

*LUCIAN BLAGA UNIVERSITY OF SIBIU*

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***DOCTORAL THESIS***

***Clinical and therapeutical assessment of  
mushroom poisoning cases in children***

***- Abstract -***

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## ***I. Theoretical background***

Since the dawn of human civilization, mushrooms have exercised a strange attraction, being ubiquitous in the natural environment, found in all areas of human activity, yet viewed in a very different manner. Depending on the time in history, on the geographical area and the type of culture they met, they were either vital food, instrument of death, means of interaction with the world of magic, panacea or poison.

The paradox of fungi begins with their classification, in the animal kingdom or as a plant. Initially regarded as plants, studied and classified in relation with them, they proved to show by scientific studies rather extensive similarities with animals. Currently, they are a part of a kingdom of its own, that of fungi. A simple definition considers animals as consuming beings, plants as producing beings, while the fungi are being recyclers, which makes it possible to close the food chains.

Loved or hated, valued or feared to the point of demonization, mushrooms accompanied human civilization in all its stages of development. Used as food or as medicine, in modern food processing or in the scientific research, they have always found a place in human society. Growing up in the shadows, discrete, but not negligible, they will be with us further, waiting for us to have patience to discover the mysteries that they are still hiding.

History of mushroom harvesting for human use and therefore of poisonings is closely intertwined with the history of mankind. During evolution, each population had a specific pattern of mushroom use and integration into their own culinary culture, economic, spiritual or artistic life.

Mycology is the branch of biology that studies the representatives of the kingdom Fungi.

Mycology includes as fields of study :

- The taxonomy of fungi
- Genetics of fungi
- The morphology of fungi
- Biogeography of fungi
- The use of fungi in the economy
- Negative effects of fungi
- Biochemical properties of fungi

Etymologically , the word is derived from the Greek Mykes / μύκης ( mushroom ) and logos / λόγος ( discourse , speech ) . Using the term to name the scientific study of fungi belongs to english naturalist Miles Joseph Berkeley, in " The English Flora of Sir James Edward Smith " Vol 5 . , in 1836 .

It is still believed that mushrooms are plants , people remained tributary , in this respect to the old conceptions formed during millennia as the basis of the classification of life forms . Echoing this view fungi are studied at school , in the class of " botanical sciences" and even in the biology colleges, mycology ( the discipline that studies fungi) belongs usually to the Department of botany / plant biology .

That is why, although the fungi are today placed in systematic of creatures in a separate kingdom , of their own , called Fungi ( recognizing that they are neither plants nor animals, or anything else – they are fungi / fungi ) , confusion is perpetuated . First, they have an entirely different nutrition : if plants contain chlorophyll and they are feeding in an autotrophic manner ( preparing their food on their own - organic substances from carbon extracted from the air , using light as an energy source ) , mushrooms only break down and then absorb the organic matter from the soil.

Therefore , their function in nature is special , quite different from that of plants : if plants are producers, mushrooms are decomposers , thus fulfilling a opposite role . Then , reproduction modes are different to those of the plantn , and the life cycles are more complex and different from the plant world .

With advances in microscopy and biochemistry has come the great revelation of the fact that plants and fungi are very different from each other, especially from the biochemical and structural point of view. One of the basic features of the plant kingdom (plants ) is the presence of rigid cell walls , consisting mainly of cellulose membranes that cover the outside of the plant cell and give rigidity to the structure . Thanks to them , the plants can be raised above the ground, rising to the sunlight - their source of energy.

Unlike the vegetable world , the fungus kingdom has the distinctive presence of cell walls constituted not of cellulose, but of chitin . Chitin is synthesized by animals - many invertebrates have a chitinous exoskeleton , a handy example are the hard wings of may beetles , which covers and protects the other pair of wings , membranous , thin and transparent - so that, at least in the biochemical and morphological aspects, fungi are closer to animals than plants.

Taxonomy and classification of fungi in different groups are in constant change due to new studies based on DNA analysis . These results change older classifications based on morphological differences . Also , certain fungal species may have different names , depending on the life cycle or sexually/asexually reproducing mode .

A comprehensive paper published in 2007 by a team of 67 researchers from several centers suggests a more complete version of the classification.

The kingdom Fungi includes 4 phylae .

- Phylum Chytridiomycota
- Phylum Zygomycota
- Phylum Ascomycota
- Phylum Basidiomycota

Phylum Ascomycota together with Basidiomycota form up the so-called higher fungi family ( Dikarya ) . This includes all the mushrooms traditionally used as food and also the poisonous species .

Basidiomycetes are divided into three classes ( Pucciniomycotina , Ustilaginomycotina , Agaricomycotina ) and two separate divisions ( Wallemiomycetes , Entorrhizomycetes ) which are not self-contained classes . According to an estimate from 2008, this branch contains 52 orders , 177 families, 1589 genera and 31,515 species. It can thus reveal the complexity and the diversity of species of fungi.

Most fungi have several common features , such as micelle structure , the propagation and lifestyle. The apparatus of growth of the fungus ( tal ) , called micelle , is missing the chlorophyll and is made up of a single cell ( single cell tall ) or cells (multicellular tal ) . Saprophytic fungal mycelium grows in dead organic substrate extracting and breaking down nutrients and producing surface structures ( bazidiocarpi ) that have different shapes and sizes .

In terms of trophic relations , fungi are heterotrophic organisms . These include:

- saprophytic
- parasitic
- symbiotic ( lichens , fungi performing mycorrhizae ) .

Not all mushrooms fall readily into one of these categories. There are numerous fungi , which typically voluntary or accidental , are either scavengers or parasites , as is the case , for example , for Mellor Armillaria or Aspergillus mold . Depending on their environment , there are fungi in the soil , in the air (especially mold spores ) in water and various organic substrates .

Mushrooms can be found in various conditions of temperature , pressure, humidity and chemical composition of the substrate. Most fungi are known and available to the public apparently adapted to common environmental conditions : warm , moist and dark places. However, members of the family can be found in some of the most extreme conditions possible , where even the idea of life seems impossible.

The seasonal nature of spontaneous growing mushrooms harvesting periods, nutritional qualities and evidence and in some cases their medicinal qualities led to people intention to practice a type of intensive farming for them .

According to the Food and Agriculture Organization of the United Nations in 2009, the largest global manufacturer of fungi was China with 4,680 million tons, followed by the U.S. with 369,000 tons to 235,000 tons and the Netherlands . Romania is ranked 36 worldwide , with about 7,300 tons.

Mycotoxicology is the mycology branch that is dealing with the analysis and study of toxins produced by fungi, substances called mycotoxins. Mycotoxins are synthesized by fungi, and are toxic to vertebrates or other animal or plant species even in very low concentrations . Other fungal metabolites , such as ethanol , whose toxicity is shown only at high concentrations are not considered as mycotoxins.

Toxic substances contained by poisonous mushrooms end up in the body by accident, through the various mechanisms, most often by confusion between species .

Mushroom poisoning , regarded as a complex array of clinical signs , biochemical and functional alterations of the body is called micetism ( fr. mycétisme , cf gr . Mykes - mushroom ) .

Mushroom poisoning, considering the multitude of species and toxins contained therein , causes a wide range of events , each having distinct pathogenic mechanisms and pathophysiology patterns . In general, however , we can speak of three or four major syndromes due to targeted organ toxicity and specific pathophysiological cascade resulting from this disorder .

Mainly we can talk about acute/fulminant liver failure with all the resulting consequences, including hepatic encephalopathy , acute renal failure and electrolyte imbalance syndrome consecutive to gastroenteritis , which , especially in young children ( 0-3 years) may develop severe forms and requires prompt therapeutic intervention .

Clinical and biological syndromes for mushroom poisoning where the pathogenic mechanisms and pathophysiological consequences are well studied are divided as follows, according to the latest classification by Diaz (2005) :

- 8 syndromes with early onset ( latency time under 6 hours) , of which 4 are neurotoxic , two gastrointestinal and two allergic
- Three syndromes with late onset ( 6-24 hours) , hepatotoxic , accelerated nephrotoxic erythromelalgia ;
- Three syndromes with late onset (over 24 hours) , delayed nephrotoxic , delayed neurotoxic rhabdomyolysis .

Of these , 4 are considered newer syndromes : delayed neurotoxic syndrome, delayed nephrotoxic syndrome, erythromelalgia and rhabdomyolysis.

Early onset syndromes

Neurological syndromes

A ) Cholinergic syndrome , also known as Muscarinian . The toxin responsible is muscarine , this is not quickly changed similar to acetylcholine by the acetylcholinesterase and the cholinergic effects lasts as long as its concentration does not decrease or the substance it is not antagonized by atropine .

The cellular toxin induces a permanent depolarization by binding to cholinergic receptors – muscarinic type ( parasympathetic postganglionic receptors of smooth muscles and glands )

B. ) Glutaminergic or Pantherinian syndrome ( toxin comes from *Amanita pantherina* )

The toxin is one isoxazole derivative of the same structural form with glutamic acid, the ibotenic acid , and acts as an antagonist of its receptor . Muscimol , referred to as muscazol , has a structure identical to that of the gamma- amino butyric acid ( GABA ) and has an antagonistic effect on its receptor.

C. ) Epileptogenic syndrome .

Toxin responsible ( Monomethyl ) is found in *Gyromitra esculenta* . Symptoms start after about 2 hours and lasts about 2 days. The most frequently encountered are seizures , hence the name of the syndrome.

D. ) Hallucinogenic syndrome or Psilocybin syndrome .

The toxins that are responsible for the induction of psilocin and psilocybin syndrome , are derivatives of tryptamine and 5 hydroxy tryptamine , serotonin antagonists .

Clinical effects are similar with those of lysergic acid diethyl - amide (LSD) . Symptoms have rapid onset and disappear after about 2 hours.

Effects of serotonin receptor stimulation of medullary reticular nuclei are of hallucinogen type. Clinical and biological status include: euphoria , hallucinations , impaired perception of time and space , mydriasis , hyperkinetic movements , tachycardia , hypertension, fever, headache , dizziness, weakness , anxiety , paresthesia , myalgia, hyperpyrexia, dysphoric reactions .

#### Gastrointestinal syndromes

##### A. ) Disulfiram reaction / coprinian syndrome .

The toxin , referred to as coprin is a cyclopropyl derivative of glutamic acid ( aminocyclopropanol ) disulfiram -like, which has inhibitory effects on acetaldehiddehydrogenase , blocking the metabolism of alcohol and allowing the acetaldehyde to accumulate . Toxin effects disappear after about 72 hours .

Clinical manifestations include headache, vomiting , flushing, sweating , chest pain, dyspnea , palpitations ( arrhythmia , tachycardia ) , tinnitus , prostration .

##### B ) The gastro-intestinal syndrome .

In the common form , can be produced by over 100 species of mushrooms. Toxins involved in the triggering of the syndrome are resinoids , ketones , quinones which determines the severe forms of gastroenteritic syndrome acute dehydration of varying degrees , hypovolemic shock ± hemolytic syndrome.

#### Allergic syndromes .

We describe two types of allergic syndromes : immune hemolytic type and pneumonic.

For immune hemolytic the fungus called *Paxillus involutus* is incriminated, with the toxin called involutin. Onset is of gasteoenteritic type, 3 hours after ingestion and symptoms are dominated by haemolytic anemia, hemoglobinuria , acute renal failure.

Pneumonic syndrome is triggered by *Lycoperdon* (Puffball mushroom type - *Calvatia* genres , *Calbovista* and *Lycoperdon* ) and consists of an allergic bronchial syndrome responsible for acute respiratory failure .

## Late-onset syndromes

### **Hepatotoxic syndrome .**

Toxins involved are part of the cyclopeptides family: amatoxin ( high toxicity ) , phalloidin ( average toxicity ) virotoxin (although it is considered non toxic ) . Amatoxin is responsible for 95 % of deaths caused by mushroom poisoning . 35 known species of fungi are containing amatoxin (10 of Amanita group , 9 of Galerina group and 16 of the Lepiota group) . Amanita phalloides is common in North America and central and southern Europe, and Amanita virosa - in northern Europe.

A.) Phalloidian syndrome .

Amatoxin is 10-20 times more toxic than Phalloidin . It is rapidly absorbed from the gastrointestinal tract , from where is passing to the liver ( at 60 %). It is actively transported into hepatocytes and then excreted in the bile juice . A significant amount is returned to the liver via enterohepatic circulation , which increases the exposure to the toxin . Phalloidin is a cyclic haptopeptid that is destroying the cell membrane by actin G and F irreversible polymerization. It is not absorbed in the intestinal tract , but is responsible for the first clinical symptoms : nausea , vomiting .

B ) Gyromitrian syndrome .

In the stomach, the gyromitrin ( incriminated toxin ) is rapidly hydrolyzed in acetaldehyde and N -methyl -N - formylhydrazine ( M.F.H. ) , the latter being converted slowly to N- methylhydrazine (M.H. ) . M.F.H. inhibits P450 cytochrome and glutathione , causing hepatic necrosis . M. H. piridoxinkinase inhibits and interferes with other enzymes piridoxin-dependent (those that synthesizes G.A.B.A.) , with the following effects : seizures, methemoglobinuria , haemolysis, acute renal failure.

The latency period is 6-10 hours , in the first stages patients showing abdominal pain , vomiting , diarrhea . Patients receiving concomitant treatment with isoniazid in the continuation phase may present with delirium, convulsions , coma . The mortality rate is 2-4% .

### Accelerated nephrotoxic syndrome

Syndrome first described in 1992 in U.S. and Canada, with the Amanita smithiana mushroom incriminated, in France , Spain and Italy - Amanita proxima and Japan - Amanita pseudoporphyria .



2-amino - 4 ,5 – hexadienoic acid ( the responsible toxin ) produces renal tubulopathy with faster onset than orellanian type intoxication , but with better prognosis .

### Erythromelalgia

It was described in the late 19th century in Japan and South Korea ( *Clitocybe acromelalga* ) and since 1996 in France and Italy ( *Clitocybe amoenolens* ) . The responsible toxin ( acromelic acid ) produces necrosis of the hand extremities, skin ulcer , acrocyanosis .

## **Late onset syndromes**

### Late nephrotoxic syndrome

Toxin involved is orellanin ( mushroom of the genus *Cortinarius* ) . This is converted into orellin , whose main effect is the renal tubular necrosis . Fatty degeneration of the liver and intestinal inflammation accompanies the renal effect . Very long latency period (from 3 days to 3 weeks). At the onset of symptoms patients may experience diarrhea , vomiting , abdominal pain (lasting 24-48 hours ) , and signs of acute renal failure.

### Delayed neurotoxic syndrome

It presents as a convulsive encephalopathy -like syndrome . It has been described in patients with a history of chronic renal failure , in Germany in 1992 ( after consumption of *Hapalophilus rutilans* ) and Japan , 2004 ( after consumption of *Pleurocybella porrigens* ) .

### Rhabdomyolysis syndrome

Described in 1993 in France , the main manifestation is acute myocarditis after ingestion of mushrooms of the genus *Tricholoma Equestre* .

## ***II. Special Part***

Although in recent years a series of campaigns tried to educate consumers regarding the dangers related to the use of spontaneous growing mushrooms , mushroom poisoning remains a serious public health problem , especially when it occurs in children, because the clinical and treatment features occurring in this age group .

In order to present the motivation for choosing the theme of this study we will review recent data from the literature related to the incidence of this disease. To illustrate the magnitude of the problem, it is enough to note that a simple search in the database of the U.S. National Library of Medicine reports no less than 158 articles indexed in just the last five years regarding mushroom poisonings in children.

The pattern of mushroom poisoning is different in adult compared to the child , and it is an area where we can intervene in the prevention of such cases . Mechanisms of contact with toxins from fungi are the most diverse , but in all cases prevention through education activities may reduce the number of illnesses .

While adults use mushrooms collected without knowledge of the morphology , confusion of the species is the most common route of poisoning in children; most of the reported cases are occurring after mushroom ingestion during meals shared with parents and injuries related to unintentional consumption , especially in young children that eat certain fungi found incidentally during unsupervised activities .

A relatively new way of contact with poisonous mushrooms , at least in our country, is the consumption of hallucinogenic mushrooms, in dried form or in combination with other substances - the so -called ethnobotanical substances , which were widely spread in recent years . Mushroom poisoning cases of this type are less recognized or classified summary in thr category of drug addictions , and consequently underreported . Incriminated in these cases are mushrooms with psychotropic effects , which can be from spontaneous flora of our country or imported in dry form , in which case there is more difficult to identify the species.

Epidemiological data about mushroom poisonings in Europe are not collected in an integrated manner, especially in states non-member of the European Union .

The tradition of collecting mushrooms of spontaneous flora, much better developed in Europe and Asia, generates a large number of poisonings, resulting in about 50 deaths annually, compared with an average of 4 deaths in North America. In all Anglo-Saxon countries, the tradition of collection and consumption of wild mushrooms is poorly developed, although in recent years there has been a growing interest in them.

In Eastern Europe, due to local traditions and lower living standards, in addition to the greater percentage of the population living in rural areas one can meet more serious mushroom poisoning cases in children. Minor forms of poisoning in children often remain unreported due to low addressability of groups at risk. Poor education, lack of childcare are additional factors that increase the incidence of exposures and poisonings in this age group.

For Romania, unfortunately, currently there is no unified system of registration for toxicological data, here including eating poisonous mushrooms. In recent years a number of initiatives have appeared to align with European standards, such as the fact that the "Grigore Alexandrescu" Hospital in Bucharest has a Clinical Toxicology Department, which is at least of regional addressability. Associate to this clinic works the TOXAPEL telephone line, the result of the efforts of the group from Emergency Hospital for Children "Grigore Alexandrescu". Besides the existing clinical database, the cases reported in this way are recorded and stored for scientific study. The existing data is related to aspects of local or regional studies. In our country, at present there are known more than 50 species of poisonous mushrooms, and mushroom eating of species picked from uncontrolled sources is still very high.

#### Acute hepatic failure in mushroom poisoning in children

The forms of mushroom poisoning in children include different grades of severity, varying according to the type and amount of toxin ingested. The most severe organ damage occurs in amanitin-containing mushroom poisoning, where liver failure of varying degrees appears, responsible for most deaths after eating poisonous mushrooms. After ingestion and intestinal absorption of toxins, they cause damage to nuclear and cell wall with consecutive structural disorganization. Protein synthesis of the liver is inhibited by blocking the action of RNA polymerases II and III, which makes the repair of injuries that occur at the cellular or subcellular level impossible.

## Acute renal failure in mushroom poisoning in children

In the clinical picture of mushroom poisoning in children , renal failure occurs in late stages of poisoning with hepatotoxic mycotoxins , that of hepato-renal insufficiency , or as an independent clinical entity , if there is the case of ingestion of toxins with direct nephrotoxic action such as orellanin ( paraphalloidian syndrome , orellanian syndrome ) .

## Acute dehydration syndrome in children

This event may occur in association with any form of mushroom poisoning in children, as the consequence of massive fluid loss through vomiting , diarrhea, and subsequent lack of oral intake . Active metabolism of children , especially in infants , where the exchange rate of water per unit of body weight is three times higher than in adults , makes water homeostasis to be more fragile , with faster installation of dehydration syndrome . Acute dehydration syndrome is most often the only clinical consequence of intoxication with mushrooms that produce the gastro-intestinal syndrome.

## Treatment of mushroom poisoning in children - current data

The goals of treatment in mushroom poisoning in children are:

- Preventing or reduction of the absorption of toxin from the gastrointestinal tract and promoting its elimination .
- Decreasing serum concentration of toxins , shortening of the time during which the cells are susceptible to damage are " exposed" to it.

## Detoxification

### A. Primary detoxification

Comprises therapeutic interventions aimed at decreasing the absorption of toxins contained in mushrooms . It is useful in the early hours of ingestion , where it is assumed that there is still undigested and unabsorbed food residue in the digestive system, and it is desirable to be done in an medicalized environment , or even at home but assisted by qualified personnel.

## B. Secondary detoxification

Aims to remove the toxins from the bowel or blood circulation . Among the methods used there are:

Oral detoxification or enterodialysis is achieved by repeated administration of oral activated charcoal , which blocks the toxins eliminated through the bile into the intestine , interrupting their hepatoenteral cycle .

Renal detoxification is achieved by increasing the urinary diuresis . The method has to be used in situations in which there is no severe renal impairment , and the increases renal excretion of toxins by the administration of diuretics , while supplementing parenteral fluids .

### Extracorporeal detoxification

It has the following objectives:

- ‖ To remove the initial toxins ( amatoxin , phalloidin ) .
- ‖ To remove the secondary toxins by removal from circulation of cytotoxic cytokines released from Kupfer cells , stellate and sinusoidal , which also contribute to the installation and progression of liver failure .
- ‖ To stimulate the liver regeneration by removing growth inhibitors ( Interleukin 1).
- ‖ Hemodynamic stabilization of the patient.
- ‖ To avoiding emergency liver transplantation .

This may be accomplished by extracorporeal hemodialysis , peritoneal dialysis or haemoperfusion on column of activated charcoal. It is used only in cases where the poisoning took place up to 36-48 hours before admission , because after this time the blood concentration of mycotoxins is too low to justify the use of the method.

## C. Administration of antidotes

The antidote is a substance used with the intention of counteracting a poison . The term comes from the Greek αντιδιδοναι - antididonai , which means " given against" .

## The pathophysiological treatment of "big failures "

Treatment of patients with severe hepatic failure due to mushroom poisoning in the pre-hospital and the emergency units.

- Resuscitation fluid and electrolyte monitoring .
- Because patients present sometimes several days after ingestion, gastric decontamination ( gastric lavage , administration of activated charcoal) is quite inefficient. If ingestion is recent , administration of activated charcoal may prove effective unless recent emetic syndrome was present or impaired consciousness .
- Correct rehydration and shock treatment .
- Monitorisation of urine output .
- Administration of antiemetic medication to treat nausea and possible vomiting episodes.
- Benzodiazepines followed by phenytoin for seizures .
- Hemodialysis may be required in emergency cases with fulminant renal failure or severe diselectrolytemya . Hemoperfusion or hemodialysis were proposed early in the treatment regimen and early after ingestion, even if there are no signs of kidney damage , but there is not enough evidence to support their effectiveness.

Treatment of acute liver failure (A.L.F.) or fulminant hepatic failure (F.L.F.) - current data

The most important aspect of the management of patients with A.L.F. is the appropriate intensive care. Patients with grade II or more severe encephalopathy should be referred to the intensive care unit for monitoring . With the progression of encephalopathy , airway protection becomes important.

Most patients with A.L.F. tend to have some degree of circulatory failure . Increased attention should be given to hemodynamics monitoring, fluid balance , metabolic parameters and infection surveillance .

Good nutrition and early diagnosis of possible gastrointestinal bleeding are also important . The coagulation pannel , blood count , and metabolic tests will be evaluated frequently. Intensive care should include early recognition and treatment of complications .

## Artificial liver substitution systems

They are divided into two major categories - biological ( bio-artificial ) or non-biological.

→ Bioartificial liver is comprised of an dialysis cartridge containing the porcine hepatocytes and other mammalian cells into the extracapillary spaces . These devices have been evaluated in several studies . A multicenter study reported improved short-term survival in patients with A.L.F. treated with a porcine hepatocyte based artificial liver .

→ Non-biological systems for extracorporeal liver support , such as hemodialysis, haemofiltration , haemoperfusion by activated charcoal , plasma transfusions have also been used. This methods provide a temporary liver substitution until a suitable transplant donor is identified. Although hemoperfusion over charcoal or other inert substances provides a degree of detoxification, liver synthetic function can not be substituted .

→ Among the other liver support systems studied is the albumin dialysis adsorption recirculating system (Molecular Adsorbent recirculating System M.A.R.S. ), which is one of the most thoroughly studied . In this system, blood is dialyzed through a albumin impregnated membrane, against a 20 % albumin solution . Anion exchanging resins and activated carbon are purifying and regenerating the albumin dialysate. Clinical studies have shown that it improves the hyperbilirubinemia and the encephalopathy .

- Two other systems based on extracting toxins linked to protein, called Prometheus , which uses the principle of fractionated plasma separation and adsorption ( Fractional Plasma Separation and Adsorption F.P.S.A. ) and albumin dialysis ( S.P.A.D. Single Pass Albumin Dialysis ) are currently evaluated in clinical trials .

## Surgery

Orthotopic liver transplantation remains the only effective method of treatment of A.L.F. in advanced stages, with no response to the classical therapy . This option is selected in any patient who is diagnosed with A.L.F. , regardless of etiology , including mushroom poisoning . A.L.F. accounts as indication for 11-13 % of liver transplants , and leads to a significant improvement in the vital prognosis .

## Treatment of acute renal failure in mushroom poisoning in children

- Aggressive treatment should be started at the earliest signs of renal failure. Much of the renal parenchyma may already be destroyed before any change occurs in the biochemical parameters, because the relationship between glomerular filtration rate and serum creatinine level is exponential, not linear.
- The increase in serum creatinine levels may not be obvious to the stage where 50 % of the glomerular filtration rate is lost. In this state, the recognition of the presence of acute renal damage and rapid initiation of the therapy, in order to minimize the destruction of the remaining functional renal mass is essential. This can help restore already damaged parenchyma. Stopping the damage and a complete restoration can only be achieved through accurate identification of the cause and appropriate treatment setting. Keeping the water balance and correction of any biochemical changes are the main goals of treatment. Also, all the drugs with renal elimination should be avoided, or the dosage should be adjusted accordingly. It is important to correct acidosis by administering bicarbonate.
- Hyperkalemia, which can be potentially fatal, should be treated by lowering potassium intake, delayed absorption in the intestinal mucosa by specific substances (fixating resins), by controlling the cellular channels, or by dialysis.
- Correction of haematological (anemia, thrombocytosis / thrombocytopenia) also requires appropriate measures.

## Treatment of acute dehydration syndrome in mushroom poisoning in children

Correction of acute dehydration syndrome in children is part of the complex therapy of mushroom poisoning. The method of administration and quantity of the various solutions used are chosen depending on the degree of dehydration, age and patient consciousness, nutritional status of the patient, type of poisoning.

### Oral rehydration

Indicated in light and medium forms as it is a simple method, convenient and well tolerated by patients, with reduced cost and risk.



The objectives are :

- Electrolyte administration, in order to compensate for the loss of sodium , potassium, chloride
- Preventing the installation of metabolic acidosis by increasing the bicarbonate intake
- Providing nutritional energy
- Stimulating the sodium absorption by enteral glucose intake
- Respect intraluminal osmolarity

Parenteral rehydration

Indications:

↳ Severe Dehydration

↳ Dehydration syndrome regardless of the degree, which also involves :

- Seizures
- Swallowing disorders
- Alteration of consciousness
- Untreatable vomiting
- Distended abdomen / ileus
- Newborn age group

## **Clinical study**

The objectives of the clinical trial are as follows:

- a) Collecting of current data showing the incidence of mushroom poisoning in children in a nationally representative sample .
- b ) Evaluation of the number of mushroom poisoning over more years, the study of their incidence variation during the months of a year.
- c ) Research over the patient admission type , taking into account the specific centers where cases were selected , and also that they are university clinics and regional centers of excellence.
- d ) Study of the correlations between types of intoxication and parameters such as age, gender, origin , season , method of preparation , with respect of individual variations in clinical manifestations and severity of symptoms depending on them.
- e) The study of the correlation between the severity of intoxication and age, gender and metabolic features of the patient .
- f ) Research for potential parameters that correlate the degree of toxicity of ingested mushroom with the season when they are collected or how they are prepared .
- g ) Selection of groups of signs and symptoms of different poisoning types , the study of these groups and their comparison with the datas from the literature .
- h ) Definition of possible correlations between age groups , origin of patients and the severity of mushroom poisoning .
- i ) Evaluating of the toxicity types and prognosis in the group of patients included in the study.
- j ) Assessment of prognosis factors in fatal poisonings or potential lethality in the studied cases .
- k ) To study the period of hospitalization of patients, its variation according to clinical and biological parameters .
- l) Long-term estimate prognosis .
- m ) Specification of the extracorporeal detoxification maneuvers's role as modern method and results of their use.
- n) Mushroom poisoning mortality assessment , selection of adverse prognostic factors present in the group of patients with fatal outcome .

## Materials and methods

The study was retrospective multi-center, of longitudinal type .

Data were obtained from: Sibiu Pediatric Hospital ("Victor Papilian " Faculty of Medicine Sibiu ) ,, Grigore Alexandrescu" Emergency Hospital for Children " Bucharest ( „Carol Davila" University of Medicine and Pharmacy Bucharest), Second Pediatric Clinic Cluj- Napoca („Iuliu Hatieganu" University of Medicine and Pharmacy Cluj- Napoca ) . The period studied was established between January 2009 - June 2013. The collected data were taken from the patient's clinical observation sheets and discharge notes.

The inclusion criteria for the study was the term mushroom poisoning diagnosis founded in the discharge summary .

Exclusion criteria were the absence of a diagnosis of mushroom poisoning , transfer of patients during admission to other services.

After applying these criteria , the results created a group of study comprised of 146 cases .

We have followed and statistically interpreted the following parameters:

- Age of patients
- Gender
- The area of origin (urban/rural)
- The month of hospitalization , the annual change in the number of poisonings
- Type of fungus that caused poisoning
- Method for preparation of the mushrooms
- The presence of symptoms in entourage
- Type of hospital admission
- Latent period from ingestion to onset of symptoms and presentation to medical care units / hospitalization
- Symptoms at intoxication onset and at hospitalization time
- Changes in laboratory parameters
- The treatment followed
- The period of hospitalization
- The evolution of symptoms and laboratory parameters
- Mortality in the studied group .

## Results and Discussion

### Sex of patients

Of the 146 enrolled patients , 79 were males and 67 females.

Males	79 patients	54,11%
Females	67 patients	45,89%
Total	146	100%

There is a slight difference in favor of poisoning cases in males . Groups of boys frequently tend to imitate adults habits , especially those related to life in the wild , hunter - gatherer type behaviors .

### Distribution by age of patients

Distribution by age of patients in the study was as follows:

Age group	Number	Percent
0-1 years	1	0,68%
1-2 years	9	6,16%
2-3 years	5	3,42%
3-4 years	6	4,11%
4-5 years	8	5,48%
5-6 years	13	8,90%
6-7 years	5	3,42%
7-8 years	14	8,59%
8-9 years	9	6,16%
9-10 years	12	8,22%
10-11 years	9	6,16%
11-12 years	7	4,80%
12-13 years	7	4,80%
13-14 years	14	8,59%
14-15 years	8	5,48%
15-16 years	7	4,80%
16-17 years	7	4,80%
17-18 years	5	3,42%

47 cases ( 32.19 % of total) were poisonings treated in children of preschool age , 0-7 years. For this subgroup , the mechanism of poisoning is either accidental ingestion of mushrooms if left children are unattended or consumption together with the caregivers of mushrooms collected and prepared for common meals .

72 poisonings ( 49.32 % of total) occurred in children aged 7 to 14 years . In this case the possible mechanism is the ingestion of mushrooms collected from the spontaneous flora , following the example of their parents , but without a good knowledge of their morphology. All other mechanisms presented above remain possible, which explains the highest percentage of cases that fall into this group .

27 poisonings ( 18.49 % of total) were found in the age group 14-18 years . Education begins to play an important role in this case , therefore poisonous mushroom ingestion occurs rarely , usually by the confusion of species. Mechanisms to produce intoxication are relatively identical to those reported in the adult population .

Percentage of cases encountered at early age allows the formulating of this conclusions: eating habits , living standards and low educational level , lack of constant supervision of children exposed them to the risk of poisoning with mushrooms, even for very young children . The number slightly decreased of pre-school age group compared with literature data in our study may be explained either by a lack of reporting ( minor forms that are not recognized and registered as such, cases treated at home or as outpatient ), or by diagnosis coding errors .

#### The area of origin

50 patients were from urban areas (34.25 % ) , and 96 from rural areas ( 65.75 %).

The difference between the two groups is statistically significant , which leads us to say that in our group of patients the origin is predominantly rural .

The data presented show that most poisonings occur in rural areas. In Romania, the demographic structure of the population is 55.2 % in urban areas and 44.8 % in rural areas.

However, the number of poisoning is much higher in rural areas. The explanation comes from the food habits of the rural population, which is used to collect and consume a range of wild growing species products , including fungi.

Lack of education and lack of proper morphology knowledge leads to ingestion of poisonous species , with all the consequences arising therefrom.

Easier access to areas of forest or grassland with fungi facilitates contact with them for the people in rural areas . Some of these will be kept for their own use , and some may still be sold in markets and fairs without checking them thoroughly by specialists. This is one of the common ways for the origin of poisonous mushrooms consumed by urban population .

Hospitalization time

Changes in the number of cases by year :

Year	Cases
2009	35
2010	43
2011	11
2012	28
2013	29

Average annual number of cases is  $29.2 \pm 11.8$  cases per year with a maximum of 43 cases in 2010. We have observed a minimum in incidence in 2011.

Distribution by centers was as follows :

Year	Sibiu	București	Cluj-Napoca	Total
2009	10	8	17	35
2010	6	12	25	43
2011	3	4	4	11
2013	1	10	17	28
2013	10	7	12	29

Geographical variation observed respected the annual change of temperature and precipitation , with no statistically significant differences between the number of cases reported in the three centers included in the clinical trial . Although they are located in different geographical areas as altitude , landforms and climate, the number of cases was up to the general climatic characteristics of our country .

The number of poisoning cases reported and treated in the hospital is directly linked to the life cycle of fungi . The June and July , which are the rainy months that have among the highest thermal values are the months in which there have been reported most of the mushroom poisoning . Together, these two months account for more than half of the cases included in the study ( 85 cases - 58.22 % of the total) .

#### Type of admission

A total of 71 patients ( 48.63 % ) were admitted by direct presentation to the emergency room or pediatric clinic , while 75 patients ( 51.37 % ) were transferred from other hospitals or admitted by referral from general practitioner's office .

Distribution of cases that were presented directly to the emergency room of the hospital versus those transferred from other hospitals or GP's office was approximately equal . Given that in most cases the rapid initiation of specific treatment , or in severe cases the use of advanced methods of treatment have a vital influence on prognosis , recognition by experts in primary care of potentially severe situations (hepatotoxic syndromes , nephrotoxic ) is very important .

#### The distribution of symptoms to the entourage

When mushrooms are consumed at home, cooked after being picked of spontaneous flora, the symptoms are present in most cases to all members , in varying degrees of severity.

If accidentally ingested poisonous mushrooms ( more often raw ) are eaten by young children or after the confusion of species, the clinical manifestations are present only at the victim, and often they are the most severe forms as the dose / kilogram body is the highest. The type of cooking also affects the distribution and severity of symptoms.

In our study similar symptoms were present to others who consumed mushrooms in 45 cases (31 % ) , or were limited to the treated persons in 101 cases ( 69%).

### The origin of ingested mushrooms , method of culinary preparation

As expected, the majority of cases - 142 ( 97.26 %) had symptoms after ingestion of mushrooms collected from wild flora or bought from vendors - gatherers ( usually from markets ),while in 4 cases (2.74 % ) symptoms started after ingestion of cultivated mushrooms (based on anamnestic data). In these cases it may be the case of either poisoning associated with poor hygiene conditions, or a gastrointestinal intolerance with dyspepsia, or non-recognition of wild mushroom consumption , which is why the cases were not excluded from our study .

The method of mushrooms preparation can only influence the severity of poisoning , meaning that a poisonous mushroom can be consumed by a single individual when fried or roasted on the stove / grill , as opposite with the case when prepared as a stew / salad with other toxic mushrooms consumed by many individuals, and its toxicity is shared between more individuals. By the same mechanism , related to the dose distribution , symptoms may affect just one person, or several people in the entourage , who ate the same dish.

Poisoning in children can follow both patterns : young children by the accidental ingestion of a raw mushrooms and the symptoms are limited to a patient, or older children who consumed mushrooms cooked with the rest of the family , in which symptoms occur together with the whole group , but sometimes with lower intensity . In our group, most cases of poisoning in children occurred after ingestion of cooked mushrooms (119 cases - 81.5%) .

### Latency time of intoxication

Due to the relatively small number of syndromes and the difficulty encountered in current practice to obtain accurate anamnestic data , patients from the study were divided into two groups , with short latency time (time between ingestion at the onset of clinical symptoms of 6 hours or less) and those with long latent period (time from ingestion to the onset of clinical symptoms longer than 6 hours) .

	Number	%
Short latency time	111	76,03%
Long latency time	35	23,97%



## Distribution of the cases into clinical and biological syndromes

Based on the latency of clinical symptoms and biochemical changes detected during hospitalization, patients were included in the following syndromes :

Syndrome	No. of cases	Percent from total
Muscarinian	9	6,16%
Pantherinian	3	2,06%
Psihotropic	5	3,42%
Gastroenteritic	94	64,38%
Phalloydian	31	21,24%
Orellanian	4	2,74%

## Changes in laboratory parameters

Of the 146 patients, 39 had a number of alterations of laboratory parameters ( 26.71 %) related to liver function. In the group with phalloidyan type syndrome in 29 patients ( 93.55 %) abnormal liver function was objectivated.

Laboratory parameters related to impaired renal function were present in 21 patients in the study group ( 14.38 %). The causes may be related to a severe dehydration syndrome ( pre-renal cause of failure ), the direct nephrotoxic effect of toxinf within the orellanian syndrome ( all 4 cases ) or hepatic - renal insufficiency in advanced stages of severe poisoning.

## Duration of hospitalization

Average length of stay was  $4.06 \pm 1.82$  days, with extreme to 1 day (2-4 hours), and 23 days. Most cases required hospitalization for a period greater than 96 hours ( 45 patients, 30.82 % of the total ), followed by cases with a period of hospitalization between 48-72 hours ( 41 patients, 28,08 % of the total ).

Lowest average duration of hospitalization occurred in patients treated for gastroenteritic syndromes ( 94 patients, mean 1.98 days ). In many cases the attitude was the primary detoxification and supportive treatment, followed by a brief period of observation.

If the patient's general condition permitted it , discharge was done relatively quickly.

At the opposite pole are inpatients with orellanian type syndrome (4 cases , average length of stay of 7.81 days ) . They required multiple sessions of hemodialysis , followed by a prolonged surveillance to assess the dynamics of renal function .

In cases discharged with the diagnosis of phalloidian syndrome, the average hospitalization was relatively short ( 5.32 days on average) . Changes concerning a severe hepatic impairment had a fulminant character, in cases resulting in deaths ( average length of stay for cases with fatal outcome of 3.33 days). Note , however, that these cases have come to the university centers where they were treated after a relatively long latency , and in most cases after a prior hospitalization in a city or county hospital .

#### Evolution, mortality

In the study group , a number of 9 deaths was recorded (6.16 %).

The overall rate of deaths by poisoning with mushrooms in different studies varies between 0.2% and 6.8 % . Relatively high percentage recorded in our group shows the fact that the study sample included cases treated in specialized centers , with regional absorption of severe forms .

In the remaining cases ( 137 to 93.84 % ) the evolution was towards healing , special mention being made for the 4 cases with orellanian syndrome who presented total functional recovery without signs of chronic renal failure .

All deaths occurred by acute liver failure in the phalloidian syndrome ( 29.03 % death rate in the group ) . Other studies on the species Amanita mushroom poisoning reported death rates varying from 1.9% ( 66 ) to 63.63 % . The variation comes from the different centers treatment options , ranging from classic detoxification treatment and support to modern methods of detoxification and accessibility of a liver transplant center .

There is a statistically significant correlation between the number of reported poisonings by year and the number of deaths. It is obvious that in years with favorable climatic conditions and high quantities of wild of wild mushrooms , poisoning probability is higher, and hence evolving of severe cases .

In the group of patients who had a fatal outcome , the average latency from ingestion to onset of symptoms and hospitalization was  $2 + / - 0.33$  days .

Of the 9 patients , 7 ( 77,7 % ) were admitted by transfer from other hospitals where there is no option to initiate more modern treatment procedures .

Treatment of cases included for 8 out of 9 patients an extrarenal detoxification method , in addition to the supportive treatment .

Duration of hospitalization in this group was 3.33 days . At this time we must add the time spent in hospitals from where it was transferred ( in 7 of 9 cases). Recognition of fulminant hepatic failure and swift initiation of aggressive treatment may reduce mortality .

## **Conclusions**

1 . Mushroom poisoning is a serious public health problem , especially when it occurs in children, due to the number of cases that continues to be high , and to special clinical features and treatment particularities of this age group .

2 . Poisoning in children includes forms of variable severity , depending on the type and amount of toxin ingested. The most severe damage occurs in intoxications with amanitin - containing mushrooms , who lead to liver failure of varying degrees , responsible for most deaths after poisonous mushrooms consumption.

3 . Our study showed a slight difference in the incidence of mushroom poisoning in children according to sex, with 79 male patients ( 54.11 % ) compared to 67 females ( 45.89 %).

4 . 47 cases ( 32.19 % of total) were poisonings treated in children of preschool age , 0-7 years. 72 poisonings ( 49.32 % of total) occurred in children aged 7 to 14 years . 27 poisoning ( 18.49 % of total) were found in the age group of 14-18 years .

5 . Eating habits , living standards and low educational levels , lack of constant supervision of children exposed to the risk of poisoning with mushrooms, expose even very young children to the risk. The number slightly decreased compared with literature data for pre-school group poisonings in our study may be explained either by a lack of reporting ( minor forms that are not recognized and registered as such, cases treated at home or as outpatient ), or by diagnosis coding errors .

6 . 50 patients were from urban areas ( 34.25 % ) , and 96 from rural areas ( 65.75 %). In our study the origin of the patients is mostly rural .

7 . Average annual number of cases is  $29.2 \pm 11.8$  cases per year with a maximum of 43 cases in 2010. We observe a minimum incidence in 2011.

8 . Geographical variation respected annual change of temperature and precipitation , with no statistically significant differences between the number of cases reported in the three centers included in the study . Although they are located in different geographical areas as altitude , landforms and climate, the number of cases was up to the general climatic characteristics of our country .

9 . The number of poisoning cases reported and treated in the hospitals is directly linked to the life cycle of fungi . The June and July , which are rainy months and that have among the highest thermal values are the months in which there have been most poisonous mushroom intoxications . Together, these two months account for more than half of the cases included in the study ( 85 cases - 58.22 % of the total) .

10 . Distribution of cases that were presented directly to the emergency room of the hospital or were transferred from other hospitals or general practitioner's offices was approximately equal .

11 . In our study similar symptoms were present to others who consumed mushrooms in 45 cases (31 % ) , or were limited to people treated in 101 cases ( 69%).

12 . Most cases - 142 ( 97.26 % ) had symptoms after ingestion of mushrooms collected from wild flora or bought from vendors - gatherers ( in markets usually ), and in 4 cases (2.74 % ) symptoms started after ingestion of cultivated mushrooms (based on anamnestic data). In these cases it may be the case of either poisoning associated with poor hygienic preparation , or a gastrointestinal intolerance with dyspepsia, or non-recognition of wild mushroom consumption .

13 . Depending on the degree of thermal preparation of mushrooms, they were cooked in various forms in 119 cases ( 82 % ) , and eaten raw in 27 cases ( 18%). In our group, most cases of poisoning in children occurred after ingestion of prepped mushroom (119 cases - 81.5%) .

14 . Prevalent in the study group were poisoning syndromes with short latency ( 111 cases - 76.3% of total) .

15 . Most poisonings showed clinical and biological syndrome type of gastroenteritic type ( 94 cases - 64.38 % of the total) .

16 . The other types of syndromes were represented as follows: phalloidian syndrome 31 cases ( 21.24 % ) , muscarinian syndrome 9 cases (6.16 % ) , psychotropic syndrome 5 cases ( 3.42 % ) , orellanian syndrome 4 cases (2.74 % ) pantherinian syndrome 3 cases (2.06 %).

17 . Out of the 146 patients , 39 had a number of alterations of the laboratory tests suggestive for a diagnosis of acute toxic hepatitis ( 26.71 % ) .

18 . Laboratory samples related to impaired renal function were changed in 21 patients in the study group ( 14.38 %).

19 . Average length of stay was  $4.06 \pm 1.82$  days , with extreme to 1 day (2-4 hours) , and 23 days.

20 . Most cases required hospitalization for a period greater than 96 hours ( 45 patients , 30.82 % of the total) , followed by cases with a period of hospitalization between 48-72 hours ( 41 patients , 28, 08 % of the total) .

21 . Lowest duration of hospitalization occurred in patients treated for gastroenteritic type syndromes ( 94 patients , mean 1.98 days ) .

22 . The greatest duration of hospitalization was shown by orellanian syndrome cases (4 cases , average length of stay of 7.81 days ) . They required multiple sessions of hemodialysis , followed by a prolonged surveillance to assess the dynamics of renal function .

23 . In cases where it was possible , using extracorporeal detoxification treatment methods had good results , especially for orellanian syndrome , which allowed the recovery and preservation of renal function.

24 . In cases discharged with the diagnosis of phalloidian syndrome , the average hospitalization was relatively short ( 5.32 days on average) . Changes demonstrating severe hepatic impairment had a fulminant character in cases resulting in deaths ( average length of stay for cases with fatal outcome of 3.33 days).

25 . In the study group , it was recorded a number of 9 deaths (6.16 %).

26 . The evolution was towards complete healing for 137 patients ( 93.84 % ), with a special mention being made for the 4 cases with orellanian syndrome who presented total functional recovery without signs of chronic renal failure .

27 . All deaths occurred by acute liver failure in the phalloidian syndrome ( 29.03 % death rate in the group ) .

28 . There is a statistically significant correlation between the number of reported poisonings by year and the number of deaths. In years with favorable climatic conditions and high quantities of wild mushrooms , poisoning probability is higher, and hence evolving of severe cases .

29 . Sex of patients who died of liver failure was 3 male ( 33.33 % ) cases and 6 female (66.66 %).

30 . In the group of patients who had a fatal outcome , the average latency from ingestion to onset of symptoms and hospitalization was  $2 \pm 0.33$  days .

31 . Of the 9 patients who died , seven (77.7 % ) were admitted by transfer from other hospitals where there is no opportunity to initiate advanced treatment procedures .

Based on the final conclusions of our study , we developed a number of proposals to improve the treatment of this type of poisonings :

⊖ It would be useful to launch campaigns to educate the population , especially in rural areas, through schools , written or audio- visual media , by general practitioners , pharmacy .

⊖ To create regional centers with complete toxicology laboratory and treatment option, territorial assignation of sanitary units , setting transfer protocols .

⊖ To establish a single register of mushroom poisoning for collecting and storage of clinical data , enabling scientific monitoring of the phenomenon.

⊖ To develop clinical guidelines containing a unique algorithm of diagnosis and treatment for major syndromes encountered in our country.

⊖ To adapt and upgrade the legislation governing the sale of mushrooms collected from the spontaneous flora , prophylactic toxicological check-ups .