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Amanita Phalloides intoxication - methods of treatment and epidemiology in Lublin voivodeship in last 5 years

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Abstract:

Introduction: In Poland, mushrooms poisonings, are still quite often, especially in autumn. Each year, in our country 500-1000 cases of mushrooms poisoning are registered, from which 70% are adults, and 30% children. *Amanita Phalloides,* also known as a 'death cap' is one of the most poisonous mushrooms in our climatic zone, and is responsible for ca. 90-95 % of all deadly mushroom poisonings.

Aim of the study: is to present an epidemiology of *Amanita* poisonings in a Lublin voivodeship in a last 5 years, as well as the up to date methods of managing this kind of poisonings.

Materials and methods: Data comes from the database of the Department of the Toxicology of Medical University of Lublin. To present the methods of treatment, the analysis of the available publications was made.

Results: In years 2013-2018 in a Clinical Department of Toxicology of the Medical University in Lublin, 78 patients were hospitalized because of the mushroom intoxication. 37 (47.5%) of them were male and 41 (52,5%) - women. In 27 patients

(34%), the poisoning with *Amanita Phalloides* was confirmed. The most mushrooms poisonings occurred in 2017 (21). Mushroom poisoning is the most common in summer and autumn - the most cases occured in August, September and October.

Discussion: First steps in case of suspecting amatoxins intoxication is to take the clinical history of the patient and start stabilizing measures. To confirm *Amanita* poisoning, a test that allows to detect α-amanitine in urine can be made. Several drug treatments have been applied in intoxications by amatoxins, from which the biggest role plays sylibin and N-acetylcystein.

Introduction:

In Poland, mushrooms poisonings, are still quite often, especially in autumn [1]. In years 1970-2000 mushrooms were responsible for from 3 to 8% of all acute poisoning cases [2].Each year, in our country 500-1000 cases of mushrooms poisoning are registered, from which 70% are adults, and 30% children, younger than 14 y.o. *Amanita Phalloides,* also known as a 'death cap' is one of the most poisonous mushrooms in our climatic zone, and is responsible for ca. 90-95 % of all deadly mushroom poisonings [3]. Mortality in adults is ca. 20% and in children up to 50% [4]. The most serious complication is acute liver failure, in which the mortality varies from 40 to 80% [5].

Amanita Phalloides belongs to the most notorious group of the toxic mushrooms - cyclopeptides. Only one cap of this mushroom can cause hepatic failure and death in an adult [6]. Cyclopeptides consist of two main hepatotoxic peptides: amatoxins and phallotoxins. Phallotoxin, basing on animal studies, is not absorbed from the intestine, therefore it does not seem to play a significant role in human toxicity [7]. From the group of amatoxins, α-amanitine (amanitin) appears to be the most physiologically active [8]. It is a thermostable bicyclic octapeptide that inhibits RNA polymerase II and therefore DNA transcription. That results in stoppage of protein synthesis and cell necrosis [9]. Mostly affected are cells of the metabolically active tissues, dependant on high rates of protein synthesis, eg. cells of the gastrointestinal tract, hepatocytes, and the proximal convoluted tubules of kidneys. Post mortem studies also showed cellular damage in the pancreas, adrenal glands, and testes [10].

Stages of the cyclopeptide toxidrome are showed in the Table 1.

Table 1. Stages of the cyclopeptide toxidrome [10].

Stage	Time from the ingestion	Clinical presentation
Stage 1 - Latent	0-24 h	Asymptomatic
Stage 2 - Gastroenteritis	6-24 h	Nausea, vomiting, profuse diarrhea (cholera - like), abdominal pain, bloody diarrhea, hematuria
Stage 3 - Apparent convalescence	24-72 h	Asymptomatic, hepatic enzymes rising
Stage 4 - Hepatic	4-9 days	Hepatic and renal failure, cardiomyopathy, encephalopathy, convulsions, coma, death

The first stage, that lasts from 6 to 24 hours is characterized by the lack of symptoms [11]. Second phase is characterized by intense cramping abdominal pain, nausea, vomiting, and severe secretory diarrhea [12]. It may be severe enough to result in acid-base disturbances, electrolyte abnormalities, hypoglycemia, dehydration, and hypotension. In this stage liver function tests are usually normal, and there is a risk, that the patient could be erroneously diagnosed with gastroenteritis and discharged home [10].

Aim of the study:

Aim of the study is to present an epidemiology of *Amanita* poisonings in a Lublin voivodeship in a last 5 years, as well as the up to date methods of managing this kind of poisonings.

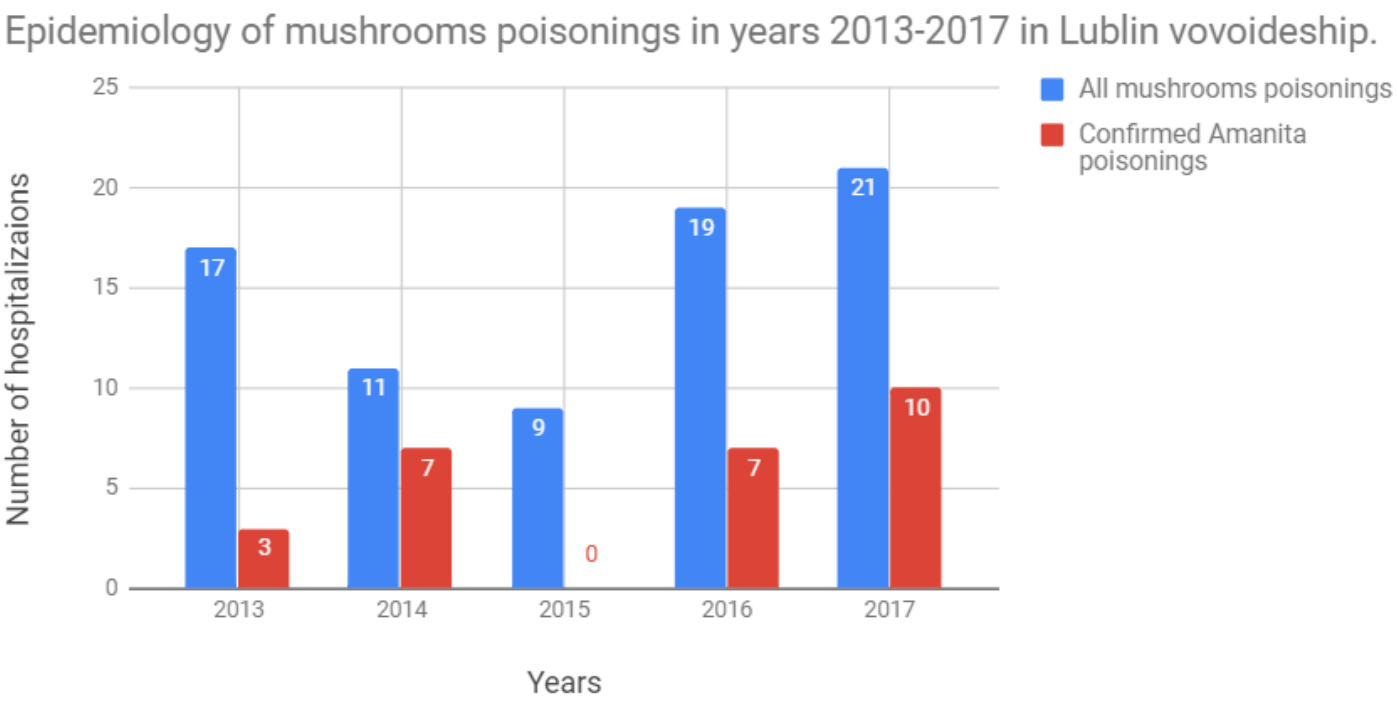
Materials and methods:

Data comes from the database of the Department of the Toxicology of Medical University of Lublin. To present the methods of treatment, the analysis of the available publications was made.

Results:

In a years 2013-2018 in a Clinical Department of Toxicology of the Medical University in Lublin, 78 patients were hospitalized because of the mushroom intoxication. 37 (47.5%) of them were male and 41 (52,5%) - women. In 27 patients (34%), the poisoning with *Amanita Phalloides* was confirmed, using the test detecting α-amanitine in urine, or mycological tests. The most mushrooms poisonings occurred in 2017 (21). That year, there were also the most confirmed *Amanita* poisonings (10). Epidemiology of mushrooms and Amanita poisonings is presented on the Figure 1.

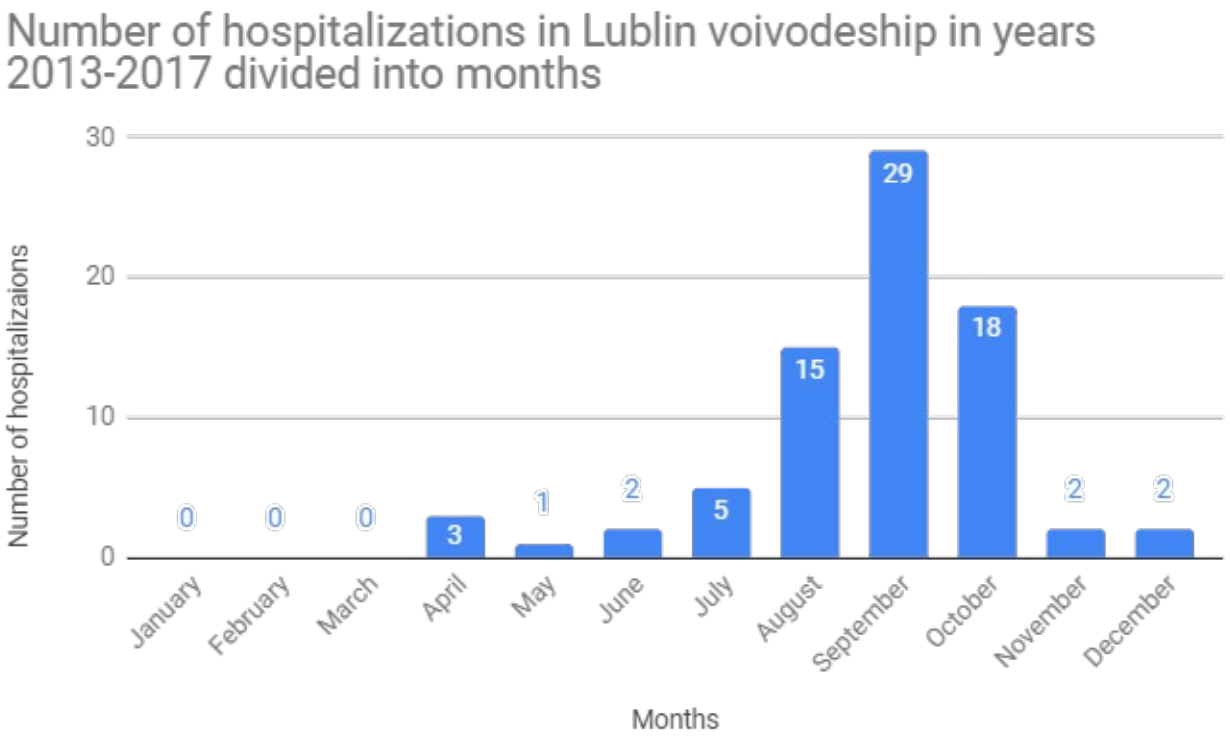
Figure 1.



During that period none of the patients died, however 2 of them had to be qualified for a liver transplantation. The average time of the hospitalization was 5.8 day. However, this value may be underestimated, because patients in the most severe condition were directed to the transplantation centers. 4 patients, at the time of admission were under the influence of alcohol. From the patients, that had a confirmed *Amanita* poisonings (27), the most popular answer on the question 'What kind of mushroom did you think you were eating?' were: *Macrolepiota Procera* (parasol mushroom) - 10 (37%) and mushrooms of the genus *Russula* - 8 (29%). The third most popular mushroom was *Tricholoma* - 3 (11%). 6 patients (22%) named some other species.

Amanita poisoning is the most common in autumn - the number of cases in a different months in years 2013-2017 is presented on Figure 2.

Figure 2.



Discussion:

Since, the *Amanita Phalloides* poisonings, are still quite often, there is definitely a need of effective therapy, that prevents severe consequences of this intoxication. In the treatment of *A. phalloides* poisoning, currently multiple antidotes are used [13]. However, for all the methods of treatment, the evidence of efficacy is limited. Two observational studies of poisonings in human supported the efficacy of silibinin and acetylcysteine [14]. None of the treatments have been subjected to dose-response or controlled trials in human [15].

The initials steps in case of suspecting amatoxins intoxication is to take the clinical history of the patient and start stabilizing measures, if required. Doctors should try to obtain all the basic information, such as amount, type, time of mushrooms ingestion, the first evidence of symptoms and the symptoms present at the moment of hospitalization [16]. Laboratory evaluation should include liver and kidney function, testing aminotransferases, prothrombin time, blood urea nitrogen, creatinine, ammonia, fibrinogen, bilirubin, complete blood count, electrolyte analysis, amylase, lipase, and urinalysis [17]. It is also very important to try to get a sample of a mushroom-containing meal, that was eaten by the patient, that can be used in mycological tests [18].

To confirm *Amanita* poisoning, a test that allows to detect α-amanitine in urine can be made [19]. However, the results of this test are only credible, if it is performed up to 48 hours after the ingestion of mushrooms [1].

Very important role in managing amatoxins poisoning, plays minimizing absorption and inactivation of amatoxins in the gastrointestinal tract [16]. Several methods that can be used alone or in combination include gastric lavage, whole bowel irrigation, administration of activated charcoal, and endoscopic or surgical removal of the ingested poison [20]. Unfortunately most of the patients reach the hospital a long time after ingesting the mushrooms, therefore these clinical measures have limited efficacy. However they are undertaken to assure the best clinical treatment available in a life risk situation, even before confirmation of amatoxin poisoning [21].

Excretion of amatoxins is mainly urinary. For this reason, diuresis would potentially increase the renal clearance and could be a potential good therapy for this intoxication [16]. Forced diuresis is recommended, with urine output of 100–200 ml/h for 4–5 days, especially in the first 48 h after ingestion [18].

Several drug treatments have been applied in intoxications by amatoxins, namely hormones (insulin, growth hormone, glucagon), steroids, vitamin C, vitamin E, cimetidine, α-lipoic acid, antibiotics (benzylpenicillin, ceftazidime), N-acetylcysteine, and silybin [13]. However only ceftazidime, N-acetylcysteine, and silybin were proven to have some degree of therapeutic efficacy [14].

Silybin is one of the flavonolignans, implicit in *Silybum marianum* (‘milk thistle’) - the most widely researched plant used in the treatment of liver diseases [22]. The postulated protective mechanisms are associated to its strong antioxidant activity [16]. Moreover, studies suggest that silybin is able to enter the nucleus and stimulate RNA polymerase I activity which allows to increase the transcription of ribosomal RNA and counterbalance the inhibition of RNAP II induced by amatoxins [23]. All of the patients in our clinic , that had confirmed Amanita poisoning were treated with Silybin.

N-acetylcysteine has been used in medicine for more than 50 years as a mucolytic agent. It is also a well-known treatment for acetaminophen overdose, and related liver damage [24]. It is a precursor of GSH and due to its antioxidant and liver protecting effects it is postulated to play a protective role in patients poisoned with *A. phalloides* [16]. The results of most of the studies showed showed that N-acetylcysteine has a statistically positive impact on amatoxin poisoning [13,14,25,26].

Although research previously conducted by Schneider et al. and Tong et al. failed to show any relevant clinical efficacy of N-acetylcysteine in the treatment of *A. phalloides* intoxication in mice [27,28], it seems that it is reasonable to consider that there is no reason to not include N-acetylcysteine in the treatment regimen 16].

Amanita Phalloides poisonings are still significant problem and a challenge for doctors. Knowledge about symptoms of intoxication and taking it into account during the differential diagnosis is necessary. There are still no unambiguous guidelines for this poisoning, however treatment schemes described in the available literature may allow to make the right therapeutic decisions and implement effective treatment.

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