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REVIEW ARTICLE

Amatoxin-Containing Mushroom Poisonings: Species, Toxidromes, Treatments, and Outcomes

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Amatoxins are produced primarily by 3 species of mushrooms: *Amanita*, *Lepiota*, and *Galerina*. Because amatoxin poisonings are increasing, the objective of this review was to identify all amatoxin-containing mushroom species, present a toxidromic approach to earlier diagnoses, and compare the efficacies and outcomes of therapies. To meet these objectives, Internet search engines were queried with keywords to select peer-reviewed scientific articles on amatoxin-containing mushroom poisoning and management. Descriptive epidemiological analyses have documented that most mushroom poisonings are caused by unknown mushrooms, and most fatal mushroom poisonings are caused by amatoxin-containing mushrooms. *Amanita* species cause more fatal mushroom poisonings than other amatoxin-containing species, such as *Galerina* and *Lepiota*. *Amanita phalloides* is responsible for most fatalities, followed by *Amanita virosa* and *Amanita verna*. The most frequently reported fatal *Lepiota* ingestions are due to *Lepiota brunneoincarnata*, and the most frequently reported fatal *Galerina* species ingestions are due to *Galerina marginata*. With the exception of liver transplantation, the current treatment strategies for amatoxin poisoning are all supportive and have not been subjected to rigorous efficacy testing in randomized controlled trials. All patients with symptoms of late-appearing gastrointestinal toxicity with or without false recovery or quiescent periods preceding acute liver insufficiency should be referred to centers providing liver transplantation. Patients with amatoxin-induced acute liver insufficiency that does not progress to liver failure will have a more favorable survival profile with supportive care than patients with amatoxin-induced acute liver failure, about half of whom will require liver transplantation.

Keywords: mushrooms, poisonous, amatoxin-containing, Amatoxins, alpha-amanitin

Introduction

Amatoxin-containing mushrooms are responsible for most fatal mushroom ingestions as a result of delayed-onset hepatocellular necrosis.[1] Amatoxin-containing mushroom poisonings are increasing worldwide as young adults mistake poisonous mushrooms for hallucinogenic ones, immigrants mistake poisonous mushrooms for edible ones from their home country, and trekkers inadvertently ingest poisonous mushrooms in the wilderness.[2] Soldiers are also at risk of mushroom poisoning. In 1980, Supramaniam and Mohanadas reported an outbreak of mushroom poisoning with one fatality among 12 Malaysian soldiers on survival training exercises.[3]

With the exception of liver transplantation, the current treatment strategies for amatoxin poisoning are all supportive and have not been subjected to rigorous efficacy testing in randomized controlled trials. Because the number of amatoxin-containing mushroom poisonings is increasing and the most effective prevention strategies are correctly identifying poisonous mushrooms and entertaining earlier diagnosis, the objectives of this review were to identify all mushroom species containing amatoxins and to present a toxidromic approach to earlier diagnosis. In addition, several nonspecific and untested drug treatment strategies for amatoxin poisoning are described, with 2 recommended for potential prehospital field applications.

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Methods

To meet the objectives of this narrative review article, Internet search engines including PubMed, Medline, Ovid, Google, Google Scholar, and Cochrane were queried with the keywords as medical subject headings to identify peer-reviewed scientific articles on amatoxin-containing mushroom poisonings and their treatments over the study period, 1986 to 2017. The keywords included mushrooms, poisonous, amatoxin-containing, amatoxins, and alpha-amanitin.

The articles selected to meet the first objective to identify all mushroom species containing amatoxins included case reports and case series of mushroom poisonings and observational, longitudinal, and surveillance studies. The articles selected to meet the second and third objectives to present a toxidromic approach to earlier diagnosis and to compare the efficacies and outcomes of multiple drug and other treatment strategies included epidemiological and toxicological studies and comparative analyses of various treatment strategies and their outcomes. Articles that treated poisonings by mushrooms not containing amatoxins were excluded from review. These selected methodologies met all recommended criteria for narrative reviews, including keywords, use of 2 or more search engines, defined study period, and article inclusion and exclusion criteria.[4]

Results

AMATOXIN-CONTAINING MUSHROOM SPECIES

The amatoxins are a collective group of oligopeptides found in only 3 genera of mushrooms and one additional species from a separate genus: *Amanita*, *Lepiota*, *Galerina*, and *Conocybe filaris*. The amatoxins include at least 9 different toxins: α, β, γ, and ε-amanitins, amanullin, amanullinic acid, amaninamide, amanin, and proamanullin.[5] The amatoxins are selective inhibitors of RNA polymerases, which are critical enzymes required for the synthesis of messenger RNA and micro RNAs.[5] Among the amatoxins, α-amatoxin is considered the most hepatotoxic.[5] The estimated median lethal dose of α-amanitin in humans is 0.1 $mg{\cdot}kg^{-1}$, or about 7 to 8 mg of toxin in adults.[5] All amatoxins are thermally stable and are not inactivated by boiling, cooking, drying, steaming, or freezing.[5]

The liver is the main target organ for ingested amatoxins and the first organ to receive absorbed amatoxins from the gastrointestinal tract via the portal venous circulation. Without messenger RNA, protein synthesis stops in the liver, and cellular-level metabolism is halted.[6] Because amatoxins inactivate both RNA polymerase II (α-amanitin) and RNA polymerase III (β-amanitin), the protein synthesis–dependent regenerative capacity of the liver is disrupted; the liver cannot repair the lysis it sustains; and centrilobular and periportal hemorrhagic hepatic necrosis ensues. Subsequently, there is a rapid rise in hepatic damage biomarkers, principally the serum transaminases, and coagulopathies result from deficiencies in hepatic clotting factors. As liver function fails, tubulointerstitial nephropathy follows and precipitates a hepatorenal syndrome that is rapidly fatal without liver transplantation.

IDENTIFYING AMATOXINS IN MUSHROOMS AND POISONED PATIENTS

Although it can be performed in the field, unlike most laboratory measurements, the Meixner test is an older, visual spot test for amatoxins that is unreliable if improperly performed and may yield false positives.[7] Currently, amatoxins can be more accurately measured directly in the serum and urine of poisoned patients using immunological and chromatographic techniques, specifically enzyme-linked immunosorbent assay and gas chromatography–mass spectrometry, respectively. In addition to serological and chromatographic analyses, mushrooms can now be tentatively identified as potentially amatoxin-containing in the field using digital telephone images transmitted to expert mycologists.[8,9]

EPIDEMIOLOGY OF AMATOXIN-CONTAINING MUSHROOM POISONING

In a 2005 meta-analysis of 28,018 cases of mushroom poisonings worldwide over the period of 1951 to 2002, Diaz found a significant increase in the frequency of reported mushroom poisonings over time.[10] More mushroom foraging by amateurs misidentifying poisonous mushrooms as edible was primarily responsible for the increase in poisonings and was supported by case reports and series.[10] Because the causative species in most mushroom poisonings is not confirmed by an expert, it is difficult to determine accurate, annual worldwide incidence rates for poisonings by amatoxin-containing mushrooms.[1,10]

In the United States, Mowry et al analyzed the 6600 cases of mushroom poisonings reported to the National Poison Data System of the American Association of Poison Control Centers in 2012.[11] Among these, 44 cases were caused by amatoxin-containing mushrooms, resulting in 4 fatalities; most cases (82.7%) were attributed to unknown mushrooms.[11] Similar findings were reported in European longitudinal studies. A retrospective analysis of 93 mushroom poisoning