists) were ultimately found to have an alternative diagnosis unrelated to mushroom poisoning explaining their presentations, such as cholecystitis or an abdominal aortic aneurysm with an iliac dissection.

The analysis is further confounded by various therapies given in different combinations. In the present study, some patients received supportive care alone, which by itself is not easily defined. Others received combinations of either single or multiple doses of activated charcoal, acetylcysteine, silibinin/silymarin (oral or intravenous), penicillin G, biliary drainage, and some form of renal replacement therapy. While all of these therapies have the potential to mitigate poisoning, no single therapy has been subjected to a randomized clinical trial in humans, much less the combinations of therapies.

Cyclopeptide-associated mushroom toxicity remains an important clinical dilemma. Newer therapies such as polymyxin are under consideration and older therapies such as silibinin are being evaluated in an attempt to gain FDA approval. Unless these therapies are subjected to randomized controlled trials, they will likely be compared to historical controls. Thus knowing the fatality rate in these historical controls is essential. As noted above, after analyzing data from over 2000 reported cases, the fatality rate with supportive care alone in one review was reported to be over 47% [2]. Other reviews found case fatality rates following various therapies to range from 4.8% to 40% [4]. While at least one paper claims that silibinin reduces mortality by 50% (from over 20% to 10%), this analysis is highly flawed by comparison to the historical controls noted above [6]. We are intrigued that the case fatality rate in silibinin-treated patients noted by those authors is no different than the case fatality rate in patients reported in the present study, regardless of whether they were treated with silibinin or not. Consequently, we believe that claims of antidotal efficacy of silibinin in cyclopeptide mushroom poisoning can only be established by well-designed randomized clinical trials of either laboratory or mycologist-confirmed poisonings in humans.

We believe that our data have several strengths. With 148 cases studied, this represents one of the largest series of suspected cyclopeptide mushroom ingestions reported to date and what we believe to be the largest in both North America and the current century. Cases come from across a broad geographical area and a limited time period. It uses a clinical criteria for cyclopeptide mushroom poisoning that mimics a “real-world” experience in which expert mycologist evaluation is not always available and toxin concentrations are either never obtained, or determined long after poisoning has evolved. In addition, it overcomes some of the limitations of NPDS data in that it asks individual centers to examine the clinical case notes and confirm the accuracy of

data entry and inclusion and exclusion criteria. Finally, it studies a population that is generally quite ill based on their aminotransferase concentrations.

There are some limitations that must be mentioned. This is a retrospective analysis of voluntarily reported data that suffers from reporting biases. While it is unclear how these biases relate to the outcomes described, it is certain that these data are not a substitute for a prospective case series with mandatory reporting. Unlike some other NPDS data, it is unlikely that this data is diluted by a large number of exposures that were never ingestions given that in addition to a history of eating foraged mushrooms, both clinical and laboratory abnormalities were required for inclusion. It is possible that we failed to identify some patients who might have qualified for the study but were excluded because either gastrointestinal symptoms or aminotransferases were not recorded in NPDS. However, obtaining that level of detail on all the excluded cases was impractical as most PCCs only had a limited amount of time to assist with the study. Additionally, although the survey response rate was incomplete, we have no reason to believe that missed cases had different outcomes. In fact, we have the clinical outcomes in the data set provided by NPDS and while these data are not verified at the PCC level, only 6 (4.9%) of the 122 cases not returned in the survey were listed as fatalities. Finally, although the majority of mushrooms were neither identified by a mycologist nor proven by qualitative or quantitative toxin concentrations, those cases identified by a mycologist had outcomes very similar to those not identified by a mycologist. This suggests that the clinical criteria used here were likely sufficient.

Conclusions

In this retrospective review of NPDS data, the fatality rate was 8.5% in patients with presumed cyclopeptide-mushroom poisoning who did not receive silibinin. This contemporary case fatality rate is much lower than the 22% previously reported and likely represents improved supportive care for patients with acute liver injury. These results should be considered the current standard for historical controls in North America. We urge the manufacturers and the FDA to demand that a well designed, powered, and implemented controlled trial occur prior to obtaining approval for silibinin or any other antidote for suspected cyclopeptide mushroom poisoning.

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- Iowa PCC
- Jacksonville, FL, PCC
- Minnesota PCC
- Missouri PCC
- National Capital PCC
- Nebraska Regional PCC
- New Jersey PCC
- North Carolina PCC
- North Texas PCC
- New York City PCC
- Oregon PCC
- Palmetto PCC
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- Virginia PCC
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Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Eric Villeneuve http://orcid.org/0000-0003-0510-8144
Sophie Gosselin http://orcid.org/0000-0002-0694-5588
Mark K. Su http://orcid.org/0000-0001-5211-5334
Robert S. Hoffman http://orcid.org/0000-0002-0091-9573

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