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ARTICLE

Treatment of Amatoxin Poisoning: 20-Year Retrospective Analysis

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ABSTRACT

Background: *Amatoxin poisoning is a medical emergency characterized by a long incubation time lag, gastrointestinal and hepatotoxic phases, coma, and death. This mushroom intoxication is ascribed to 35 amatoxin-containing species belonging to three genera:* Amanita, Galerina, *and* Lepiota. *The major amatoxins, the α-, β-, and γ-amanitins, are bicyclic octapeptide derivatives that damage the liver and kidney via irreversible binding to RNA polymerase II.* ***Methods:*** *The mycology and clinical syndrome of amatoxin poisoning are reviewed. Clinical data from 2108 hospitalized amatoxin poisoning exposures as reported in the medical literature from North America and Europe over the last 20 years were compiled. Preliminary medical care, supportive measures, specific treatments used singly or in combination, and liver transplantation were characterized. Specific treatments consisted of detoxication procedures (e.g., toxin removal from bile and urine, and extra-corporeal purification) and administration of drugs. Chemotherapy included benzylpenicillin or other β-lactam antibiotics, silymarin complex, thioctic acid,*

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antioxidant drugs, hormones and steroids administered singly, or more usually, in combination. Supportive measures alone and 10 specific treatment regimens were analyzed relative to mortality. ***Results:*** *Benzylpenicillin (Penicillin G) alone and in association was the most frequently utilized chemotherapy but showed little efficacy. No benefit was found for the use of thioctic acid or steroids. Chi-square statistical comparison of survivors and dead vs. treated individuals supported silybin, administered either as mono-chemotherapy or in drug combination and* N-*acetylcysteine as mono-chemotherapy as the most effective therapeutic modes. Future clinical research should focus on confirming the efficacy of silybin,* N-*acetylcysteine, and detoxication procedures.*

Key Words: Amanita*; Amatoxins;* Galerina*;* Lepiota*; Poisoning; Treatment*

INTRODUCTION

The hunting and eating of wild higher fungi is a traditional activity in many European countries and has become an increasingly popular pastime in the United States. Despite warnings on the risks of eating wild mushrooms, collectors continue to confuse edible and toxic species. There are few data defining the number of worldwide mushroom exposures;[1-11] but poisonings are a relatively common medical emergency. Among severe mushroom intoxications, the amatoxin syndrome is of primary importance because it accounts for about 90% of fatality.[12]

Amatoxin poisoning is characterized by a long asymptomatic incubation delay (from 6 to 12 hours) and three clinical phases. The first phase, or gastrointestinal phase (12–24 hours), consists of cholera-like diarrhea, vomiting, abdominal pain, and dehydration. During the second phase, or hepatotoxic phase (24–48 hours), clinical signs and biochemical evidence of hepatic damage leading to a progressive and irreversible coagulopathy appear. With the development of hepatorenal syndrome (third phase), hemorrhages, convulsions, and fulminant hepatic failure (FHF) occur resulting in coma and death (4–7 days). Symptoms and clinical course of amatoxin-containing mushroom poisoning have been thoroughly reported.[13-23] Damage to the liver is characterized by massive centrilobular necrosis, vacuolar degeneration, and a positive acid–phosphatase reaction. The kidney shows signs of acute tubular necrosis and hyaline casts in the tubules.[24]

Amatoxin poisoning is caused by mushroom species belonging to three genera, *Amanita*, *Galerina*, and *Lepiota*[12,25,26] with the majority of lethal mushroom exposures attributable to *Amanita* species. Some Amanitas contain two major groups of toxins, amatoxins, and phallotoxins. Both are bicyclic peptides composed of an amino acid ring bridged by a sulfur atom. The chemical structures of nine amatoxins have been elucidated as bicyclic octapeptide derivatives; the major ones are the α-, β-, and γ-amanitins (α-Ama, β-Ama, γ-Ama). The three amanitins are also present in some *Galerina* and *Lepiota* species responsible for deceased persons. Phallotoxins, detected only in *Amanita* species, have only slight absorption after oral administration and should not contribute to amatoxin poisoning.[27-31]

The molecular mechanism of toxicity has been studied in detail. Amatoxins bind with eukaryotic DNA-dependent RNA polymerase II, and inhibit the elongation essential to transcription. Pharmacokinetic studies have shown that amatoxins use the physiological transport system for biliary acids to reach the liver, the site of irreversible binding to RNA polymerase II. Enterohepatic circulation perpetuates high toxin concentration in the hepatocytes.[32,33]

Our survey based on the literature over the last two decades lists 2108 detailed cases of amatoxin poisoning from North America and Europe. Treatment strategies were characterized as preliminary medical care, supportive measures, and specific therapies. Specific therapies included toxin removal from the digestive, biliary, and urinary systems, and blood as well as the administration of drugs. Experimental investigations and hypotheses concerning the hepatoprotective properties of each therapeutic modality justifying its use in human amatoxin intoxication were also described. The use of liver transplantation (LT) in amatoxin-induced FHF was also characterized as a specific therapy among this retrospective patient group.

The aim of this review is a critical analysis of the different treatments that were applied to amatoxin poisoned patients by determining for each therapeutic

mode its use and its efficacy. Two complementary statistical analyses were carried to compare the number of survivors and dead for each group of patients, which received a particular mode of therapy, liver transplant cases being either included as fatalities or excluded from each analyzed series. These data enabled a classification of therapeutic modalities based on relatively effective, ineffective, or unproven asset.

AMATOXIN-CONTAINING MUSHROOM SPECIES

According to the currently available literature,[12,25,26,34] 35 species belonging to the genera *Amanita*, *Galerina*, and *Lepiota* contain amatoxins. There is agreement on amatoxin-containing *Amanita* and *Galerina* species but the occurrence of amatoxins in some species of *Lepiota* genus is uncertain.

In the genus *Amanita*, the nine amatoxin-containing mushrooms are (1) *Amanita phalloides* (Fr.) Secr.[26] and the related species, the so-called "deadly white *Amanita* species," (2) *A. bisporigera* Atk., (3) *A. decipiens* (Trimbach) Jacquetant, (4) *A. hygroscopica* Coker, (5) *A. ocreata* Peck, (6) *A. suballiacea* Murr., (7) *A. tenuifolia* Murr., (8) *A. verna* (Bull.:Fr.) Lamarck, and (9) *A. virosa* (Lamarck) Bertillon.[12,25,26,34] *A. magnivelaris* Peck was suspected of containing amatoxins since intoxications with a 24-hour latency, liver failure, and hepatic necrosis were reported for patients from Guatemala and Rhode Island.[35,36] However, amatoxins have never been detected in the mushroom tissue.[25,37]

In the genus *Galerina*, nine amatoxin-containing species are reported: (1) *G. autumnalis* (Pk.) Sm. and Sing., (2) *G. badipes* (Fr.) Kühn., (3) *G. beinrothii* Brsky, (4) *G. fasciculata* Hongo, (5) *G. helvoliceps* (Berk. and Curt.) Sing., (6) *G. marginata* (Batsch) Kühner, (7) *G. sulciceps* (Berk.) Boedjin,[38] (8) *G. unicolor* (Fr.) Sing., and (9) *G. venenata* A. H. Smith.[12,26,34,39–41]

In the mycological literature on Lepiotas,[12,25,26,42–45] 24 species are presumed to be amatoxin-producing mushrooms and listed alphabetically as follows. The asterisk indicates those 16 *Lepiota* species in which amatoxins were detected by thin layer chromatography.[46–49]

L. brunneoincarnata Chodat and Martin*
L. brunneolilacea Bon and Boiffard*
L. castanea Quélet*
L. citrophylla (Berk. and Br.) Sacc.
L. clypeolaria (Bull.:Fr.) Kummer[42]
L. clypeolarioides Rea*
L. felina (Pers.:Fr.) Karsten*
L. fulvella Rea*[43] (by semiquantitative Meixner test[50,51])
L. fuscovinacea Moeller and Lange
L. griseovirens Maire*
L. heimii Locq.*
L. helveola Bres.*
L. helveoloides Bon ex Bon and Andary
L. josserandii Bon and Boiffard*
L. kuehneri Huijsm. ex Hora*
L. langei Locq.*
L. lilacea Bres.[44]
L. locanensis Espinosa
L. ochraceofulva Orton*
L. pseudohelveola Kühner ex Hora*
L. pseudolilacea Huijsm.[45]
L. rufescens Lge.[44]
L. subincarnata Lge.*[47–49]
L. xanthophylla Orton*[46]

Although α-Ama was detected in North American *Pholiotina (Conocybe) filaris* Fr.,[52] investigations of German collections of this species and other Pholiotinas reported the amatoxins neither in the mushrooms nor in cases of hepatotoxic poisoning.[12] The available information thus identifies 35 species containing amatoxins (10 Amanitas, 9 Galerinas, and 16 Lepiotas.[46–49,51]

OCCURRENCE OF AMATOXIN POISONING

Amatoxin-containing species and, consequently, amatoxin poisonings occur worldwide: Africa,[53–56] America,[25,26,35,57,58] Asia,[46,59–66] Europe,[12,67,68] and Oceania.[63,69–71] Given the few reports of the amatoxin syndrome from the African, Asian, and Oceanian continents,[55,60,61,69,70,72] our review focused on human cases (Tables 1–6) from North American and European countries.[73–204] The sites include the Canadian province Ontario,[97] Mexico,[35,78,84,85] and 21 different U.S. states namely Alabama,[89] Arkansas,[93] California,[42,74,79,90,93,102,109,119,120,151,193,205–207] Florida,[112] Georgia,[91,118] Indiana,[132] Kansas,[208] Kentucky,[209] Michigan,[108,199,209] Minnesota,[122] Mississippi,[118] Missouri,[118,141] New Jersey,[73,139,205,209] New York,[93,140,200,206,208] Ohio,[36,207] Oregon,[206,209] Pennsylvania,[124] Rhode Island,[36,104,206] Virginia,[208] Washington,[207] and Wisconsin[178] as well as 22 European countries namely Austria,[127,128] Belgium,[168,190] Bulgaria,[179,210,211] Croatia,[117] Czech

Table 1

Amatoxin Poisoning Cases Treated with Supportive Measures Alone with/without Liver Transplant

Date/Country	T/E Cases	Mushroom	LT	Survivors	References
1981 New York	1/3	a.sp	0	1	[73]
1981 California	1/10	A.ph	0	0	[74]
1981 California	4/10	a.sp	0	3	[74]
1982 France	1/1; child	G.mar	0	0	[75]
1982 Italy	2/2	L.bi	0	1	[76]
1983–1986 Spain	7/85	a.sp	0	7	[43,50]
1986 Spain	1/3	L.bi	0	1	[77]
1987 Guatemala	19/19; (children)	A.mag	0	11	[35]
1987 Mexico	8/8; 2 children	A.vi	0	6	[78]
1988 California	4/4	A.ph	0	0	[79]
1988 France	1/1; child	A.ph	1	1	[80]
1988 Turkey	11/11; 8 children	L.hel	0	0	[81]
1988 Turkey	3/27	L.cas, L.hel	0	2	[82]
1990 Italy	1/2	L.bi	0	1	[83]
1990 Mexico	7/7	A.vi	0	2	[84,85]
1992 France	1/3	L.bi	0	1	[86]
1992 France	2/3; 1 child	L.bi	2	2	[86]
1992 Germany	2/3	A.ph	0	1	[87]
1992 Germany	1/3; child	A.ph, amat	1	1	[87]
1994 Germany	9/12	A.ph	0	9	[88]
1996 Alabama	1/4; child	A.ve	0	0	[89]
1997 California	1/4	a.sp	0	1	[90]
1997 Georgia	1/1	A.ph	1	1	[91]
1998 Italy	1/1	A.ph	1	1	[92]
1999 Arkansas	1/1	A.bis	0	1	[93]

T/E Cases = treated/exposed individuals; LT = liver transplant; amat = amatoxins in biological fluids; a.sp = amatoxin-containing species; A.bis = *Amanita bisporigera*; A.mag = *A. magnivelaris*; A.ph = *A. phalloides*; A.ve = *A. verna*; A.vi = *A. virosa*; G.mar = *Galerina marginata*; L.bi = *Lepiota brunneoincarnata*; L.cas = *L. castanea*; L.hel = *L. helveola*; undefined cases are reported in brackets.

Republic,[105,157] Denmark,[154,165,202] Finland,[95,106,152] France,[75,80,86,103,121,136–138,146,148,169,191,192,194–198,212] Germany,[87,88,130,133,155,156,163,164,166,167,201] Hungary,[203,204,213] Italy,[76,83,92,94,96,100,111,116,125,126,131,143–145,147,161,176,177,181,185,186] the Netherlands,[159] Norway,[153] Poland,[99,170–173,175,214] Portugal,[162] Slovak Republic,[113,114,129,160,180,215] Slovenia,[110,174] Spain,[43,50,77,98,115,182–184,187–189] Sweden,[101,149] Switzerland,[158,216,217] Turkey,[81,82,107,134,135,142] and United Kingdom.[123]

The amatoxin poisoning cases found in the literature were divided into three groups. The first group comprised 2108 amatoxin poisoning cases that were adequately documented by hospital reports with detailed therapeutic information including 32 LTs (Tables 1–6). A second group from North American[11,36,89,93,97,108,118,199,205–209,218,219] and European sources[24,103,111,136,142,160,181,212–217,220] consisted of 169 amatoxin poisonings that were cited in clinical reports but had no treatment information. A third group contained cases of mushroom exposures reported only as "cyclopeptide intoxication with hepatotoxic effects" and with incomplete clinical data.[3–9,11,210,211,221] The majority of the cases in the second and third groups were either mildly intoxicated or asymptomatic individuals who shared the poisoned meal and did not necessarily require hospital admission. Only the cases in the first group were included in the data analysis.

Of the 35 amatoxin-containing species, 14 were responsible for most of the intoxications listed in Tables 1–6: *A. bisporigera*, *A. magnivelaris*, *A. ocreata*, *A. phalloides*, *A. verna*, *A. virosa*, *G. autumnalis*,[208] *G. marginata*, *L. brunneoincarnata*, *L. brunneolilacea*, *L. castanea*, *L. fulvella*, *L. helveola*, and *L. josserandii*. The small number of species identified may be an artifact of incomplete information; in less than 5% of the

Table 2

Amatoxin Poisoning Cases Treated with Detoxication Procedures with/without Liver Transplant

Date/Country	T/E Cases	Mushroom	Treatments: Detoxication: Oral C/GA	Urin. FD	ECP HD–HP/PL	LT	Surv.	References
1975–1990 Italy	93/93; children	a.sp	0/0	93	0–0/0	0	86	[94]
1978 Finland	2/2	G.mar	0/0	2	0–0/0	0	2	[95]
1981 California	3/10	a.sp	3/0	0	0–0/0	0	3	[74]
1981 Italy	1/1; pregnant	A.ph, amat	0/0	1	0–0/1	0	1	[96]
1982 Canada	1/2	A.bis, A.vi	0/0	0	1–1/1	0	1	[97]
1982 Canada	1/2	A.vi	0/0	0	1–0/0	0	0	[97]
1982 Spain	2/8	A.ph	0/0	0	0–0/2	0	2	[98]
1982–1983 California	11/21	a.sp	11/0	0	0–0/0	0	11	[42]
1982–1983 California	4/21	A.o, amat	4/0	0	0–0/0	0	4	[42]
1982–1983 California	1/21; child	A.ph, amat	1/0	0	0–0/0	0	1	[42]
1982–1986 Poland	7/7	A.ph	0/0	0	0–0/7	0	4	[99]
1982–1991 Italy	2/8; 1 child	A.ph	0/0	0	0–0/2	0	1	[100]
1983–1986 Sweden	93/93	A.ph, A.vi, a.sp, amat	0/0	93	93–93/0	0	93	[101]
1988 Turkey	3/27; 1 child	L.cas, L.hel	3/0	0	0–0/0	0	3	[82]
1988 Turkey	6/27; children	L.cas, L.hel	0/0	0	6–0/0	0	0	[82]
1989 California	2/2	A.ph	2/2	0	2–0/0	2	2	[102]
1990 France	1/1	A.ph	0/0	0	1–0/0	1	1	[103]
1990 Rhode Island	1/1	A.vi	1/0	0	0–0/0	0	0	[104]
1990–1991 Czech	35/35	A.ph	0/0	0	0–35/0	0	28	[105]
1990–1991 Czech	38/38	a.sp	0/0	0	0–38/0	0	38	[105]
1991–1999 Italy	6/8	A.ph	0/0	0	0–0/6	1	6	[100]
1994 Finland	1/1	A.vi	0/0	0	1–0/0	1	1	[106]
1994–1995 Turkey	52/60	A.ph	0/0	0	0–52/0	0	52	[107]
1994–1995 Turkey	8/60	A.ph	0/0	0	8–0/0	0	4	[107]
1995 Michigan	1/1	A.vi	1/0	0	0–0/0	0	1	[108]
1996 Alabama	3/4	A.ve	3/0	0	0–0/0	0	3	[89]
1996–1997 California	2/10	A.ph, a.sp	1/0	0	2–0/0	0	0	[109]
1997 California	1/4	a.sp	0/0	0	1–0/0	0	0	[90]
1997 Slovenia	1/1; child	a.sp	0/0	1	0–0/1	0	0	[110]
1998 Italy	2/2	a.sp	0/0	0	2*–2/0	0	2	[111]
2000 Florida	1/1	a.sp	1/0	0	0–0/0	1	1	[112]

T/E Cases = treated/exposed individuals; Oral = oral detoxication using C = activated charcoal and GA = gastroduodenal aspiration; Urin. = urinary detoxication by FD = forced diuresis; ECP = extra-corporeal detoxication including * = continuous venovenous hemofiltration, HD = hemodialysis, HP = hemoperfusion, and PL = plasmapheresis; LT = liver transplant; Surv. = survivors; amat = amatoxins in biological fluids; a.sp = amatoxin-containing species; A.bis = *Amanita bisporigera*; A.o = *A. ocreata*; A.ph = *A. phalloides*; A.ve = *A. verna*; A.vi = *A. virosa*; G.mar = *Galerina marginata*; L.cas = *Lepiota castanea*; L.hel = *L. helveola*.

Table 3

Amatoxin Poisoning Cases Treated with Mono-chemotherapy, with/without Detoxication Procedures and with/without Liver Transplant

			Treatments						
				Detoxication					
Date/Country	T/E Cases	Mushroom	Drugs	Oral C/GA	Urin. FD	ECP HD–HP/PL	LT	Surv.	References
1988 Turkey	1/27; child	L.cas, L.hel	1ATB	0/0	0	1–0/0	0	0	[82]
1971–1995 Slovak Republic	103/103; 14 children	A.ph, a.sp	B.pen	0/0	(FD)	(HD–HP)/0	0	95	[113,114]
1981 Spain	2/2	A.ph	B.pen	0/2	0	2–0/0	0	2	[115]
1982 Spain	6/8	A.ph	B.pen	0/0	0	0–0/6	0	5	[98]
1982–1986 Spain	13/85; 1 child	5 A.ph, 2 A.ve, 3 L.bi, 3 a.sp; amat	B.pen	2/2	9	0–1/2	0	12	[43,50]
1986 Spain	2/3	L.bi	B.pen	0/0	0	0–0/0	0	2	[77]
1986–1989 Italy	12/12	A.ph	B.pen	12/0	0	12–0/0	0	9	[116]
1988 Croatia	18/18; (children)	A.ph	B.pen	18/18	18	2–0/16	0	14	[117]
1991 Ohio	1/1	G.sp	B.pen	1/0	0	0–0/0	0	1	[36]
1994 Missouri	2/2	A.bis	B.pen	0/0	0	0–0/0	0	1	[118]
1996 California	3/3	A.ph	B.pen	0/0	0	0–0/0	1[a]	3	[119,120]
1998 France	1/1	A.ph	B.pen	1/0	0	0–0/0	0	1	[121]
1998 Minnesota	1/1; child	A.vi	B.pen	1/0	0	0–0/0	0	1	[122]
1982 U.K.	2/2	A.ph	Cimetid	0/0	0	0–2/0	0	0	[123]
1999 Pennsylvania	1/6	a.sp	Cimetid	1/0	0	0–0/0	0	1	[124]
1987–1993 Italy	86/86	A.ph	NAC	86/0	86	0–0/0	0	80	[125]
1994 Italy	1/1; pregnant	A.ph, amat	NAC	1/0	1	0–0/1	0	1	[126]
1996–1997 California	1/10	A.ph	NAC	1/0	0	0–0/0	0	1	[109]
1997 California	1/4	a.sp	NAC	1/0	0	0–0/0	0	1	[90]
1980–1986 Europe	25/252	A.ph, a.sp	Silybin	0/0	(FD)	(HD–HP)/0	0	24	[127,128]
1991–1999 Slovak Republic	20/20; (children)	A.ph, a.sp	Silybin	20/0	20	0–0/0	0	20	[129]
1993 Germany	26/154	a.sp	Silybin	0/0	0	0–0/0	0	26	[130]
1994 Germany	3/12	A.ph	Silybin	0/0	0	0–0/0	3	2	[88]
1981 California	1/10	A.ph	Steroid	0/0	0	0–0/0	0	1	[74]
1982–1983 California	2/21	a.sp, amat	Steroid	2/0	0	0–2/0	0	0	[42]
1982–1983 California	3/21	a.sp	Steroid	3/0	0	0–0/0	0	3	[42]
1988 Turkey	1/27	L.cas, L.hel	Steroid	0/0	0	0–0/0	0	1	[82]
1997 Italy	1/1	A.ph	Steroid	0/0	0	0–0/1	0	1	[131]
1981 New York	2/3	a.sp	Thioc.a	0/0	0	1–0/0	0	2	[73]
1981 California	1/10	a.sp	Thioc.a	0/0	0	0–0/0	0	0	[74]
1982 Indiana	1/1	A.vi	Thioc.a	0/0	0	0–0/0	0	1	[132]
1982–1986 Spain	4/85; 1 child	A.ph, amat	Thioc.a	2/3	3	0–2/0	0	4	[43,50]

T/E Cases = treated/exposed individuals; Oral = oral detoxication using C = activated charcoal and GA = gastroduodenal aspiration; Urin. = urinary detoxication by FD = forced diuresis; ECP = extra-corporeal detoxication including HD = hemodialysis, HP = hemoperfusion, and PL = plasmapheresis; LT = liver transplant; Surv. = survivors; amat = amatoxins in biological fluids; undefined cases are reported in brackets.

Drugs: ATB = antibiotic agent; B.pen = benzylpenicillin; Cimetid = cimetidine; NAC = *N*-acetylcysteine; Thioc.a = thioctic acid.

a.sp = amatoxin-containing species; A.bis = *Amanita bisporigera*; A.ph = *A. phalloides*; A. ve = *A. verna*; A.vi = *A. virosa*; G.sp = *Galerina* species; L.bi = *Lepiota brunneoincarnata*; L.cas = *L. castanea*; L.hel = *L. helveola*.

[a] Auxiliary liver transplant.

poisoning cases is the mushroom species actually identified.[222] When the species attribution is uncertain the onset of clinical symptoms may be a useful indicator of potential amatoxin ingestion.

Amatoxin exposures were more frequently caused by *A. phalloides* in Central and Southern Europe, *A. virosa* in Northern Europe, and *A. phalloides* and related deadly white Amanitas in North America. Unidentified amatoxin-containing species caused 21% of poisonings and are listed as a.sp. in Tables 1–6.

STATISTICAL ANALYSIS

An overall table (189 rows, 12 columns) was constituted from Tables 1–6 with the actual or coded values of the following parameters: date; country; modes of care, number of exposed individuals and treated patients; number and percentage of survivors and nonsurvivors; mushroom or mixture of mushrooms; single drug or drug combination; and LTs. A general frequency table was constructed of the observed frequencies for each mode of care. Eleven modes of care had a sufficient representation for analysis: one treatment mode (supportive measures alone, Table 1) and 10 specific treatments: detoxication procedures (Table 2) and nine chemotherapies from Tables 3–6 (mono-chemotherapies: benzylpenicillin, *N*-acetylcysteine (NAC), silybin; bi-chemotherapies: benzylpenicillin/antioxidant drug, β-lactam antibiotic (benzylpenicillin or ceftazidime)/silybin, benzylpenicillin/steroid, benzylpenicillin/thioctic acid; and tri- and poly-chemotherapies: benzylpenicillin combinations with any before mentioned drug, with or without silybin).

Due to small numbers of treated victims, 13 other specific chemotherapies were not analyzed: mono-chemotherapy with cimetidine, vitamin C, thioctic acid, steroid or antibiotic agent (20 cases from Table 3); and bi-, tri-, and poly-chemotherapies with silybin/thioctic acid, antibiotic/antiseptic/vitamin C, steroid/thioctic acid/vitamin C, antibiotic/thioctic acid/vitamin C, two antibiotics/steroid, two antibiotics/NAC, antiseptic/silybin/steroid/vitamin C and three antibiotics/steroid (26 cases from Tables 5 and 6).

Outcome without surgery for the 32 cases who received liver transplant (LT > 0) combined with one or more from the 11 analyzed therapeutic modes cannot be known. Therefore, in order to assess the effectiveness of the nontransplant therapies in preventing the fatal stage of the disease, statistical analyses were performed both with and without the transplanted cases. The suffixes LTi and LTe were added to all numbers, percentages, and probabilities listed or calculated including or excluding the LT cases, respectively. For each observation (line of the general table) with LT > 0, the number of treated patients, survivors, and deceased persons were corrected as follows: (i) for mortality rate excluding the transplant cases (MRLTe), the LT cases were removed from the data set, i.e., both treated patient and survivor numbers were decreased by the number of transplants, (ii) for mortality rate including the transplant cases (MRLTi), each LT patient was considered as a deceased person; only survivor numbers were decreased by the number of transplants.

Complementary statistical analyses were carried out for 2062 LTi patients (2108 victims minus 46 nonanalyzed-treatment cases) and 2031 LTe cases (2062 victims minus 31 LT cases); one LT case was in an unanalyzed mode of care.

The global performance evaluation of each therapeutic mode was achieved by a statistical comparison of the number of survivors and nonsurvivors using a Chi-square calculation from the two rows (survivors, fatalities) and six columns (six tables) contingency table. The effect of each mode of care was studied by comparison of survivor and dead numbers in the 2×2 tables constituted from the general table.

The Chi-square test applied to the general frequency tables rejected the hypothesis that outcome and treatment were independent; the distribution of survivors and deceased persons was statistically different for Tables 1–6, both including and excluding the LT patients. When the p-value was ≤ 0.05, the null hypothesis was rejected at the 95% confidence level. The Yates' correction was applied when the number of survivors or deceased patients was ≤ 5, and the Fischer's exact test was calculated in the case of contingency table 2×2 with less than 100 observations. The statistical analysis was carried out using STATGRAPHICS® PLUS software version 3.3 (Manugistics, Inc., Rockville, MD, USA).

DESCRIPTION OF TREATMENTS

The management of amatoxin poisoning involves four main categories of therapy: preliminary medical care, supportive measures, specific treatments, and LT. Since there is a relative consensus of opinion about the preliminary medical care and supportive measures,[14,18–20,23,223–228] only their major features are described. The specific treatments consisting of detoxication procedures, chemotherapies, and LT are described below in detail.

Table 4

Amatoxin Poisoning Cases Treated as Bi- and Tri-chemotherapy with Benzylpenicillin, with/without Detoxication Procedures and with/without Liver Transplant

Date/Country	T/E Cases	Mushroom	Treatments						References
			Drugs	Detoxication			LT	Surv.	
				Oral C/GA	Urin. FD	ECP HD–HP/PL			
1977–1994 Germany	9/12	A.ph, a.sp	ATB, silybin	0/9	9	9–9/0	0	8	[133]
1977–1994 Germany	3/12	A.ph	ATB, silybin	0/3	3	3–3/0	3	3	[133]
1988 Turkey	2/27; 1 child	L.cas, L.hel	ATB, steroid	2/0	0	1–0/0	0	0	[82]
1988 Turkey	1/3; child	A.ph	ATB, steroid	1/0	0	1–0/0	0	1	[134]
1995 Turkey	3/3; 1 child	A.ph, amat	ATB, steroid	3/0	3	2–3/0	0	3	[135]
1988 France	1/1	A.ph	ATS, steroid	1/0	0	0–0/0	1	1	[136]
1980 France	1/1	A.ph	ATS, Vit.C	0/0	0	0–0/0	0	1	[137]
1984 France	1/29	A.ph	ATS, Vit.C	1/0	0	0–0/0	0	1	[138]
1992 New Jersey	3/3	A.ph	Cimetid	3/0	0	1–2/0	0	3	[139]
1992–1993 New York	2/2	a.sp, amat	Cimetid	2/0	0	0–0/0	0	1	[140]
1999 Pennsylvania	5/6	A.ph, a.sp	Cimetid	5/0	0	0–0/0	0	5	[124]
1996–1997 California	1/10	a.sp	Cimetid, NAC	1/0	0	0–0/0	0	1	[109]
2000 Missouri	2/2	A.ph, amat	Cimetid, NAC	2/0	0	2–2/0	0	2	[141]
2000 Turkey	1/1; child	a.sp	Cimetid, Vit.C	1/0	0	0–0/1	0	1	[142]
1986–1992 Italy	73/73; (child.)	A.ph, amat	NAC[a]	73/0	73	0–0/0	0	67	[143–145]
1996 France	1/1	L.bi, amat	NAC	0/0	0	0–0/0	0	1	[146]
1996–1997 California	6/10	1A.ph, 5 a.sp	NAC	6/0	0	0–0/0	0	6	[109]
1996–1998 Italy	11/11	A.ph, amat	NAC	11/0	0	11–0/0	1	11	[116]
1997 California	1/4	A.ph	NAC	1/0	0	0–0/0	0	0	[90]
1990 Italy	1/1; child	a.sp, amat	NAC, steroid	0/0	1	0–0/0	0	1	[147]
1994 France	5/29	A.ph	NAC, Vit.C	5/0	0	0–0/0	0	5	[138]
1979–1988 France	29/29; (child.)	A.ph, amat	Silybin	0/0	0	(HD)–0/0	0	26	[148]
1980–1986 Europe	159/252	A.ph, a.sp	Silybin	0/0	(FD)	(HD–HP)/0	0	156	[127,128]
1985–1994 Sweden	22/41	A.ph, A.vi, a.sp, amat	Silybin	22/0	0	22–22/0	0	22	[149]
1988 California/Oregon	5/5	A.ph	Silybin	0/0	5	0–0/0	4	5	[150,151]
1988 Finland	4/4	A.vi	Silybin	0/0	1	0–3/0	0	4	[152]
1988 Norway	2/2	A.vi, amat	Silybin	2/0	2	0–0/0	0	2	[153]
1988–1994 Denmark	8/8	A.ph, A.vi	Silybin	5/8	0	0–3/1	1	6	[154]
1989 Italy	1/2	a.sp, amat	Silybin	1/0	1	0–0/0	0	1	[83]
1992 Germany	1/1	A.ph	Silybin	1/1	0	0–0/1	0	1	[155]

1992 Germany	4/4; 1 child	A.ph, amat	Silybin	4/0	0	0–4/0	1	4	[156]
1993 Czech	1/1; child	A.ph	Silybin	0/0	0	0–0/0	0	1	[157]
1993 Germany	128/154	a.sp	Silybin	0/0	0	0–0/0	0	113	[130]
1993 Switzerland	5/5	A.ph, amat	Silybin	5/0	0	0–0/0	0	5	[158]
1994 The Netherlands	2/2	A.ph	Silybin	2/0	0	0–0/0	0	2	[159]
1994 Slovak Republic	1/1; pregnant	A.ph	Silybin	0/0	0	1–1/0	0	1	[160]
1996 Italy	3/4	A.ph	Silybin	3/0	0	0–0/0	0	3	[161]
2001 Portugal	4/4; 1 child	A.ph, a.sp	Silybin	3/2	0	0–0/2	2	4	[162]
1981–1983 Germany	6/13	A.ph, amat	Silybin, steroid	0/0	0	0–6/0	0	6	[163]
1983 Germany	3/3	A.ph	Silybin, steroid	0/0	0	0–0/0	0	3	[164]
1986 Denmark	11/11	A.ph, amat	Silybin, steroid	0/11	11	0–0/0	0	10	[165]
1994 Germany	2/2	A.ph	Silybin, steroid	2/0	2	0–0/0	0	2	[166]
1980–1986 Europe	62/252	A.ph, a.sp	Silybin, Thioc.a	0/0	(FD)	(HD–HP)/0	0	62	[127,128]
1982–1986 Spain	2/85	a.sp, amat	Silybin, Thioc.a	2/2	2	0–2/0	0	2	[43,50]
1986 Germany	1/1	A.ph, amat	Silybin, Thioc.a	1/0	1	0–1/0	0	1	[167]
1991 Belgium	1/1	A.ph, amat	Silybin, Vit.C	0/0	0	1–0/0	0	1	[168]
1992 France	1/4; 1 child	L.hel	Silybin, Vit.C	1/0	0	0–0/0	0	1	[169]
1993 France	1/29	a.sp	Silybin, Vit.C	1/0	0	0–0/0	0	1	[138]
1983–1987 Poland	5/90	A.ph, a.sp, amat	Steroid	5/0	5	(HD)–0/0	0	4	[170–172]
1984–1985 Poland	8/30	A.ph, a.sp	Steroid	0/8	0	0–8/0	0	7	[173]
1984–1985 Poland	22/30	A.ph, a.sp	Steroid	0/22	0	0–0/0	0	16	[173]
1988 Slovenia	10/10; 1 child	A.ph, amat	Steroid	10/0	0	0–0/10	0	9	[174]
1988 Turkey	2/3; child.	A.ph	Steroid	1/0	0	1–0/0	0	2	[134]
1988 Turkey	1/27	L.cas, L.hel	Steroid	1/0	0	0–0/0	0	1	[82]
1988–1989 Poland	47/90	A.ph, a.sp	Steroid	47/47	47	0–0/27	0	42	[170,175]
1979–1981 Italy	64/64	a.sp	Steroid, Thioc.a	64/0	0	0–0/0	0	58	[176]
1981 Italy	44/44; 4 child.	A.ph, amat	Steroid, Thioc.a	44/0	0	0–0/0	0	40	[177]
1981–1983 Germany	1/13	A.ph, amat	Steroid, Thioc.a	0/0	0	0–0/0	0	1	[163]
1990 Wisconsin	2/2	A.vi	Steroid, Thioc.a	1/1	2	0–2/0	0	2	[178]
1984 France	2/29	A.ph	Steroid, Vit.C	0/0	0	0–0/0	0	2	[138]

(*continued*)

Table 4. Continued

Date/Country	T/E Cases	Mushroom	Treatments: Drugs	Detoxication: Oral C/GA	Detoxication: Urin. FD	Detoxication: ECP HD–HP/PL	LT	Surv.	References
1991–1998 Bulgaria	25/25	A.ph, a.sp	Steroid, Vit.E	25/0	25	(HD–HP)/(PL)	0	15	[179]
1977–1992 Slovak Republic	58/58	A.ph	Thioc.a	0/0	44	17–58/12	0	38	[180]
1979–1985 Sweden	19/41	A.ph, A.vi, a.sp	Thioc.a	19/0	0	19–19/0	0	19	[149]
1982–1984 Italy	2/6; child.	A.ph, a.sp, amat	Thioc.a	2/0	0	2–0/2	0	0	[181]
1982–1986 Spain	59/85; (child.)	27 A.ph, 24 a.sp, 7 L.bi, 1 L.f	Thioc.a	18/15	28	0–4/2PL 3 EXE	0	56	[43,50,182–184]
1985 Italy	53/53; 6 child.	A.ph, amat	Thioc.a	53/53	(FD)	(HD)–0/(PL)	0	47	[185]
1986–1988 Spain	2/4	A.ph, amat	Thioc.a	2/0	2	0–0/0	0	0	[182,183]
1987 Italy	2/2	A.ph, amat	Thioc.a	0/0	0	0–0/2	0	2	[186]
1988 Spain	1/1	A.ph	Thioc.a	0/0	0	0–1/0	0	1	[187]
1989 Spain	10/10	3 L.bi, 7 L.hel, amat	Thioc.a	10/0	0	0–10/0	0	8	[188]
1990 Spain	1/1	A.ph	Thioc.a	0/0	0	1–0/0	0	1	[189]
1982 Belgium	4/4; 1 child	A.ph, amat	Thioc.a, Vit.C	0/0	[b]	0–0/0	0	3	[190]
1990–1994 France	11/29	5 A.ph, 6 a.sp	Vit.C	4/0	0	1–0/0	0	10	[138]
1992 France	3/4	L.hel	Vit.C	1/0	0	0–0/0	0	3	[169]

T/E Cases = treated/exposed individuals; Oral = oral detoxication using C = activated charcoal and GA = gastroduodenal aspiration; Urin. = urinary detoxication by FD = forced diuresis; ECP = extra-corporeal detoxication including HD = hemodialysis, HP = hemoperfusion, and PL = plasmapheresis (or EXE = exsanguino transfusion); LT = liver transplant; Surv. = survivors; amat = amatoxins in biological fluids; undefined cases are reported in brackets; ATB = antibiotic agent; ATS = antiseptic agent (nifuroxazide); Cimetid = cimetidine; NAC = *N*-acetylcysteine; Thioc.a = thioctic acid; Vit.C = vitamin C; Vit.E = vitamin E; a.sp = amatoxin-containing species; A.ph = *Amanita phalloides*; A.vi = *A. virosa*; L.bi = *Lepiota brunneoincarnata*; L.cas = *L. castanea*; L.f. = *L. fulvella*; L. hel = *L. helveola*.

[a] Neomycin instead of benzylpenicillin.

[b] Spironolactone.

Table 5

Amatoxin Poisoning Cases Treated as Bi- and Tri-chemotherapy without Benzylpenicillin, with/without Detoxication Procedures and with/without Liver Transplant

			Treatments						
				Detoxication					
Date/Country	T/E Cases	Mushroom	Drugs	Oral C/GA	Urin. FD	ECP HD–HP/PL	LT	Surv.	References
1996 France	1/1; pregnant	A.ph	2 ATB, NAC	1/0	0	0–0/0	0	1	[191,192]
1983 California	1/1; child	A.o	2 ATB, steroid	1/0	0	0–0/1	1	1	[193]
1981 France	3/3	A.ph	ATB, ATS, Vit.C[a]	0/0	0	0–0/0	0	3	[194]
1986 France	5/5; (child.)	L.blil	ATB, ATS, Vit.C[a]	0/0	0	0–0/0	0	4	[195]
1988 Turkey	3/27	L.cas, L.hel	ATB, Thioc.a, Vit.C	3/0	0	3–0/0	0	1	[82]
1989 France	6/6	A.ph, amat	Ceftazid, silybin	6/0	0	0–0/0	0	6	[196]
1990 France	5/5	A.ph, amat	Ceftazid, silybin	5/0	0	0–0/0	0	5	[197]
1994 France	1/1	L.blil	Ceftazid, silybin	0/0	0	0–0/0	1	1	[198]
1980–1986 Europe	6/252	A.ph, a.sp	Silybin, Thioc.a	0/0	(FD)	(HD–HP)/0	0	5	[127,128]
1982–1984 Italy	4/6; child.	A.ph, a.sp, amat	Steroid, Thioc.a, Vit.C	4/4	0	0–0/4	0	4	[181]

T/E Cases = treated/exposed individuals; Oral = oral detoxication using C = activated charcoal and GA = gastroduodenal aspiration; Urin. = urinary detoxication by FD = forced diuresis; ECP = extra-corporeal detoxication including HD = hemodialysis, HP = hemoperfusion, and PL = plasmapheresis; LT = liver transplant; Surv. = survivors; amat = amatoxins in biological fluids; undefined cases are reported in brackets; ATB = antibiotic agent; ATS = antiseptic agent (nifuroxazide); Ceftazid = ceftazidime; NAC = *N*-acetylcysteine; Thioc.a = thioctic acid; Vit.C = vitamin C; a.sp = amatoxin-containing species; A.o = *Amanita ocreata*; A.ph = *A. phalloides*; L.blil = *Lepiota brunneolilacea*; L.cas = *L. castanea*; L.hel = *L. helveola*.

[a] Bastien protocol.

Table 6

Amatoxin Poisoning Cases Treated as Poly-chemotherapy with/without Benzylpenicillin, with/without Detoxication Procedures and with/without Liver Transplant

			Treatments						
				Detoxication					
Date/Country	T/E Cases	Mushroom	Drugs	Oral C/GA	Urin. FD	ECP HD–HP/PL	LT	Surv.	References
1992 Michigan	1/1	a.sp	3 ATB, B.pen	0/0	0	0–0/0	1	1	[199]
1996 Italy	1/4	A.ph	2 ATB, B.pen, Silyb	1/0	0	0–0/0	0	1	[161]
1983 New York	1/1	L.jos, amat	3 ATB, Ster	0/0	0	0–1/0	0	0	[200]
1984–1993 Germany	21/21; (child.)	A.ph, amat	ATB, B.pen, Silyb, Ster, TA	10/0	0	0–0/21	0	20	[201]
1988 Turkey	2/27	L.cas, L.hel	ATB, B.pen, Ster, TA	2/0	0	0–0/0	0	2	[82]
1988 Turkey	1/27	L.cas, L.hel	ATB, B.pen, Ster, TA, Vit.C	1/0	0	0–0/0	0	1	[82]
1988 Turkey	4/27	L.cas, L.hel	ATB, B.pen, Ster, Vit.C	4/0	0	0–0/0	0	2	[82]
1984 France	4/29	A.ph	ATS, B.pen, Silyb, Vit.C	0/0	0	0–0/0	0	4	[138]
1988 France	2/29	A.ph	ATS, B.pen, Ster, Vit.C	0/0	0	0–0/0	0	2	[138]
1990 France	2/29	A.ph	ATS, Silyb, Ster, Vit.C	0/0	0	0–0/0	0	1	[138]
1988 Denmark	4/4	1 A.ph, 1 A.vi, 2 a.sp	B.pen, Cimet, Silyb, Ster	4/0	4	0–4/0	0	3	[202]
1993 France	1/29	A.ph	B.pen, NAC, Silyb, Vit.C	0/0	0	0–0/0	0	0	[138]
1981–1983 Germany	6/13	A.ph, amat	B.pen, Silyb, Ster, TA	0/0	0	0–5/0	0	5	[163]
1991 Hungary	4/4; 1 pregnant	A.ph, A.ve	B.pen, Silyb, Ster, TA	4/0	4	0–0/0	0	3	[203]
1993 Hungary	8/8; (child.)	A.ph	B.pen, Silyb, Ster, TA	0/0	0	0–6/1	0	7	[204]
1983–1987 Poland	57/90	A.ph, a.sp, amat	B.pen, Ster, Insul, Gluc	57/0	57	(HD)–0/0	0	47	[170–172]
1988–1989 Poland	2/90	A.ph, a.sp,	B.pen, Ster, Insul, Gluc	2/2	2	0–0/1	0	2	[170,175]
1983–1987 Poland	28/90	A.ph, a.sp, amat	B.pen, Ster, Insul, hGH	28/28	28	0–0/11	0	25	[170–172]
1988–1989 Poland	41/90	A.ph, a.sp	B.pen, Ster, Insul, hGH	41/41	41	0–0/29	0	33	[170,175]

T/E Cases = treated/exposed individuals; Oral = oral detoxication using C = activated charcoal and GA = gastroduodenal aspiration; Urin. = urinary detoxication by FD = forced diuresis; ECP = extra-corporeal detoxication including HD = hemodialysis, HP = hemoperfusion, and PL = plasmapheresis; LT = liver transplant; Surv. = survivors; amat = amatoxins in biological fluids; ATB = antibiotic agent; ATS = antiseptic agent (nifuroxazide); B.pen = benzylpenicillin; Cimet = cimetidine; Insul, Gluc = insulin and glucagon; Insul, hGH = insulin and human growth hormone; NAC = *N*-acetylcysteine; Silyb = silybin; Ster = steroid; TA = thioctic acid; Vit.C = vitamin C; a.sp = amatoxin-containing species; A.ph = *Amanita phalloides*; A.ve = *A. verna*; A.vi = *A. virosa*; L.cas = *Lepiota castanea*; L. hel = *L. helveola*; L. jos = *L. josserandii*; undefined cases are reported in brackets.

Preliminary Medical Care

Preliminary medical care consists of gastrointestinal decontamination procedures if appropriate, to make an attempt at obtaining baseline values of key biological parameters for diagnostic monitoring. When a patient develops a gastroenteritis 6–24 hours after mushroom ingestion, all asymptomatic and symptomatic persons who consumed the same meal should be immediately evaluated and treated as appropriate to prevent toxin absorption. Because of the long asymptomatic latency, the clinical utility of most gastrointestinal decontamination procedures seems limited. Although effective in inducing emesis, there is no evidence from clinical studies that ipecac syrup improves the outcome of poisoned individuals; data to support or exclude its administration are insufficient.[229] Gastric lavage should be considered only when it could be performed within 60 minutes after ingestion of a life-threatening amount of toxin.[230] It is contraindicated if the patient has loss of airway protective reflexes or a decreased level of consciousness without endotracheal intubation.[230,231] There is no conclusive evidence for the use of whole bowel irrigation (WBI), which appears to decrease the binding capacity of the activated charcoal.[232] Some authors[13,14,22,23,233] advocate the administration of activated charcoal alone or with cathartics whereas others find no data supporting a cathartic in combination with activated charcoal.[234]

The regional poison center can provide appropriate decontamination information and also suggest and track mycological, clinical, and biological data for each amatoxin victim.[223,231] The identification by a mycologist of any remaining mushrooms can be a key to diagnosis. The time lag between mushroom ingestion and hospital admission is an essential information.

Biological parameters including blood sugar, serum transaminases (aspartate aminotransferase, ASAT; alanine aminotransferase, ALAT), lactate dehydrogenase (LDH), serum bilirubin, urea, and coagulation studies [prothrombin time (PT)] are proposed as indicators of hepatotoxicity.[18,19] Ryzko et al.[235] and Parra et al.[236] noted that hypocalcemia and alkaline phosphatase isoenzyme (ALP) are also indicators of amatoxin poisoning. Horn et al.[124] recommended concurrent measurement of serum markers of hepatocellular necrosis combined with markers of hepatocellular regeneration (γ-glutamyl transferase and α-fetoprotein).

Analysis of diarrhea fluids has been recommended since high levels of amatoxins are eliminated in feces. Amatoxins may also be assayed in urine and serum by radio-immunoassay,[237,238] high-performance liquid chromatography with UV detection method as reviewed by Dorizzi et al.,[239] electrochemical detection,[240] and capillary electrophoresis.[241] Thin layer chromatography using a color index of amatoxins by Schiff's test is reported by Russian authors.[242] Unfortunately, the amatoxin concentrations in biological samples do not correlate with the severity of poisoning and do not indicate intra-hepatic toxin accumulation. High individual differences in urinary amatoxin concentrations may only be of qualitative value.[243]

Supportive Measures

Supportive measures for the management of gastroenteritis and hepatotoxicity are so frequently used that an analysis of their utility was not attempted with this data. In the gastrointestinal phase, diarrhea and emesis can produce hypovolemic shock requiring intensive intravenous fluid resuscitation. Electrolyte abnormalities, metabolic acidosis, hypoglycemia, impaired coagulation due to decreased hepatic synthesis of Factors II, V, VII, and X are corrected. A normal or slightly high urine output is maintained during the first 48 hours to avoid acute renal failure. Parenteral nutrition with protein intake restriction is instituted.

Specific recommendations for supportive treatment of hepatoxicity include: (i) correction of coagulation disorders by parenteral vitamin K (10 mg daily for three consecutive days), fresh frozen plasma and antithrombin III, (ii) oral lactulose and neomycin to prevent encephalopathy,[244] and (iii) mannitol to lower intracranial pressure and avoid cerebral edema.[245] Ninety-one of the 2108 patients reported since 1980, including six LT victims, were given supportive measures alone (Table 1). A total of 2017 of 2108 victims were treated with supportive measures combined with specific treatments as detoxication procedures alone (Table 2) and various protocols of chemotherapy with or without detoxication procedures (Tables 3–6).

Detoxication Procedures

Detoxication involves two different approaches: the reduction of absorption and enhancement of excretion.[246]

Oral Detoxication

Theoretically activated charcoal should bind amatoxins excreted via the bile into the duodenum and upper jejunum, although there is no evidence that its use

improves clinical outcome if it is used more than 1 hour after ingestion.[247] Toxicokinetic studies in the dog suggested amatoxin absorption or reabsorption from the intestine.[248] Given the enterohepatic circulation of amatoxins, administration of activated charcoal as multiple doses could reduce amatoxin absorption if in contact with toxin present in the gastrointestinal tract. Serial charcoal dosing either as a continuous nasogastric drip or pulse dosing with 20–40 g every 3–4 hours (for 24 hours or more) has been advocated by most authors as a relatively noninvasive enterohepatic and enteric dialysis technique.[42,74,233,249–251] However, clinical data are insufficient to support or exclude this oral detoxication method.[247]

Gastroduodenal aspiration (GA) from the upper portion of the small intestine through a nasogastric tube has been recommended as a sole technique or combined with activated charcoal to remove bile fluids and interrupt enterohepatic circulation[252] but the actual benefit of these procedures is not documented. Amatoxins are present in the gastroduodenal fluids until 60 hour after mushroom ingestion.[253] Long term intubation may lead to side effects of bleeding and pancreatitis and is not always recommended.[14]

Urinary Detoxication

Toxicokinetic reports of human mushroom poisoning have shown that diuresis substantially enhances the amatoxin elimination rate. Large amounts of amatoxins (60–80%) are filtered through the glomeruli.[254] Urinary elimination of amatoxins has been detected within the first 8 hours and for 3–4 days after mushroom ingestion.[167] Amatoxin concentrations in the urine are from 100 to 150 times higher than those of serum and can be quantified even when no serum circulating amatoxins are detectable.[50,51,255–257] Maintenance of early and adequate urine output is theoretically important even though there is no re-absorption in the proximal tubules or tubular secretion; "forced diuresis (FD)" with fluids plus a loop diuretic cannot increase amatoxin elimination.[14,248] According to Jaeger et al.,[257] there is no proof that FD decreases the amount of amatoxins bound to the hepatocytes or is more efficient than the maintenance of an adequate diuresis (from 100 to 200 mL/h). Furthermore, FD is difficult to maintain in a patient with a severe dehydration.

Extra-corporeal Purification Procedures

Amatoxins are detected in the serum from 24 to 48 hours after mushroom ingestion but at very low concentrations when compared to the urine.[253,256–258] Extra-corporeal elimination includes hemodialysis (HD), hemoperfusion (HP), plasmapheresis (PL), and related methods. HP and HD are theoretically helpful since the amatoxins are easily dialyzable due to their free circulation in the serum and their small molecular weight (about 900 Da); amatoxins also possess a high affinity for charcoal and polymers used for HP cartridges and dialyzer membranes.[249] HD initiated as sole treatment has been reported to be ineffective in the management of amatoxin syndrome[82,97] but should be instituted if renal failure occurs.[231] Given the low serum amatoxin concentration, the utility of toxin removal by extra-corporeal purification procedures is questionable. Extra-corporeal purification procedures such as HD, HP, and PL, and related methods such as continuous venovenous hemofiltration and exsanguino-transfusion, are often used in a combined mode; it is difficult to assess the efficacy of any single treatment.

HP has been applied to amatoxin-intoxicated patients since 1978 with a possibly favorable effect.[259–261] It has been carried out within the first 36 or 48 hours after ingestion[246,260,262] but is proposed as most effective if applied prior to 24 hours.[231] The survival rate of poisoned patients is claimed to depend on the time of beginning HP.[14,140,180] Polish and Turkish retrospective studies have reported increased survival for amatoxin-poisoned patients treated with HP.[107,173]

Thrombocytopenia, a major side effect of HP that increases the risk of bleeding,[123,149] diminishes when a platelet protective agent such as prostacyclin is administered.[123] Other complications of HP such as hypotension due to volume loss, hypoglycemia, and hypocalcemia must be monitored and corrected.[262]

Controversy centers on whether the blood level of amatoxins is high enough to justify this procedure.[249,258] HP performed within 12–14 hours after ingestion of amatoxin-containing mushrooms eliminated less than 4% of the ingested toxin dose.[225] Although the benefit of HP to remove amatoxins in the early stages of intoxication was debatable,[263] it may help support the patient during hepatic failure.[155] HP eliminates neurotropic and neurotoxic amino acids and mercaptans; it has been reported to ameliorate the hepatic encephalopathy in 75% of amatoxin poisoned patients.[264,265]

The HP sorbent most frequently used is activated charcoal. In the United States, the only available HP sorbent is activated charcoal-coated polymer membranes.[262] The efficacy of ion-exchange resin (Amberlite XAD-4) has been experimentally demonstrated.[266]

Czechoslovakian investigations of the in vitro absorption of α- and β-Ama standards, using charcoal as well as XAD-2 and XAD-4 resin types, found Amberlite XAD-2 synthetic resin the most effective and activated charcoal the least.[267,268] Positive results from in vitro experiments with Amberlite XAD-2 resin are said to justify further trials of this material in the detoxication procedures of clinical amatoxin poisonings.[269]

HP is often combined with HD; some reports claim it is helpful.[14,159,249] American reports on the clearance of amatoxins in a series of blood samples taken from poisoned patients before and after treatment as well as in the HD/HP circuits demonstrate no utility.[141] Italian authors have recently reported the combination of charcoal plasmaperfusion and continuous venovenous hemofiltration (Table 2) to eliminate both low and high molecular weight toxins. This new method of toxin removal might improve the liver function of amatoxin intoxicated patients.[111]

The first uses of PL in mushroom poisoning in general[270] and *Amanita* poisoning in particular,[271] were reported in the late 1970s. Several authors[98,272] and most recently Jander et al.[273] reviewed advantages and problems relevant to PL for amatoxin-intoxicated patients.

PL performed as a single detoxication procedure[98] or in combination with other extra-corporeal purification methods such as HD/charcoal HP[97] or Amberlite XAD-2 HP[215] has been reported to decrease mortality. PL plus chemotherapy are also said to improve survival as well as the general condition of poisoned patients by stabilizing biliary acid and bilirubin levels.[131,174] In a large study, mortality was 7.4% when PL plus chemotherapy was used for 68 of 180 patients and 19.6% when the PL was not used.[175] German authors also reported that early combined treatment with PL plus chemotherapy was beneficial.[273] According to 18-year Italian experience, plasma-exchange therapy associated with general intensive care may improve the health of amatoxin poisoned patients who retain sufficient capacity for liver regeneration.[100]

Patterns and Frequency of Detoxication Procedures

Of the 2017 amatoxin-poisoned individuals administered specific treatments, 385 (19.1%, Table 2) underwent only detoxication procedures (Detox-group) while 1632 (80.9%, Tables 3–6) received chemotherapy (Chem-group) either alone or combined with detoxication procedures.

Activated charcoal (C) was given to 7.5% (29/385) Detox-group patients and to 35.7% (583/1632) Chem-group patients. GA was performed in 3.6% (59/1632) Chem-group patients. Combined C + GA was reported for 2 of 385 Detox-group patients and 223 of 1632 (13.7%) Chem-group patients.

FD was undertaken in 49.4% (190/385) Detox-group patients and at least 33% of Chem-group patients.

HD was reported for 30.6% (118/385) Detox-group and at least 7.1% of the 1632 Chem-group patients. HP was reported for 57.4% (221/385) Detox-group and at least 11.4% of the Chem-group patients. PL was cited for 5.2% (20/385) Detox-group and at least 9.6% of the Chem-group patients.

The inadequate reporting of HD and extra-corporeal procedures in the sources comprised in Tables 3–6 among the patients who also received chemotherapy necessitated the pooling of patients receiving the same chemotherapy with and without detoxication procedures.

Chemotherapy with Specific Agents

No specific amatoxin antidote is available, but therapeutic agents such as β-lactam antibiotics, silymarin complex, thioctic acid, antioxidant drugs and other drugs are used in the clinical management of amatoxin poisoning. In vitro experiments and animal model investigations have been summarized along with the purported advantages and disadvantages of their clinical use. In this survey, the 1632 patients in the Chem-group received drugs as mono-chemotherapy (Table 3), bi-chemotherapy with or without benzylpenicillin (part of Table 4 and part of Table 5, respectively), tri-chemotherapy with or without benzylpenicillin (part of Table 4 and part of Table 5, respectively) or poly-chemotherapy (>3 drugs) with or without benzylpenicillin (Table 6). Patients in the Chem-group may have also received detoxication procedures.

β-Lactam Antibiotics

Benzylpenicillin (Penicillin G) and ceftazidime are β-lactam antibiotics thought to be hepatoprotective in amatoxin poisoning. Benzylpenicillin was first used to protect mice and rats against lethal doses of either *A. phalloides* extracts or α-Ama.[274,275] In dogs orally poisoned with a sub-lethal dose of *A. phalloides* preparation, intravenous benzylpenicillin injection

prevented both the rise of the liver enzymes and the fall of clotting factors in the blood.[276]

Benzylpenicillin perfusions of isolated rat liver showed a strong inhibition of α-Ama toxicity.[277] Although most β-lactam antibiotics utilize a common carrier system for uptake into isolated hepatocytes,[278] kinetic studies of α-Ama absorption in hepatocytes proved that benzylpenicillin does not inhibit the membrane transport systems used by the toxin. An intracellular mechanism rather than interference with amanitin uptake appears responsible for the purported hepatoprotective effect.[279]

Several theories have been advanced to explain the antitoxic action of benzylpenicillin. Floersheim's hypothesis[280] that the drug could displace α-Ama from its binding site on serum protein is challenged by evidence that the toxic cyclopeptide does not bind to serum albumin.[266,281] Another hypothesis suggested that benzylpenicillin reduced or eliminated the GABA-producing intestinal flora involved in hepatic encephalopathy.[250,280] Although GABA appeared to be involved in experimental hepatic encephalopathy, the inhibitory neurotransmitter does not seem to play a role in human encephalopathy.[282]

Other reports presented evidence of an anti-proliferative effect of β-lactam antibiotics on cultured eukaryotic cells including human sources and in vitro DNA replication systems. The intracellular target of β-lactams appears to be the replicative enzyme polymerase I.[283,284] Since the amatoxins, particularly α-Ama, are selective blockers of DNA-dependent RNA polymerase II, it is possible that the β-lactam antibiotics protect via their effects on eukaryotic DNA replication.[285] Although there is no formal proof, in vitro experiments on chicken embryo hepatocytes and in vivo studies on mouse liver have shown that β-lactam antibiotics inhibit the toxic effect induced by α-Ama.[286]

Unfortunately, benzylpenicillin commonly causes allergic drug reactions with an incidence of 1–10%.[126,287–289] The large amount of sodium ions administered with this antibiotic agent to amatoxin-poisoned patients may disrupt electrolyte balance.[290,291] Severe granulocytopenia has also been observed with high doses of benzylpenicillin.[292–294] Degradation products formed in vitro are often the causative agents of such adverse reactions rather than parent antibiotic. Use of freshly prepared single doses of benzylpenicillin prevents the majority of side effects.[295] However, given the bone narrow toxicity of β-lactams, these antibiotics[189,285] could affect all the hematopoietic cell lines. Lastly, massive benzylpenicillin therapy may evoke neurotoxic symptoms in patients with nervous system disease and renal insufficiency as well as induce convulsions when cerebral edema is imminent.[14,296]

Although the biological mechanism of β-lactam antibiotics in the treatment of amatoxin poisoning is still unclear and high-dose benzylpenicillin can induce adverse reactions, the literature seems to support clinical benefits. Moroni et al.[297] reported 100% recovery for 33 patients treated 1 or 2 days after ingestion of *Amanita* mushrooms with high doses of IV benzylpenicillin plus thioctic acid and steroids. Statistical analysis of a clinical study of 205 patients from Austria, France, Italy, Switzerland, and The Netherlands from 1971 to 1980 found benzylpenicillin at 300,000–1,000,000 U/kg/day IV to be significantly associated with survival.[250,298] The suggested doses for benzylpenicillin are 40,000,000 and 1,000,000 U/day in adults and children, respectively.[265] Benzylpenicillin is not approved by the US Food and Drug Administration (FDA) for treatment of *Amanita* poisonings.

In this 20-year survey, benzylpenicillin was the most frequently used drug in the management of amatoxin poisoning, either as mono-chemotherapy in 164 cases (10.1%, Table 3) or combined with other drugs as bi-chemotherapy (797 cases, 48.8%, Table 4), tri-chemotherapy (263 cases, 16.1%, Table 4), and poly-chemotherapy (187 cases, 11.5%, Table 6). In total, 86.5% of Chem-group patients (1411/1632) receiving chemotherapy were treated with benzylpenicillin.

Ceftazidime, a third generation cephalosporin, is several times more effective than benzylpenicillin by DNA replication systems testing in vitro.[284,286] According to the Neftel protocol,[196] ceftazidime is administered as 4.5 g IV every 2 hours. Despite the high drug concentrations in plasma, no renal and neurological side effects were reported.[197] Ceftazidime was the second most used β-lactam but was always combined with silybin (12 cases, Table 5).

Silymarin Complex

Silymarin is a hepatoprotectant complex of natural substances isolated from seeds of Mediterranean milk thistle, *Silybum marianum* (L.) Gaertn. (*Asteraceae*).[299] This flavonolignan group includes the three isomers silydianin, silychristin, and the major compound, silybin.[300,301] The beneficial effects of silymarin on death rate and survival time in intraperitoneal (IP) administered mice with α-Ama were reported by Hahn et al.[302] Silymarin efficacy depended on both the delay between intoxication and therapy, and the degree of liver

damage.[303] Silymarin markedly increased the survival of mice poisoned with IP *A. phalloides* extracts.[304] In dogs, which display poisoning resembling human intoxication, silymarin suppressed both the rise of liver enzymes and the fall of clotting factors, and silybin noticeably reduced the degree of bloody necrosis in animal livers after oral *A. phalloides* extract.[276,305]

Histochemical studies on isolated rat hepatocytes have elucidated the mechanism of silymarin hepatoprotection. The flavonolignan complex bound tightly to liver plasma membrane acts as a membrane stabilizer[306,307] whereas flavonoid substances such as taxifolin, morin, and quercetin have no effect.[308]

Silymarin hindered α-Ama penetration of the cell wall.[277,303,308] Silybin competed with α-Ama for the multi-specific bile salt transport systems of the hepatocyte membrane.[279] Histoenzyme analyses of liver from α-Ama poisoned mice revealed that factors disturbed by the toxin, including glucose-6-phosphatase, aminopeptidase, ATPase, glycogen, lipid, and nucleic acid, were restored by silybin.[309]

Silymarin and silybin are also radical scavengers acting as chain-breaking antioxidants.[310–315] Silymarin complex, by preserving alkaline phosphatase activity, prevented changes in membrane phospholipid composition and inhibited the lipid peroxidation in both rat liver microsomes and isolated hepatocytes.[310–312,316–318] The action site of silymarin is the hepatocyte outer membrane where the drug maintains lipid composition and aids functional integrity.[316]

Silybin in isolated rat Kupffer cells showed inhibition of the cyclooxygenase and 5-lipooxygenase pathway of arachidonic acid metabolism and the subsequent synthesis of the inflammation mediator leukotriene B_4.[319] Silymarin also produced a high anti-inflammatory effect in vivo by inhibition of leukocyte migration into the inflamed site.[320] Silymarin exerted an antifibrotic activity and retarded collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct obliteration in rats.[321–323]

Silybin favored the regenerative process of both liver and Kupffer cells of partially hepatectomized rats.[324] These results agree with the observation that silybin stimulates liver cell metabolism.[325] It increased the synthetic rate of ribosomal RNA not only in rat hepatocyte but also in the isolated hepatocyte nucleus, via activation of DNA-dependent RNA polymerase I. As a consequence of this stimulation, ribosome formation was accelerated and protein synthesis increased. Although protein and RNA syntheses are prerequisites for DNA synthesis, silybin had no effect on DNA formation in cell cultures and liver of normal rats whereas an effect could be observed in liver of partially hepatectomized rats,[326–329] suggesting that silybin stimulates protein biosynthesis and regenerates damaged liver tissue.

Levels of silymarin components are found to be low in plasma and urine after oral and IV silybin administered to rats and after oral silymarin to cholecystectomized patients.[330] The three isomers, silybin, silydianin, and silychristin (silymarin complex) were excreted mainly by the biliary route either free or as sulfate and glucuronide conjugates.[330,331] 75–90% of the administered dose of silybin is metabolized to glucuronide and sulfate conjugates, which are partly hydrolyzed and cycled enterohepatically.[315] Silybin elimination is estimated as 20–40% over a 24-hour period with a maximum between 2 and 9-hour post-administration.[332] Thus, silybin in the bile theoretically inhibits enteric absorption and interrupt enterohepatic circulation of the amatoxins.[249,333] Silybin administration within 60 hours after a toxic mushroom meal blocked the increased alanine amino transferase (ALAT) and restored other parameters of liver dysfunction.[315,334]

After oral silymarin, collected bile contained high amounts of isosilybin (a silybin isomer) and very low levels of silydianin and silychristin. The low concentrations in plasma and bile of both silydianin and silychristin indicate a minor contribution of these compounds to the hepatoprotective effect of silymarin complex.[335]

In order to increase silybin concentration in the bile, recent studies have combined silybin with phosphatidylcholine; this lipophilic complex is called silipide (IdB 1016). Silybin concentrations in patient bile after silipide administration were several-fold higher than after oral silymarin. This suggests that such complexation increased the oral bio-availability of silybin. It is likely that drug passage through membranes of the gastrointestinal tract was facilitated, favoring hepatic delivery.[335,336]

Advances in the knowledge of the hepatoprotective properties of silymarin complex have yielded convincing experimental evidence for the efficacy of silybin and justified its use in human amatoxin poisoning. However, according to Wellington and Jarvis,[315] the value of silymarin relates to the toxin dose and time lag before drug administration. In a clinical series of 205 cases, all patients who received silybin survived.[298] Reviewing the recovery of 18 cases of *Amanita* poisoning treated with silybin, Hruby et al.[290,291] concluded that the drug administered even up to 48 hour after toxic mushroom ingestion was effective in preventing severe liver

damage. In a retrospective study of 175 cases with a mortality rate of 8.6%,[315] 131 patients were treated with silybin/benzylpenicillin combination (14 deaths) and 44 patients received silybin alone (one death). However, the mean interval between mushroom ingestion and institution of silybin therapy as well as the severity of poisoning were not identical for the two therapeutic modes.

Table 3 lists 74 amatoxin-poisoning cases (4.5% of 1632) treated with silybin as mono-chemotherapy and Tables 4–6 list 550 cases (33.7% of 1632) treated with silybin in combination with other drugs. Some authors suggested the combination of silybin plus benzylpenicillin to be more beneficial than other combinations.[18,69,224,337] Faulstich and Zilker thought that both drugs act as competitive inhibitors of the amatoxin-transporting system and should not be used in combination[14] but did not consider the disparate effects of benzylpenicillin and silybin on α-Ama uptake reported by Kröncke et al.[279] In our survey, 379, 102, and 49 of 1632 amatoxin intoxicated patients received silybin/benzylpenicillin as bi-chemotherapy (23.2%, Table 4), tri-chemotherapy (6.3%, Table 4), and poly-chemotherapy (3%, Table 6), respectively.

The initial dose of silybin dihemisuccinate is 5 mg/kg by IV infusion over 1 hour followed by 20 mg/kg/day by continuous infusion for six days until transaminase levels have normalized.[315] In the United States, silymarin is available only as a food supplement; at this time there is no active Investigational New Drug (IND) application for any component of the silymarin complex in the U.S. FDA.[231,315,338]

No serious side effects have been observed with silybin[225] but nausea, epigastric discomfort, arthralgia, headaches, pruritus, and urticaria have been reported. Due to a lack of adequate clinical investigations, silybin is not administered to children under 12 years of age, unless the benefits outweigh the risks.[315] Oral silymarin, Legalon® and β-cyclodextrin silybin have been recommended as an alternative to parenteral silybin.[133,339]

Hepatoprotective activity of the *Extractum Silybi fluidum* (fluid extract) and "*Silybochol*" against rat liver damage caused by CCl_4 was recently shown. This preliminary finding suggests potential utility in clinical trials of the bio-active substances from *S. marianum* fruit powder, fluid extract, and fatty oil.[340]

Thioctic Acid

Mechanistic studies on thioctic acid (α-lipoic acid; 1,2-dithiolane-3-pentanoic acid) suggest a rationale for potential benefit in amatoxin hepatotoxicity. Acting as a free radical scavenger, it might prevent lipid peroxidation of the cell membrane by dissociating the hydrogen ion on the sulfhydryl groups of dihydrothioctic acid, its main metabolite.[354] Due to the antioxidant activity of both oxidized and reduced forms, affecting in vitro cellular metabolic processes, thioctic acid is capable of regenerating directly vitamin C and indirectly vitamin E, as well as influencing the increase of intracellular glutathione content.[355,356] Thioctic acid has a therapeutic potential in the treatment of hepatic diseases induced by chemical agents in animal models as reviewed by Bustamante et al.[356]

It was introduced for the treatment of amatoxin poisoning in the Czech Republic by Kubicka in 1969.[341] The successful use of α-lipoic acid was also reported from Italy[342,343] and then reviewed in the Eastern European literature.[344,345] In the United States, the first use of thioctic acid was described in 1972 in New Jersey for *A. verna* intoxication with apparently beneficial result.[346] The cause–effect relationship between thioctic acid administration and clinical improvement in amatoxin poisoning is not clearly established and opinion concerning efficacy is divergent.[347–351] Early enthusiasm in the United States waned as investigations of thioctic acid carried out in *Amanita* poisoned mice and dogs reported either a severe glucose imbalance[352] or ineffectiveness of the drug.[353] A controlled clinical trial was never conducted and there were too few patients enrolled in the IND study to support a claim of efficacy. This drug is unavailable for human use in the United States. Multiple authors discourage its clinical use.[74,352,357–359] According to Floersheim et al.[298] and Floersheim[360] the administration of thioctic acid is often associated with a fatal outcome and it should be removed from the therapeutic protocol.[231] Other authors support thioctic acid trials in amatoxin poisoning until its efficacy can be confirmed or refuted.[23,361,362]

Given the experimental findings of hypoglycemia as a major side effect of thioctic acid,[348,352] the drug should be administered with a sustained IV drip of glucose.[349,363] In clinical use, thioctic acid was combined with glucose in IV infusions at doses of (i) 300 mg/kg/day in four divided doses and then 600 mg/kg/day[73,361] and (ii) 50–150 mg/kg/day.[364] Allergic skin reactions have been reported.[355] Because it is sensitive to light and heat, bottles and infusion lines containing the solution must be wrapped in aluminum foil.[231,347,349]

In this 20-year case survey beginning in the 1980s, thioctic acid was used in 8 of 1632 amatoxin poisonings (0.5%, Table 3) as single chemotherapy and in 442 of

1632 (27.1%, Tables 4–6) in combined chemotherapy. Thioctic acid/benzylpenicillin was given as bi-chemotherapy (207 of 1632, 12.7%, Table 4), tri-chemotherapy (180 of 1632, 11%, Table 4), and poly-chemotherapy (42 of 1632, 2.6%, Table 6).

Antioxidant Drugs

In recent years, authors have postulated that the oxidant effects of amatoxins could be counteracted by the use of antioxidants such as ascorbic acid, cimetidine, and NAC.[116]

L-ascorbic acid (vitamin C) is widely distributed in the plant and animal kingdoms. Biochemistry, physiological properties, and clinical uses of this chemical agent have been extensively reviewed.[301,365] Vitamin C inhibits lipid peroxidation and is used as hepatocyte protector in damage due to acetaminophen and CCl_4.[366] It was introduced in the emergency treatment of *A. phalloides* intoxication 20 years ago as part of a multi-drug regimen (plus nifuroxazide and dihydrostreptomycin) devised by Bastien.[194,367,368] The regimen was reviewed by Chabré[369] and is still used in French poison centers.[231] Our survey found use of vitamin C, usually in combination with benzylpenicillin, in 60 cases (3.7%, Tables 4–6).

Cimetidine, a cytochrome P450 inhibitor, is an antioxidant agent with cytoprotective and antifibrinolytic effects.[301,370] Therapeutic use in the management of amatoxin poisoning is based on the clinical similarity of this intoxication to liver damage due to other toxins affecting cytochrome P450. Histological examination of livers from α-Ama poisoned mice revealed major mitochondrial changes while the hepatic mitochondria were preserved in α-Ama poisoned mice treated with cimetidine either prophylactically or within 6 hours.[371] A three-drug combination of cimetidine, benzylpenicillin, and ascorbic acid significantly improved enzymatic and histopathological changes and survival rate of α-Ama intoxicated mice.[372] Clinical cimetidine treatment was reported for only 21 amatoxin poisoned patients (1.3%, Tables 3, 4, and 6) at a dose of 300 mg IV administered every 8 hours and usually in association with benzylpenicillin.

NAC acts as a glutathione precursor when natural stores are depleted and is also a scavenger of free radicals formed in paracetamol poisoning.[373,374] The similarity between the clinical toxicities of α-Ama and paracetamol suggested NAC inclusion in the management of amatoxin poisoning.[125,143–145] Japanese authors investigating mushroom toxicity in isolated rat hepatocytes showed that *Amanita* extracts (in particular *A. virosa*) markedly decreased intracellular glutathione content.[375] However, the negative results observed with NAC treatment for amatoxin poisoned mice indicate that amatoxin metabolism is probably not identical to that of paracetamol and that glutathione may play little or no role in amatoxin hepatotoxicity.[376] Over the 20-year period, 89 of 1632 amatoxin cases (5.5%, Table 3) received chemotherapy with NAC alone and 103 of 1632 (6.3%, Tables 4–6) received NAC combined with other drugs, usually benzylpenicillin.

Miscellaneous Drugs and Prospective Treatments

Other drugs such as antibiotics, antiseptic agents, hormones and steroids used in the management of amatoxin intoxicated patients are listed in Tables 3–6. To our knowledge, no experimental evidence is reported of any hepatoprotective effect of antibiotics such as aminoglycoside derivatives (gentamycin, neomycin, streptomycin), cyclopeptide derivatives (vancomycin), and macrolide derivatives (clindamycin). These agents are not considered in our retrospective analysis. The antiseptic agent nifuroxazide plus dihydrostreptomycin and vitamin C is part of Bastien's regimen.[194,367,368] The role of hormones and steroids in the management of amatoxin syndrome is questionable. Other agents proposed for therapy include iridoid glycosides and immunotherapy and are discussed below.

Insulin and human growth hormone (hGH) were reported to be effective in rat liver regeneration after *Amanita* poisoning.[377] Intravenous infusion of either insulin/glucagon or insulin/hGH, in combination with glucose, was administered to amatoxin poisoned children by clinicians in Poland in an attempt to stimulate liver cell metabolism.[172,175] A randomized clinical series of FHF cases showed no effect of insulin/glucagon on liver regeneration.[378]

Experiments on α-Ama uptake into hepatocytes suggested that prednisolone might exert a protective effect by competition between the steroid and toxin for the transport systems and not by nonspecific effects upon the cell membrane.[279] Investigations of steroids in mice and dogs poisoned with either *A. phalloides* extract or α-Ama revealed a positive effect on recovery of mice but not on survival of dogs.[276,304] Since steroids have no efficacy in acute hepatic failure, the American and European Associations for the Study of the Liver excluded these drugs for this indication 25 years ago.[264] A 1979 double-blind randomized trial with acute hepatic

failure cases treated by hydrocortisone confirmed that steroids improved neither hepatic function nor survival rate.[379]

Although steroids were included as therapeutic agents for *Amanita* poisoning by Floersheim et al. in 1982,[298] he suggested removal of steroids from treatment protocols in 1985 because of lack of correlation with the outcome.[360] Despite this, in the cases published since 1980 steroids were reported in the treatment as mono-chemotherapy (8 of 1632, 0.5%, Table 3) and as bi-, tri-, and poly-chemotherapies with benzylpenicillin (443 of 1632, 27.1%, Tables 4 and 6), and without benzylpenicillin (0.5%, 8 of 1632, Tables 5 and 6).

Iridoid glycosides such as aucubin and kutkin represent a group of monoterpene glycosides with a cyclopentane-(c)-pyran ring structure widely distributed in the plant kingdom.[380] Aucubin is a common iridoid glycoside isolated from *Eucommia ulmoides* Oliver (*Magnoliaceae*),[381] *Plantago asiatica* L. (*Plantaginaceae*),[382] and *Aucuba japonica* Thunb. (*Cornaceae*).[383] Iridoid compounds have recently been successful in experimental amatoxin poisoning, and on the basis of the promising results, these drugs may merit clinical evaluation. Protective activities of aucubin against α-Ama have been reported in beagle dogs orally poisoned by *A. virosa* extract, and in mice I.P. administered with the toxin, even when the treatment was begun 12 hours later.[380,382] According to these authors, the mechanism of hepatoprotection might be attenuation of the continuous depression of liver m-RNA biosynthesis caused by α-Ama.[382,384] This mechanism was not confirmed in rat studies, however, aucubin enhanced excretion of α-Ama suggesting that it or one of its hydrolyzed products may displace the toxin from binding sites.[385] Oral administration is ineffective;[380,384] and the influence of the route of administration on efficacy may merit elucidation.[386] As far as we know, no investigation of aucubin in humans has been conducted.

Picrosides I–III and kutkoside, known collectively as kutkin, were isolated from the roots and rhizome of *Picrorhiza kurroa* Rogle ex Benth. (*Scrophulariaceae*), an Indian plant used for the treatment of liver diseases.[387] Protective activity of kutkin was demonstrated against the hepatic damage of *A. phalloides* in rodent models.[388,389] Floersheim found the protective effect of kutkin comparable to that of silybin.[390] Constituents from *P. kurroa* have demonstrated antioxidant and anti-lipid peroxidation activity as well as effects on liver regeneration in research cited by Luper.[313] Further investigations should be carried out to assess the place of kutkin in clinical amatoxin poisoning treatment.

In vitro production and cytoprotective properties of polyclonal amanitin-specific antibodies were reported in 1993.[391] However, Faulstich et al.[392] reported in 1998 that amatoxin-specific Fab fragments or monoclonal antibodies enhanced the activity of amatoxins and that this new therapeutic strategy should not be considered.

Retrospective Data on Use of Chemotherapy

Our review of chemotherapy administered to 1632 amatoxin poisoned patients underscores its typical use in combination, and makes it difficult to assess the efficacy of each therapeutic agent individually. The mechanism by which β-lactam antibiotics (benzylpenicillin, ceftazidime) afford their therapeutic effect is still scientifically uncharacterized. Considerable data support the relevance of silymarin complex in amatoxin poisoning; the mechanisms of action include an antioxidant effect, anti-lipid oxidation, enhancement of detoxication, and stimulation of the hepatic regeneration. Biochemical data suggesting hepatoprotection by antioxidants support the continued consideration of free radical scavengers such as ascorbic acid, cimetidine, and NAC in the management of amatoxin intoxication. Hepatoprotective effects of iridoid glycosides (aucubin, kutkin) have also been demonstrated with in vivo animal models; these promising findings merit further investigations.

In our compilation, 80.9% (1632 of 2017) amatoxin poisoned patients received chemotherapy (Chem-group) with or without detoxication procedures (Tables 3–6). Drugs were given as mono-chemotherapy in 347 cases (21.3%, Table 3) and in combination in 1285 cases (78.7%, Tables 4–6) either as bi-chemotherapy (815 of 1632, 49.9%) or tri-chemotherapy (280 of 1632, 17.2%) or poly-chemotherapy (190 of 1632, 11.6%). The therapeutic agents can be classified into four groups according to the frequency of their administration as single agent or chemotherapy combinations. Frequency of use ranged from 0.7 to 86.5%. The lowest frequency-of-use group among the 1632 amatoxin poisoning cases is constituted by ceftazidime (0.7%), cimetidine (1.1%), and antiseptic agent (1.2%). The second group is represented by vitamin C (3.7%), antibiotics (3.8%), and NAC (11.8%). The third group consists of thioctic acid (27.1%), steroids (27.6%), and silybin (33.7%). The highest frequency-of-use group is comprised of cases treated with benzylpenicillin (1411 of 1632 patients, 86.5%). Benzylpenicillin was the most frequently administered drug used alone (164 cases, 10.1%,

Table 3) when compared to antibiotic (one case), cimetidine (three cases), NAC (89 cases), silybin (74 cases), and steroids or thioctic acid (eight cases for each). It is also the agent most frequently represented in therapy combinations (1247 cases of 1632, 76.4%, Tables 4 and 6). The most common combinations were benzylpenicillin plus silybin (379 of 1632, 23.2%) and benzylpenicillin plus thioctic acid (207 of 1632, 12.0%), in contrast to the low representation of benzylpenicillin plus steroid (95 of 1632, 5.8%).

Retrospective Data on Use of Specific Treatments

Specific treatments consist of detoxication procedures and chemotherapy. In our review, 2017 of 2108 amatoxin-poisoned patients (95.7%) were treated with either one or both of these specific therapeutic modes. Detoxication procedures alone were applied to 385 of 2017 cases (19.1%, Table 2) whereas chemotherapy with or without detoxication procedures was administered to the majority of cases (1632 of 2017, 80.9%, Tables 3–6). Overall survivors (1810 of 2017 patients, 89.7%) as listed in Tables 2–6 are subsequently analyzed for the relation to specific therapy and to LT.

Liver Transplantation

Liver transplantation has emerged as the most important advance in the therapy of FHF and is an intervention formally validated for this disease with survival rates from 60 to 80%.[282,393] Kinetic studies have shown no risk of toxicity for the transplanted liver[257] beginning day 4 after mushroom ingestion.

Total Orthotopic Liver Transplantation and Auxiliary Partial Liver Transplantation

Two surgical options, orthotopic liver transplantation (OLT) and auxiliary LT have been developed. Total OLT is a well-established procedure for FHF but requires long immunosuppression to maintain the graft. Because some patients with partial hepatectomy and temporary support may have complete morphological and functional recovery of their own liver, auxiliary partial liver transplantation (APOLT) represents an alternative. In APOLT only a portion of the native liver is removed and the remainder is left in situ; the transplant provides temporary assistance until the native liver recovers and the immunosuppression can be withdrawn.[394–397]

Within the 20-year period of this review, 31 amatoxin poisoned patients underwent OLT: Six received supportive measures alone (Table 1), six were treated with detoxication procedures without chemotherapy (Table 2), and 19 received chemotherapy with or without detoxication procedures (Tables 3–6). The success of APOLT in one young girl was also reported,[119,120] (Table 3). These 32 LT patients represent only 1.5% of 2108 intoxicated cases reviewed in our survey. Twelve additional LT cases performed since 1985 were cited but due to lack of adequate data were not analyzed.[87,92,93,100,111,116,206,207,216,218,398,399]

The early use of specific treatments (detoxication procedures and chemotherapy) and of biological parameters predicting recovery may avoid unnecessary LT.[146,159,187–189] Many patients who originally were candidates for LT showed improvement in hepatic function and were taken off the transplant waiting list.[83,156,158,159]

The major dilemma in emergency liver failure is the right moment to transplant. The time between "too early" and "too late" may be very short. LT is considered too late when complications such as multi-organ failure with cerebral edema or renal insufficiency become contraindications to transplant because they compromise the success of surgery. The mean delay (about 2 days) between the decision for LT and finding of a liver donor must be taken into account. The shortage of available livers limits transplantation. Recently, a living, related donor of a 1-year-old boy poisoned with amatoxin provided a partial liver transplant specimen.[57] Fulminant hepatitis is rapidly fatal; only 50–85% of patients identified as candidates for LT survive long enough to receive a transplant.[400,401] An explosive course was also reported for amatoxin poisoned patients included in the emergency list for LT who died before obtaining a donor.[89,118,138,188,203]

It is essential to establish early, reliable criteria identifying the immediate prognosis.[402,403] The number of amatoxin poisoning victims considered for LT is small and the prognostic indicators for LT are not clearly defined.[120] Candidacy guidelines for OLT and APOLT have therefore been extrapolated from experience with FHF from other etiologies and include repeated clinical examination and biological investigations.[404]

Prognostic Factors

Most liver units have accepted for emergency liver transplant the King's College criteria proposed by O'Grady et al.[405] from a retrospective analysis of 278 patients with FHF not induced by acetaminophen overdose. These criteria are based on PT, age, etiology,

time between appearance of jaundice and onset of encephalopathy, and bilirubin concentration. The criteria have been recently evaluated by the University of Pittsburgh for 177 patients over a 13-year period and were found to be relatively effective in predicting death and the need for transplantation.[406] French emergency liver units rely on the combination of encephalopathy stages (III and IV) with factor V concentration and age.[407–409] Other prognostic models reviewed by Mas and Rodés[244] based on hemodynamic disturbances and clinical course of FHF have also been developed. Furthermore, other variables such as a factor VIII/V ratio[410] as well as serial α-fetoprotein levels[245] might be useful tests for predicting survival in FHF. Lastly, a Gc level $<34\ \mu g/mL$ 48 hours after admission strongly suggests a stage of liver failure beyond which recovery will not occur.[411]

Despite the lack of absolute predictors, prognostic factors such as stage of encephalopathy, coagulation tests, metabolic abnormalities, and age are useful in the rational planning of LT. Of 31 transplanted patients having undertaken OLT (including 4 children below 10 years of age), the prognostic factors used for 27 cases are listed in Table 7.

Encephalopathy Stages

The association between encephalopathy stages (I–IV)[412] and vital prognosis is controversial. According to Bernuau et al.[413] and Frohburg et al.,[399] encephalopathy does not always reflect liver function deterioration. Since advanced encephalopathy typically occurs late in the course of the FHF, the stage of encephalopathy may be of limited use.[403] Other authors promote encephalopathy stage as the most powerful clinical indicator of the severity of liver disease.[244,409,414,415] According to Gill and Sterling,[245] patients with a stage II encephalopathy have a mortality of 30% while those who progress to stage IV have a mortality rate greater than 80%. In the early use of OLT for amatoxin poisoning, encephalopathy stages (III and IV) were the major decision factors for this surgery.[80,103,106,136,154,193,199]

However, Klein's experience[102] indicated a clinical course of amatoxin poisoning characterized by slow deterioration over a week that then worsens quickly. This pattern may lead to an early underestimation of liver damage. Consequently, several authors think that LT should be considered with the onset of mild encephalopathy (stages I and II) before the onset of progressive and profound neurological signs resulting from severe amatoxin intoxication[86,156,198,199] (Table 7).

Coagulation Factors

No definitive conclusion can be drawn about the usefulness of the degree of coagulopathy as an indication for LT because too few patients are included in clinical data, and prophylactic administration of fresh frozen plasma modifies or prevents interpretation of coagulation factors.[401] The PT is considered the most satisfactory test of hepatocellular necrosis and prognosis.[405,414,415] Some authors suggest that factor V level is more sensitive and reliable than PT and a better indicator of recovery than other biological factors.[158,407,416,417] According to Izumi et al.,[418] the predictive accuracy of plasma factor V is less than that of international normalized result (INR) as advocated by Harrison et al.[419] A factor VIII/V ratio of more than 30% can be associated with a poor prognosis.[410] The dynamics of a biological marker could be of greater predictive value than the minimum or maximum level of the variable itself. The progressive prolongation of PT was noted as an outcome predictor of the patients with FHF and its evolution over 4 days after the poisonous mushroom meal was suggested as a reliable indicator of recovery or death.[14]

Metabolic Abnormalities

Metabolic abnormalities such as lactic acidosis, hypoglycemia, hyperbilirubinemia, and increased aminotransferases seen in FHF may also provide foundation for LT decisions.[244] Lactic acidosis and hypoglycemia are cited as prognostic factors associated with encephalopathy stage II and prolonged PT that determine urgent LT.[99,151,156,199] Several studies have shown that a high level of bilirubin ($>300\ \mu mol/L$) is a sign of fatal prognosis.[399,405,420] On the basis of their own experience, Faulstich and Zilker[14] suggested that LT be performed when an amatoxin poisoned patient exhibits a PT below 20% associated with both high bilirubin and creatinine (>5 and >2 mg/dL, respectively), on day 3. Patients with progressive failure have continued rise in the bilirubin and prolongation of PT despite declining aminotransferases.[245] Recent results support the hypothesis that a sustained elevation in markers of regeneration (α-fetoprotein, γ-glutamyl transferase) for more than 10–12 hours combined with a similarly maintained decline in markers of necrosis (ASAT, ALAT, alkaline phosphatase, LDH) levels could aid in prediction of recovery.[124]

Table 7

Prognosis Factors for Liver Transplant

Date/References	No. of cases	Encephalopathy Stage	Coagulation Factors		Lactic Acidosis	Hypoglycemia (mg/dL)	Hyperbilirubinemia[a] (μmol/L)
			P.T.	Factor V(%)			
1985 [193]	1/1; child	III coma	34.2 sec	NI	NI	161	39.3
1988 [136]	1/1	Coma	<20%	<20	NI	NI	180
1989 [80]	1/1; child	III–IV	<10%	<20	NI	NI	NI
1989 [102]	1/2	III	50 sec	NI	NI	NI	427.3
	1/2	III	30 sec	NI	NI	NI	341.9
1990 [151]	2/4	I	81 sec	NI	+	+	208.9
	2/4	II	81 sec	NI	+	+	NI
1991 [103]	1/1	IV coma	<10%	<10	+	+	NI
1992 [199]	1/1	III–IV	>100 sec	NI	NI	+	556.5
1994 [156]	1/1	I–II	<9%	6	NI	NI	136.8
1994 [106]	1/1	IV	28%[b]	32	NI	NI	364
1994 [198]	1/1	I	<10%	<8	NI	NI	NI
1995 [86]	2/2; 1 child	II–III	<10%	<10	NI	NI	NI
1995 [154]	1/1	III–IV	<10%[b]	NI	NI	NI	144
1996 [133]	2/2	II	<10%	<10		No prognosis values	
1997 [88]	3/3	III–IV	<20%	NI	NI	NI	78.6
1997 [91]	1/1	II–III	47.3 sec	NI	NI	NI	124.8
2000 [112]	1/1	III–IV	106 sec	NI	NI	19	158.9
2001 [162]	2/2; 1 child	NI	49 sec	7	NI	NI	49.7
			29.1 sec	15	NI	NI	NI

P.T. = prothrombin test (sec) or (%); NI = not indicated; + = presence.

[a] Normal bilirubinemia level ranges from 2 to 17 μmol/L.

[b] Thrombotest (factors II, VII, and X).

Age of Patient

The age of the amatoxin mushroom victim is another prognostic factor. Fatal outcomes are usually associated with age less than 10 years.[112,244] In the series of 205 and 83 patients reported by Floersheim et al.,[298] and Lambert and Larcan,[19] the death rates were 51 and 22% for children below 10 years and 16.5 and 8.8% for adults, respectively. The high mortality rate in children is likely related to the larger dose of the toxins per unit of body weight.

Retrospective Liver Transplantation Data

In the absence of definitive medical treatment for amatoxin poisoning, LT has changed the outlook for severe poisoning and can be the single best option for selected patients. Since 1985, 32 LTs (31 OLT and 1 APOLT) have been performed for amatoxin mushroom victims representing 1.5% of 2108 intoxicated individuals. Liver transplant increases the survival rate of amatoxin poisoning considering the LT patient was presumed as a fatal case. Easily applicable criteria are needed to identify patients for whom transplantation is indicated. Prognostic indicators such as encephalopathy stages, coagulation factors, metabolic abnormalities, and age have to be taken into account in the decision to perform liver transplant (OLT and APOLT) but do not replace intensive medical experience. Serious amatoxin intoxication must no longer be considered only as an acute disease with massive necrosis whose prognosis depends only on the early course of the poisoning. The progression of severely poisoned cases towards either massive necrosis or chronic active hepatitis from 20 to 70%[176,177] should be considered factors determining LT.

Statistical Analysis of Retrospective Data

Two general frequency tables were established including and excluding the LT cases, and composed for a systematic analysis. Statistical comparison of the 2×2 tables determined significant differences in the mortality rates of the 11 modes of care; the applied treatments were sorted by increasing efficacy, i.e., decreasing mortality rates (MR) combining MRLTi and MRLTe. Table 8 shows the 11 modes of care in order of increasing efficacy/decreasing mortality rates from #1 to #11 and the number of cases in each group including and excluding the liver transplanted patients with the related mortality rates. Then to further evaluate significant comparison between the 11 analyzed therapeutic modalities (#1 to #11), five pooled therapies from #12 to #16 have made up.

The mortality rates of the 10 analyzed specific therapeutic modes varied from 5.4 to 16.9% (MRLTi) and from 1.4 to 16.9% (MRLTe) for the 2062 LTi and 2031 LTe amatoxin victims, respectively. Mortality rates were 47.3% (No. = 91 LTi) and 43.5% (No. = 85 LTe) for amatoxin poisoned patients receiving supportive measures alone (Fig. 1).

First, the mortality rates of supportive measures alone (#11) were significantly higher than those found for the group of combined 10 specific therapies (#14, detoxication procedures plus nine chemotherapies) as reported in Tables 8 and 9. Then, the MR of detoxication procedures (#5) compared with #13, the nine combined chemotherapies, were not statistically different, but were significantly lower than those of two chemotherapies: BpThioca (#1) and BpwSilybTriPoly (#2). More importantly, the MRLTe of detoxication-procedures-alone (#5) was significantly higher than those of silybin plus benzylpenicillin (#8) and silybin (#10) as mono-chemotherapy (9.0 vs. 6.0 and 1.4%, respectively). Finally, the differences between the 9 individual applied chemotherapies were evaluated. The chemotherapies exhibiting the highest mortality rates were the combination of benzylpenicillin and thioctic acid (#1. BpThioca) followed by benzylpenicillin in drug combinations without silybin as tri- and poly-chemotherapies (#2. BpwSilybTriPoly), and by the combination of benzylpenicillin and steroids (#3. BpSter).

The chemotherapies with the lowest mortality rates were silybin as mono-chemotherapy (#10. Silyb) and silybin plus benzylpenicillin without and with other drugs (#8. BpSilyb, #9. BpSilybTriPoly) and NAC as mono-chemotherapy (#7. NAC). Both MRLTi and MRLTe of BpThioca (#1), BpwSilybTriPoly (#2), and BpSter (#3) were not statistically different between them (Table 9), and were significantly higher than those of BpSilyb (#8), BpSilybTriPoly (#9), and Silyb (#10).

Moreover no significant difference was observed between the MR of the four best therapies with the lowest mortality rates: NAC (#7), BpSilyb (#8), BpSilybTriPoly (#9), and Silyb (#10). The MR of #6, benzylpenicillin plus one or more antioxidant drug (cimetidine, NAC, or vitamin C), were significantly lower only than those of BpThioca (#1). The MR of NAC (#7) were significantly lower than those of both BpThioca (#1) and BpwSilybTriPoly (#2).

On the other hand, the statistical data were not significant for certain treatment groups whose mortality rates appear to be different in part due to the disparity of

the group size and the small number of analyzed cases: (i) the MRLTs of benzylpenicillin as mono-chemotherapy (#4) were not statistically different from those of NAC (#7) and (ii) the MRLT of mono-chemotherapies, benzylpenicillin (#4), and silybin (#10) was comparable, 11.6 vs. 5.4%, whereas the MRLTe of benzylpenicillin was significantly higher than that of silybin, 11.0 vs. 1.4% (Table 9). Furthermore, benzylpenicillin plus antioxidant (#6. BpantiOx, No. = 111 LTi treated, MRLTi 9.1%; No. = 110 LTe treated, MRLTe 8.2%) was not statistically different from benzylpenicillin plus other drugs without silybin as tri- and poly-chemotherapies (#2. BpwSilybTriPoly, No. = 299 LTi treated, MRLTi 15.4%; No. = 297 LTe treated, MRLTe 14.8%): the Chi-square values were 0.08 and 0.06, respectively; more data are needed to prove whether any statistical differences in the fatality rate between these groups were truly.

To further assess the role of silybin in affecting mortality, the three chemotherapies with the worst mortality rates (#16. BpThioca, BpwSilybTriPoly and BpSter) were pooled and compared with the pooled therapies including silybin (#12. BpSilyb and BpSilybTriPoly); the MR of #12 were significantly lower than those of #16 (MRLTi 7.9 vs. 15.8% and MRLTe 5.8 vs. 15.5%). This finding supports silybin benefit in amatoxin poisoning treatment.

Regarding benzylpenicillin, the most frequently therapeutic agent used among the reported cases, the bi-chemotherapies with this drug and without silybin were pooled (#15. BpThioca, BpSter, and BpantiOx), the MR found for this group were significantly higher than those of BpSilyb (#8) as reported in Table 9. In addition, the MR of BpwSilybTriPoly (#2) were significantly higher than those of BpSilybTriPoly (#9) (MRLTi 15.4 vs. 7.3%; MRLTe 14.8 vs. 5.4%). All these results suggest that benzylpenicillin administered with any drug except silybin as bi-, tri-, and poly-chemotherapies was not beneficial in treatment of amatoxin poisoning when mortality and/or liver transplant was used as the endpoint.

Our statistical analysis underscores that the hepatoprotective effect of the flavonolignan complex, silymarin, and the antioxidant property of NAC play a crucial role in the recovery of amatoxin-poisoned patients. The limitations of this data include its retrospective nature and the lack of standardized severity scoring by which to judge the patient mix in each treatment group. However, these analyses and literature review point out the most fruitful avenues for future

Table 8

Statistical Analysis of Amatoxin-Poisoning Therapies

#		No. LTi	No. LTe	MRLTi (%)	MRLTe (%)
	Applied therapies				
1	BpThioca	207	207	16.9	16.9
2	BpwSilybTriPoly	299	297	15.4	14.8
3	BpSter	95	95	14.7	14.7
4	Bp	164	163	11.6	11.0
5	Detox alone	385	379	10.4	9.0
6	BpantiOx	111	110	9.1	8.2
7	NAC	89	89	6.7	6.7
8	BpSilyb	391	382	8.2	6.0
9	BpSilybTriPoly	151	148	7.3	5.4
10	Silyb	74	71	5.4	1.4
11	Supportive measures alone	91	85	47.3	43.5
	Pooled therapies				
12	Bp/Silybin combinations (8, 9)	542	530	7.9	5.8
13	Combined nine chemotherapies (1–4, 6–10 above)	1586	1,567	11.2	10.1
14	Combined 10 specific therapies (1–10 above)	2062	2,031	12.6	11.3
15	Bp bi-chemotherapies without Silybin (1, 3, 6)	413	412	14.3	14.1
16	Combined three worst chemotherapies (1–3)	601	599	15.8	15.5

No. LTi = number of patients including liver transplants; No. LTe = number of patients excluding liver transplants; MRLTi = mortality rate including liver transplants; MRLTe = mortality rate excluding liver transplants.

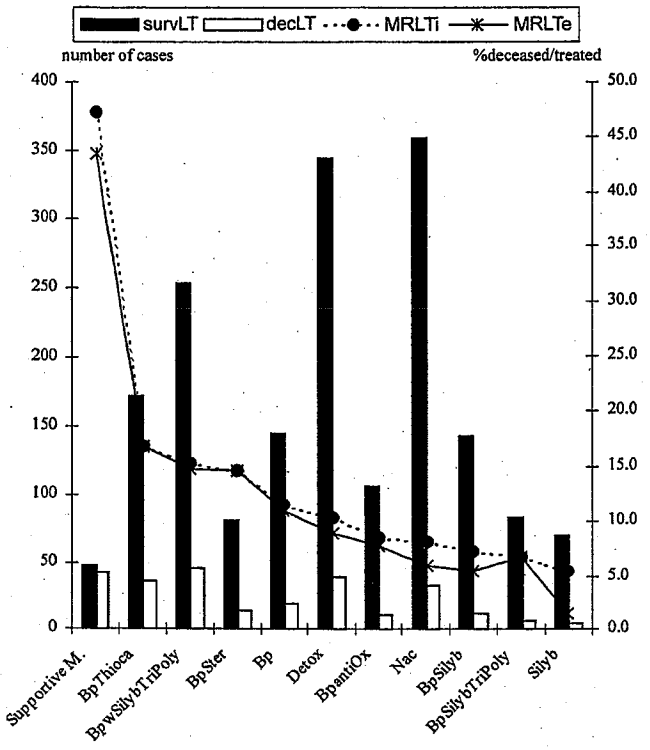

Figure 1. Effect of the modes of care (supportive measures alone and 10 specific treatments) on the distribution of treated patients in terms of survivors and deceased (histograms including liver transplants), and percentages of deceased patients vs. treated with and without liver transplants (curves). survLT: survivors including liver transplants; decLT: deceased including liver transplants; MRLTi: mortality rate including liver transplants; MRLTe: mortality rate excluding liver transplants. Supportive M. = supportive measures alone (Table 1); BpThioca = benzylpenicillin/thioctic acid; BpwSilybTriPoly = benzylpenicillin/drugs without silybin as tri- and poly-chemotherapies; BpSter = benzylpenicillin/steroid; Bp = benzylpenicillin; Detox = detoxication procedures alone (Table 2); BpantiOx = benzylpenicillin/antioxidant drug (cimetidine, *N*-acetylcysteine or vitamin C); Nac = *N*-Acetylcysteine; BpSilyb = benzylpenicillin/silybin; BpSilybTriPoly = benzylpenicillin/drugs with silybin as tri- and poly-chemotherapies; Silyb = silybin.

clinical research to pursue, and provide a basis for the discontinuation of the clearly less effective therapies. Investigations for amatoxin treatment should focus on detoxication procedures, silybin, and NAC. Assessment of more cases would be useful to confirm their benefit. Clinical data from this 20-year period do not show benzylpenicillin to be an effective drug; this antibiotic agent did not enhance the efficacy of either silybin or NAC in the treatment of amatoxin syndrome. Perhaps benzylpenicllin, thioctic acid, and steroids should be abandoned as therapeutic modalities.

SUMMARY

Although the treatment of patients exposed to amatoxin-containing mushrooms has become more sophisticated, the optimal management of the poisoning is still not determined. Options include various detoxication procedures, chemotherapies, and liver transplant in case the hepatic disease reaches a potentially fatal stage.

The clinical efficacy of any modality of treatment for amatoxin poisoning is difficult to demonstrate since randomized, controlled clinical trials verified within the frame of multicenter studies have not been reported. The use of drug combinations also limits the evaluation of individual efficacy of the therapeutic modalities. The theoretical and experimental bases for antitoxic action of most of these agents are not clearly established. Silymarin complex and free radical scavengers (cimetidine, NAC, vitamin C) have respective hepatoprotective and antioxidant properties that yield convincing support for their use.

LT is accepted as a life-saving procedure in amatoxin poisoning cases leading to acute massive hepatic necrosis. Early identification of liver dysfunction, rapid evaluation of suitability for transplant, immediate listing, and an available donor research are crucial. It is important to verify that the prognostic indications for LT are defined and met.

Our retrospective data determined the use and the mortality rate for each treatment in this overall compilation of heterogeneous subjects. For statistical analysis relative to MR, the 32 amatoxin victims receiving LT were considered as special cases and were either excluded from the group of treated patients (MRLTe), or since their outcome was considered virtually fatal without transplantation, were included as deadly cases (MRLTi).

Benzylpenicillin, despite mechanism of its action poorly argued, was the most frequently administered agent (86.5%). Silybin was given to 38.2% of patients. Among the antioxidant drugs, NAC was the most frequently prescribed agent, utilized in 11.8% of cases.

Comparison of the mortality rates of 11 modes of care representing sufficient numbers of patients for statistical analysis showed that supportive measures alone resulted in high mortality comparable to historical data (>40%). The mortality rates of detoxication procedures alone were comparable to those of the nine combined chemotherapies suggesting a benefit due to amatoxin removal after initial absorption. Case data and numbers were insufficient to allow a comparison of the MR of the nine chemotherapies used with and without detoxication

Table 9

Comparison of Mortality Rates Relative to the Different Therapies of the Amatoxin-Poisoning: (a) Including Liver Transplants (MRLTi) and (b) Excluding Liver Transplants MRLTe

# Therapies	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
(a) Including liver transplants (MRLTi)																
1. BpThioca	16.9				*	*	*	**	*	*	**					
2. BpwSilybTriPoly		15.4			*		*	**	**	*	**					
3. BpSter			14.7					*	**	*	**					
4. Bp				11.6							**					
5. Detox alone	*	*			10.4						**					
6. BpantiOx	*					9.1					**					
7. NAC	*	*					6.7				**					
8. BpSilyb	**	**	*					8.2			**				**	
9. BpSilybTriPoly	*	**	**						7.3		**					
10. Silyb	*	*	*							5.4	**					
11. Supportive measures alone	**	**	**	**	**	**	**	**	**	**	47.3	**	**	**	**	**
12. Bp combinations with Silybin (8, 9)											**	7.9				**
13. Combined nine chemotherapies (1–4, 6–10 above)											**		11.2			
14. Combined 10 specific therapies (1–10 above)											**			12.6		
15. Bp bi-chemotherapies without Silybin (1, 3, 6)								**			**				14.3	
16. Combined three worst chemotherapies (1–3)											**	**				15.8
(b) Excluding liver transplants (MRLTe)																
1. BpThioca	16.9				**	*	*	**	*	**	**					
2. BpwSilybTriPoly		14.8			*		*	**	**	**	**					
3. BpSter			14.7					**	**	**	**					
4. Bp				11.0						*	**					
5. Detox alone	**	*			9.0			*		*	**					
6. BpantiOx	*					8.2					**					
7. NAC	*	*					6.7				**					
8. BpSilyb	**	**	**		*			6.0			**				**	
9. BpSilybTriPoly	*	**	**						5.4		**					
10. Silyb	**	**	**	*	*					1.4	**					
11. Supportive measures alone	**	**	**	**	**	**	**	**	**	**	43.5	**	**	**	**	**
12. Bp combinations with Silybin (8, 9)											**	5.8				**
13. Combined nine chemotherapies (1–4, 6–10 above)											**		10.1			
14. Combined 10 specific therapies (1–10 above)											**			11.3		
15. Bp bi-chemotherapies without Silybin (1, 3, 6)								**			**				14.1	
16. Combined three worst chemotherapies (1–3)											**	**				15.5

Significant comparisons of mortality rates (*: $p \leq 0.05$; **: $p \leq 0.01$); 1 > 5 (MRLTi*, MRLTe**); 1 > 6 and 1 > 7 (MRLTi*, MRLTe*); 1 > 8 (MRLTi**, MRLTe**); 1 > 9 (MRLTi*, MRLTe*); 1 > 10 (MRLTi*, MRLTe**); 2 > 5 (MRLTi*, MRLTe*); 2 > 7 (MRLTi*, MRLTe*); 2 > 8 (MRLTi**, MRLTe**), 2 > 9 (MRLTi**, MRLTe**); 2 > 10 (MRLTi*, MRLTe**); 3 > 8 (MRLTi*, MRLTe**); 3 > 9 (MRLTi**, MRLTe**); 3 > 10 (MRLTi*, MRLTe**); 4 > 10 (MRLTe*); 5 > 8 and 5 > 10 (MRLTe*); 11 > 1 to 10 (MRLTi**, MRLTe**); 12 > 16 (MRLTi**, MRLTe**); 15 > 8 (MRLTi**, MRLTe**); 16 > 8 (MRLTi**, MRLTe**).

procedures in order to assess a beneficial toxin elimination for each applied chemotherapy.

A ranking of therapies was based on significant differences in effectiveness as measured by decreasing mortality rates (Fig. 1, Tables 8 and 9). The highest mortality/lowest efficacy was observed with combinations of benzylpenicillin with thioctic acid, steroid, and other drugs except silybin as bi-, tri-, and poly-chemotherapies. The lowest mortality rates were observed with silybin and NAC both administered as mono-chemotherapy, and silybin associations with benzylpenicillin as bi, tri-, and poly-chemotherapies. Since no significant difference between silybin singly and silybin/benzylpenicillin combinations was found, it appears that the flavonolignan complex is effective in reducing mortality and/or avoid LT whereas benzylpenicillin singly is ineffective. Similarly, NAC statistically appears to be a potentially more effective chemotherapy than the other drug options.

Review of the modes of care reported for amatoxin-intoxicated patients over the last 20 years demonstrates wide variability in treatment and response to treatment. Of particular interest in the environment of evidence-based medicine is the prevalent use of a therapy, benzylpenicillin, which has little theoretical foundation and little evidence of efficacy when compared to treatment alternatives. It exemplifies the fallacy of consensus judgments and recommendations based solely on widespread use of a treatment. These case analyses and literature review have a number of limitations due to the disparity in severity grades. However, our work suggests the most successful orientation for prospective clinical research and provides a basis for the discontinuation of the clearly less effective chemotherapies. Efficacy of several drugs is not supported in this review: the most widely used agent, benzylpenicllin, as well as thioctic acid and steroids; perhaps their use should be discontinued. Amatoxin poisoning cases whose treatment focuses on detoxication procedures, silybin, and NAC would be useful to confirm their relevance revealed by our statistical analysis. Future research should be directed towards the iridoid glycosides being potential agents to inhibit amatoxins and stimulate hepatocyte regeneration.

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