10.4.3 Poisonous fungi 1817

10.4.3 Poisonous fungi 1817

10.4.3 Poisonous fungi 1817 Karunaratne AH, et al. (2015). A Rare Case of Vaginal Bleeding in a Child Due to a Leech Bite and Review of the Literature. Wilderness Environ Med, 26, 579–84. Keegan HL (1963). Leeches as pests of man in the Pacific region. In: Keegan HL, McFarlane WR (eds) Venomous and poisonous ani- mals and noxious plants of the Pacific region, pp. 99–104. Pergamon Press, Oxford. Sawyer RT (1986). Leech biology and behaviour. Oxford University Press, Oxford. 10.4.3 Poisonous fungi Hans Persson and David A. Warrell ESSENTIALS Phylum Ascomycota includes ergot and aflatoxin-producing Aspergillus; phylum Basidiomycota includes the larger umbrella- shaped gilled mushroom/toadstools (order Agaricales). Epidemiology—most fungi are nontoxic and most fungal pois- onings are not severe, but morbidity and mortality remain high in Eastern and Central European countries and the Far East and may be increasing worldwide with globalization of exotic species. Fungal poisoning usually results from mistaking poisonous mushrooms for edible ones, it may be accidental in children, or intentional for hallu- cinogenic effects, suicide, or even homicide. Prevention—educational campaigns should emphasize risks of careless harvesting and eating. Diagnosis: morphology and habitat of the ingested fungi (and residue in vomitus) and nature and timing of symptoms are informative. Poison information centres may be consulted. Laboratory methods can detect amatoxins, aflatoxins, and ergot alkaloids. Ergot (Claviceps purpurea poisoning)—results from ingestion of contaminated grains, cereals, and foods (bread). Toxic sclerotia de- velop in ovaries of parasitized grass flowers. Ergot alkaloids cause uterine contraction and vasoconstriction, employed therapeutically in migraine and obstetrics. Lysergic acid derivatives are psychedelic. Chronic ingestion causes gastrointestinal and neurological symp- toms, peripheral vasocontriction, burning pain (‘St Anthony’s fire’) and peripheral gangrene. Larger doses cause acute gastrointestinal symptoms, paraesthesiae, hallucinations, convulsions, and death. Treatment involves vasodilator drugs and anticoagulants. Aspergillus aflatoxin poisoning—aflotoxins from saprophytic Aspergillus flavus contaminate peanuts, maize, and other grains, seeds, and spices, especially in tropical countries. Outbreaks of aflatoxicosis-induced hepatitis leading to fatal hepatic necrosis and portal hypertension occur in undernourished rural popula- tions and, in areas of hepatitis B endemicity, cause hepatocellular carcinoma. Mushroom poisonings—classification is based on toxic effects and related symptoms. Group 1—Cytotoxic mushroom poisoning 1A—primary hepatotoxicity (amatoxin poisoning) is caused by Amanita, Lepiota, and Galerina species, notably death cap Amanita phalloides, responsible for 90% of mushroom fatalities (case fatality 10–20%). Amatoxins block RNA polymerases, inhibiting protein synthesis and damaging intestinal mucosa, kidneys and especially liver. After an ominously long latent period of 8–24 (mean 12) h, intense GI symptoms followed by transient improvement and inexorably fulminant hepatic failure may de- velop. Attempted

decontamination employs multidose activated charcoal. Silibinin, high-dose benzyl penicillin, and N-acetyl cyst- eine have been tried and polymyxin B suggested. Liver transplant- ation is life-saving. 1B—early primary nephrotoxicity (aminohexadienoic acid poi- soning): Amanita smithiana and some other Amanita species cause acute gastrointestinal symptoms followed a few days later by acute kidney injury. 1C—late primary nephrotoxicity (orellanine poisoning): two Cortinarius species can cause insidious poisoning with acute kidney injury, 4–15 (mean 8) days after ingestion. Group 2—Neurotoxic mushroom poisoning 2A—hallucinogenic mushrooms ('magic mushrooms') (psilocybin poisoning): Psilocybe, Panaeolus, Conocybe, and other species con- taining potent hallucinogens cause LSD-like euphoria, hallucinations, depersonalization, and anxiety within 10–60 minutes. Treatment is with diazepam. 2B—autonomic-toxicity mushrooms (muscarinic poisoning): some Inocybe, Clitocybe, Mycena, and Rubinoboletus species contain muscarine causing parasympathetic stimulation after 15 minutes to 2 h. Treatment is with atropine. 2C—central nervous system-neuroexcitatory mushrooms (ibotenic acid/muscimol poisoning): fly agaric (A. muscaria) and some other Amanita species contain GABA agonists causing exhil- aration and euphoria alternating with anxiety, agitation, and hallu- cinations within 0.5–1.5 h, sometimes with cholinergic symptoms. Treatment is with diazepam. 2D—Morel neurological syndrome: inadequately cooked 'morels' (Morchella species), popular 'edible' mushrooms, cause GI symp- toms, while M. esculenta and M. conica can cause severe neurological symptoms (tremor, ataxia, visual disturbances, and so on), even if cooked. Group 3—Myotoxic mushroom poisoning 3A—early myotoxicity (cycloprop-2-ene carboxylic acid poisoning): Russula subnigricans causes gastrointestinal symptoms followed a few h later by generalized myalgia and rhabdomyolysis. 3B—late myotoxicity (saponaceolide B and M poisoning): large/repeated meals of Tricholoma equestre/ flavovirens, a popular 'edible' mushroom, cause generalized rhabdomyolysis 1–3 days after ingestion. Group 4—Metabolic toxicity mushroom poisoning 4A—GABA-blocking mushroom poisoning (gyromitrin poisoning): inadequately cooked 'false morel' (Gyromitra esculenta) and other Gyromitra species contain gyromitrin that impairs central ner- vous system GABA synthesis. After 5—8 h gastrointestinal symp- toms, cerebellar disturbances, seizures, coma, hepatic damage, haemolysis, and hypoglycaemia may ensue. Treatment is with pyridoxine. 4B—disulfiram-like mushroom poisoning (coprine poisoning): antabuse syndrome occurs when alcohol is drunk up to a week after eating Coprinus atramentarius, and some other Coprinus, Clitocybe Boletus species.

 4C—polyporic mushroom poisoning (polyporic acid poisoning): ingestion of the bracket mushroom Hapalopilus rutilans causes gastrointestinal symptoms, neurological effects, acute kidney injury, and passage of purple urine 12 h later. 4D—trichothecene mushroom poisoning (trichothecene poi- soning): Podostroma cornudamae ingestion has caused fatal multi system poisoning with peeling skin in Japan and Korea. 4E—hypoglycaemic mushroom poisoning: 'Yunnan Sudden Unexplained Death' has been explained by 'little white mushroom' (Trogia venenata) poisoning. 4F—hyperprocalcitoninaemic mushroom poisoning is caused by 'Satan's bolete' (Rubroboletus satanas) associated increased cir- culating procalcitonin and C-reactive protein causing GI symptoms and fever. 4G—pancytopenic mushroom poisoning: has been caused by Ganoderma neojaponicum, a popular herbal medicine in Asia. Group 5—Gastrointestinal irritant mushroom poisoning This common type of poisoning can follow ingestion of many genera of mushrooms (Agaricus, Boletus, Entoloma, and so on) including many popular, 'edible' mushrooms. They cause gastrointestinal symptoms alone, starting within a few hours and usually self-limiting. Fluid and

electrolyte replacement may be necessary, especially in children and older people. In North America and Hawai'i, 'false parasol' (Chlorophyllum/Lepiota molybdites) and 'Morgan's mush- room' cause gastrointestinal symptoms and cholinergic effects within 30 min to 4 h. Group 6—Miscellaneous adverse reactions to mushrooms 6A—shiitake mushroom dermatitis (lentinan poisoning): inad- equately cooked shiitake mushrooms (Lentinola edodes) can cause a generalized, linear prurigo 24 h after ingestion. 6B—erythromelalgic mushroom poisoning (acromelic acid poi- soning): Clitocybe acromelalgia/amoenolens can cause acromelalgia. 6C—paxillus syndrome: severe gastrointestinal symptoms, haem- olysis, and acute kidney injury can follow repeated ingestion of Paxillus involutus. 6D—encephalopathic syndrome Pleurocybella gyrometrinporrigens, Pleurotus eryngii and some other popular 'edible' mushrooms have caused encephalopathy in elderly people suffering from chronic renal or hepatic disease. Cyanide is implicated. Introduction This chapter covers poisoning by members of the fungal sub- kingdom Dikarya that includes most of the 'higher fungi'. The phylum Ascomycota contains the medically important toxic fungi Claviceps purpurea, the cause of ergotism, Aspergillus flavus, a source of hepatotoxic and carcinogenic aflatoxins, the edible but potentially toxic morel mushrooms (Morchella species), Gyromitra species, and Podostroma cornudamae that has caused multisystem symptoms and signs. The phylum Basidiomycota includes the order Agaricales (gilled mushrooms/toadstools or agarics) to which most of the med- ically important larger fungi belong. 'Mushroom' and 'toadstool' may suggest 'edible' and 'poisonous' respectively, but these terms are not strictly applied. They refer to the visible, above-ground, fleshy, fruiting bodies of these fungi which are typically umbrella-shaped with a cap (pileus) with spore-bearing gills (lamellae) on its under- side, on top of a stalk (stipe), with or without a ring and a volva at its base. Poisonous species must be distinguished from field (Agaricus campestris) and cultivated (A. bisporus) mushrooms and from the many other mushrooms that are considered to be delicious and are passionately sought after by mycophiles worldwide. History Assyrian and pharaonic references to dangerous outgrowths in ears of grain date from 600 to 400 BC. In Europe, epidemics of gangrenous ('St Anthony's fire') and convulsive ('St Vitus's dance') ergotism, ini- tially killing tens of thousands, have occurred between the 9th and early 20th centuries AD. These followed the introduction of rye, a host of ergot, as a major food crop for impoverished rural popula- tions. The poisonous properties of mushrooms/toadstools have been recognized since ancient Greek and Roman times. Among famous fatalities, homicidal, accidental, or mythical, attributed to poisonous mushrooms, were Siddhartha Gautama (the Buddha), the Roman Emperor Claudius, Pope Clement VII, the Holy Roman Emperor Charles VI, the Russian Tsar Alexis and his wife, and the 18th- century German composer Johann Schobert. Aetiology The most common cause of fungal poisoning is confusing poisonous mushrooms with edible ones. Safe mushroom hunting requires skill and experience, as there are many possible sources of dangerous confusion. Too many people harvest, cook, and eat mushrooms whose identity is uncertain. Toddlers may accidentally try mush- rooms and serious poisoning may occur, but this is fortunately un- common. Intentional ingestion of toxic fungi is mostly related to abuse of hallucinogenic fungi. Suicidal ingestion is rare. Illness after eating mushrooms is not necessarily related to poi- soning. Large mushroom fragments or raw mushrooms may prove hard to digest, there may be anxiety that toxic mushrooms might have been ingested, bacterial toxins may be present in mushrooms that have been stored for too long and fungi may be contaminated with toxic heavy metals. There are individual differences in sensibility to some fungal toxins. One example is false morels Gyromitra spp. Toxin contents may also vary between mushrooms of the same species. Epidemiology The incidence of fungal poisoning varies greatly worldwide. Availability of fungi, depending on climate and geographical

con- ditions, economics, and lifestyle determine different local traditions for harvesting and eating mushrooms. In some parts of the world mushrooms are part of the normal diet, but more commonly they are eaten as a delicacy. In most places, mushrooms cannot be con- sidered indispensable for nutrition and so it remains an unaccept- able paradox that self-harvested mushrooms, enjoyed as a delicacy,

10.4.3 Poisonous fungi 1819 still kill people in the 21st century. Most fungi are nontoxic and most fungal poisonings are not severe. However, in certain regions such as Russia and other Eastern and Central European countries, morbidity and mortality is high. Recent publications suggest an increasing incidence of poisoning worldwide, or at least increased recognition and reporting. As in other branches of medicine, there is globalization, such that exotic fungi are being eaten across ex- panding geographical areas and being introduced into places where their effects are unfamiliar. Prevention With a few exceptions, fungal poisoning is accidental. Many people develop severe and life-threatening illness after mushroom meals. Some die; others suffer chronic, irreversible organ damage requiring transplantation. Since mushrooms are eaten mostly as a delicacy and not as a basic nutritional requirement, it is a paradox that poisoning is so common. The solution is prevention. Educational campaigns should be launched to improve knowledge about mushrooms and raise awareness of the risks involved in careless harvesting and eating. To many people mushroom hunting is an adventure, al- most a game, but this easy-going attitude must be changed. Because the geographical distribution and appearance of certain fungi are variable, people who are not familiar with the local area tend to be overrepresented as victims of fungal poisoning. Educational mater- ials should therefore be multilingual and specifically addressed to immigrants. Diagnosis Diagnosis may be difficult, as the circumstances are often con- fusing. It is important to consider any disease that may mimic fungal poisoning. The history is crucial. Attention should be paid to the appearance of mushrooms ingested and the habitat where they were harvested. The speed of onset of symptoms and their character, intensity, and duration are often informative. Some fungal poisonings may present with characteristic symp- toms, for example, those caused by muscarine, psychotropic toxins, and amatoxins (see following paragraphs). Careful observation and evaluation of evolving clinical features may, in combination with the history, allow a diagnosis. In difficult cases where a dangerous poisoning cannot be excluded, macro- and microscopic examination of the fungi (using online keys and apps), including fragments recovered from vomitus, may prove diagnostic. In many countries, poison information centres may as- sist, either by identifying the mushrooms themselves or by obtaining advice from external experts. Laboratory methods: DNA-based macroarrays have been used to identify mushroom fragments. α-amanitin is detectable in serum by high-performance liquid chromatography (HPLC), and amatoxins by RIA, EIA, EPLC, LC/MS/MS and mass LC/MS in urine. Aflatoxins are detected by thin-layer chromatography and HPLC (EIA is too in- sensitive) and ergot alkaloids by HPLC and HPLC-MS/MS. Specific types of fungal poisoning Ergotism (ergot Claviceps poisoning) Ergotism results from ingestion of uncleaned grains and cereals, or their products such as bread, contaminated with Claviceps species, an Ascomycota fungus. Ideal climatic conditions exist when a warm wet spring and summer follow a cold winter. Claviceps purpurea, the most important species, parasitises grasses and cereals, notably rye but also wheat; C. fusiformis pearl millet in Africa and East Asia; and C. africana sorghum in Africa. Claviceps spores infect the ovaries of flowering grasses from which the poisonous ‘ergot’ or sclerotium develops. It protrudes from the seed head, an odoriforous, hard, curved, blackish-purple body about 4 cm long shaped like a rooster’s spur (Fig. 10.4.3.1). There are three groups of ergot alkaloids: amines (e.g. ergonovine/

ergometrine); aminoacids (ergopeptides) (e.g. ergotamine); and semi synthetic dehydrogenated compounds (e.g. dihydroergametrine). Ergonovine/ergometrine causes powerful uterine contraction; er- gotamine causes vasoconstriction, uterine contraction, α-adrenergic blockade, and central emesis; while dihydroergotamine causes vaso- constriction, α-adrenergic blockade, and emesis. Beneficial effects of vascular and uterine smooth muscle contraction have been im- plemented for treatment of migraine and to promote delivery of the placenta and prevent post- partum haemorrhage. Psychedelic lysergic acid diethylamide (LSD) was first synthesized from ergotamine. The ergot alkaloid ergine (d-lysergic acid amide—LSA), also found in seeds of the flowers of 'morning glory' (Ipomoea tricolor, Rivea/ Turbina corymbosa), has similar effects. Clinical features Ingestion of relatively small amounts of C. purpurea ergot over long periods causes chronic drowsiness, vomiting, diarrhoea, muscle twitching, ataxia, and hallucinations. Eventually, the vasocon- strictive effects of ergot alkaloids cause ischaemia and gangrene of the feet. The associated burning (ischaemic) pain led to the name 'St Anthony's fire' (not to be confused with erysipelas known as 'the rose'). Larger doses cause acute vertigo, tinnitus, headache, high fever, nausea, vomiting, other gastrointestinal disturbances, uterine con- tractions, paraesthesiae, hallucinations, behavioural abnormalities, weakness, convulsions, and death. Claviceps fusiformis poisoning causes self-limiting acute gastro- enteritis and drowsiness. A similar range of symptoms is described in patients who took excessive doses of therapeutic ergot alkaloids. Treatment For peripheral ischaemia, parenteral nitroprusside or nitrogly- cerin, oral prazosin, or ACE-inhibitors and anticoagulants are recommended. Prevention Selection of less susceptible strains, development of ergot-resistant crops, improved crop husbandry through minimizing ergot-susceptible grass weeds (e.g. black grass), azole-treatment of grains, surveillance of milling, and use of food processing and baking reduce the risk of ergotism.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1820 Aspergillus aflatoxin poisoning Apergillus species are conidial Ascomycota fungi that are ubiqui- tous saprophytes of soil and vegetation, including agricultural crops. Aspergillus flavus is the most widespread species. About 30% of its strains produce aflatoxins. These were first recognized, isolated, and characterized in 1960, after the death of more than 100 000 turkeys from 'turkey X disease', attributed to consumption of Aspergillus- contaminated peanut meal. Among at least 14 of these naturally occurring thermostable mycotoxins, the most important are the difurocoumarocyclopentenones: aflatoxins B1 (AFB1, the most dan- gerous) and AFB2, produced by Aspergillus flavus, A. parasiticus and A. nomius; and AFG1 and AFG2, produced by A. parasiticus and A. nomius. AFM1 and AFM2 in milk or urine of poisoned humans or animals results from 4-hydroxylation of AFB1 and AFB2 in the liver. Foodstuffs that are commonly contaminated with aflatoxins include ground (peanuts) and tree nuts, maize, corn, and other grains, seeds, cassava, dried fish, chilli peppers and other spices, especially in India, the Far East, and South America. Clinical features Outbreaks of aflatoxicosis-induced hepatitis have occurred in undernourished rural populations in tropical countries such as Fig. 10.4.3.1 Ergot (Claviceps purpurea) showing development of the sclerotium in the ovary of the host grass flower (3–5), and fruiting bodies (6–8). Reprinted from P. Esser (1910). Die Giftpflanzen Deutschlands. Braunschweig, Friedrich Vieweg und Sohn. Copyright © 1910, Springer Fachmedien Wiesbaden, with permission from Springer.

10.4.3 Poisonous fungi 1821 India (maize diet) and Kenya (corn diet). Jaundice, ascites, portal hypertension, and fatal portal variceal haemorrhage were features of these epidemics. High doses of aflatoxins B1 and G1 cause prolif- eration of bile duct epithelium, fatty infiltration, and

centrilobular necrosis. In areas of hepatitis B endemicity, aflatoxicosis is a co- carcinogen for hepatocellular carcinoma. AFB1 is the most potent naturally occurring carcinogen. It is metabolized in the liver to a reactive epoxide, which forms DNA adducts at some guanine res- idues. The epoxide adduct catalyses a G → T mutation in the p53 tumour suppressor protein gene, causing a missense mutation that inactivates its product. Treatment is supportive. Prevention Risk of aflatoxicosis can be reduced by improving agricultural prac- tices, including storage, and surveillance of AF levels in key crops and foodstuffs. Classification of mushroom poisonings (mycetismus, mycetism, mycotoxicosis) Fungal toxins are a heterogeneous group, chemically and toxi- cologically. In clinical practice, the most relevant approach is a classification based on toxic effects and related symptoms (see Table 10.4.3.1). The scheme adopted here is the new classification recently proposed by White, Weinstein, De Haro, Bédry, Schaper, Rumack and Zilker (2016). These authors have also developed a useful diagnostic algorithm that is colour-coded for key clinical features of poisoning. Group 1—Cytotoxic mushroom poisoning 1A—Primary hepatotoxicity (amatoxin poisoning) The highly poisonous amatoxins occur in species of the families Amanitaceae (genus Amanita), Agaricaceae (genus Lepiota), and Cortinariaceae (genus Galerina). The death cap Amanita phalloides (Fig. 10.4.3.2), destroying angel A. virosa (Fig. 10.4.3.3), eastern North American destroying angel A. bisporigera, Western North American destroying angel A. ocre- ata, Guangzhou destroying angel A. exitialis, and fool’s mushroom A. verna are the most commonly involved in human poisoning. Galerina species such as L. marginata and Lepiota species such as L. helveola may also be implicated. Epidemiology Amatoxin poisonings are reported from all continents, but are most frequent in Europe, accounting for more than 90% of mushroom fatalities (case-fatalities 18–22% in adults, 33–51% in children in the 1970s and 1980s). Case fatality has declined in Western countries but remains alarmingly high in other parts of the world. Pathogenesis The eight amatoxins, of which α-amanitin is the most toxic, are cyclic octapeptides that inhibit transcription of DNA to mRNA by blocking nuclear RNA polymerases II and III ac- tivity. This results in defective protein synthesis and cell death. Amatoxins also act with endogenous cytokines to induce apop- tosis, and there is glutathione depletion. The main target organs are intestinal mucosa, liver, and kidneys. Hepatotoxicity deter- mines prognosis. Clinical features After a latent period of 8–24 (mean 12) h after ingestion, gastro- intestinal symptoms start violently with intense, watery diarrhoea, and vomiting and persist for 36 h. This latency has great diagnostic significance. Patients become rapidly dehydrated and develop oli- guria, hypoglycaemia, hypokalaemia, and metabolic acidosis. After apparent improvement, biochemical signs of liver damage appear after 36–48 h and progress over the next few days. Fulminant hepatic failure may develop. Initial disturbances of renal function will re- solve after rehydration, but within another 3–4 days, renal function may again deteriorate because of toxic kidney damage, a sign of poor prognosis. Treatment Decontamination Forced emesis or gastric lavage is performed if the patient is admitted within 4–6 h and this can be accomplished safely. Multidose activated charcoal is always given. Toxin removal • Multiple-dose activated charcoal is administered for 3 days after ingestion (20–40 g every 3–4 h or 50 g every 6 h). • Diuresis of about 200 ml/h (adults) is maintained for the first 24– 48 h after ingestion. • Haemoperfusion or haemodialysis is not indicated unless the pa- tient has pre-existing renal disease or is admitted very early and in the asymptomatic period (very rare). Reduction of hepatic toxin uptake Silibinin (a component of silymarin from milk thistle—Silybum marianum) (Legalon® SIL) is a free radical scavenger, an anti-inflammatory agent that stimulates protein synthesis and inhibits amatoxin uptake by hepatocytes. 5 mg/ kg is given by intravenous infusion over 1 h, followed by 20 mg/kg/ 24 h as a continuous infusion for 3 days after ingestion. The effective- ness of this treatment is not entirely established.

Parenteral silibinin is not always available, even in Western countries. High-dose benzyl penicillin (600 mg or 1 megaU/kg/day is an alternative. Recently, evidence has been produced that polymyxin B, which, prevents α- amanitin from binding to RNA polymerase II, might be a promising new treatment. Symptomatic and supportive care • Symptomatic care is crucial and includes cautious monitoring, fluid replacement, and correction of metabolic disturbances. Hepatic and renal support may be required. • There is some experimental, theoretical, and clinical support for the use of N-acetylcysteine (300 mg/kg as a continuous IV infu- sion over 21 h) as a liver-protective agent. • If fulminant hepatic failure is pending, a liver unit should be consulted for advice on treatment and with a view to possible transplantation. Prognosis and comments The prognosis is related to toxic dose and start of treatment. Case fatality is high after heavy exposure. Vigorous symptomatic and supportive care, maintenance of an ad- equate diuresis, and multiple-dose activated charcoal are accepted treatments. Silibinin may modify toxicity to some extent through

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1822 Table 10.4.3.1 Classification of mushroom poisoning according to principal clinical features of poisoning and causative toxin(s) where known Group Toxin Commonly implicated species Clinical effect Time of onset 1—Cytotoxic poisoning 1A—1° hepatotoxic Amatoxins Amanita phalloides, A. virosa, A. bisporigera, A. ocreata, A. exitialis, A. verna, Galerina marginata, Lepiota helveola Intense gastroenteritis after 8–24 h, liver and kidney damage 8–12 h 1B—1° early nephrotoxic Aminohexadienoic acid A. smithiana, A. proxima Gastroenteritis, headache, fatigue, myalgias, rash, AKI, cardiotoxicity 1–12 h 1C—1° late nephrotoxic Orellanine Cortinarius orellanus, C. rubellus (speciosissimus) Gastroenteritis, headache, drowsiness, sweating, rash, AKI 4–15 days 2—Neurotoxic poisoning 2A—Hallucinogenic ‘magic mushrooms’ Psilocybins, psilocins, gymnopilins Psilocybe semilanceata, Panaeolus, Conocybe, Gymnopilus, Copelandia, Pluteus, Stropharia species Euphoria, anxiety, agitation, aggression, hallucinations, depersonalization, tachycardia, flushing 10–60 minutes 2B—Autonomic Muscarine Inocybe patouillardii, Clitocybe dealbata, C. rivulosa), Mycena, Rubinoboletus species Nausea, diarrhoea, sweating, salivation, miosis, bradycardia, hypotension, lacrimation, chills,
tremor, bronchospasm, and so on 15–120 minutes 2C—CNS toxic Isoxazoles (ibotenic acid, muscimol, muscazone) A. muscaria, A. pantherina, A. strobiliformis, A. regalis Inebriation, euphoria, confusion, agitation, anxiety, delusions, hallucinations, violent behaviour, seizures, tachycardia, mydriasis, urinary retention, Minutes—3 h 2D—Morel neurological syndrome ? Morchella Gastroenteritis, dizziness, ataxia, visual disturbances, headache, paraesthesiae, trismus, muscle spasms, drowsiness/ confusion, dysarthria 12 h 3—Myotoxic poisoning 3A—Early myotoxic Cycloprop-2-ene
carboxylic acid Russula subnigrans Gastroenteritis, rhabdomyplysis,
2° AKI, collapse 2+ h 3B—Late myotoxic Saponaceolides B & M Tricholoma equestre/flavovirens Fatigue, myalgia, weakness, rhabdomyolysis, sweating, AKI, collapse 1–3 days 4—Metabolic toxicity poisoning 4A—GABA-blocking Gyromitrins/ monomethylhydrazine Gyromitra esculenta Neurological, gastrointestinal, and hepatic symptoms; haemolysis 6–12 h 4B—Disulfiram-like Coprines Coprinus atramentarius, Clitocybe clavipes, Boletus luridus Antabuse-like reaction after alcohol 4C—Polyporic Polyporic acid Hapalopilus rutilans Gastroenteritis then neurotoxic effects, purple urine, AKI, increased aminopeptidases 12 h 4D—Trichothecene Trichothecenes Podostroma cornudamae Gastroenteritis, hypertension,
oliguria, pancytopenia, skin peeling, alopecia Hours–days 4E—Hypoglycaemic γ-guanidinobutyric

acid, 2R-amino-4S-hydroxy-5- hexynoic acid, 2R-amino-5- hexynoic acid Troiga venenata Profound hypoglycaemia (severe), dizziness, SOB, syncope 2 h 4F—Hyperprocalcitoninaemic ? Boletus satanas Gastroenteritis, low grade fever, increased plasma procalcitonin, C-reactive protein 2 h 4G—Pancytopenic ? Ganoderma neojaponicum Fever, pancytopenia ? 5—Gastrointestinal irritant poisoning Many different and unidentified Agaricus, Entoloma, Boletus, Hebeloma, Tricholoma, Russula, Lactarius, Ramaria, Chlorophyllum/Lepiota molybdites, Macrolepiota/Lepiota morganii Gastrointestinal symptoms 1–3 h (continued)

10.4.3 Poisonous fungi 1823 reduction of the hepatic uptake of amatoxin. In some cases, liver transplantation may be the ultimate way of saving the patient. 1B—Early primary nephrotoxicity (aminohexadienoic acid poisoning) Allenic norleucine (aminohexadienoic acid) and chlorocrotylglycine in Amanita smithiana, A. pseudoporphyria, A. proxima, and some other Amanita species can cause acute kidney injury (AKI). Initial gastrointestinal and other symptoms develop between 20 minutes and 12 h after ingestion, followed by AKI a few days later. This was reported from North America after ingestion of A. smithiana, mis- taken for Tricholoma magnivelare, and in southern France, in pa- tients who had eaten A. proxima, mistaken for A. ovoidea as part of ‘proximien syndrome’. ‘Proximien syndrome’ consists of gastro- intestinal symptoms starting 8–14 h after ingestion, followed after 4 days by AKI with evidence of transient liver damage and severe cardiotoxicity in some cases. 1C—Late primary nephrotoxicity (orellanine poisoning) Orellanine is a potent nephrotoxin present in certain species of the family Cortinariaceae, genus Cortinarius. C. orellanus and C. rubellus (speciosissimus) (‘cortinar’ or webcap”) (Figs. 10.4.3.4 and 10.4.3.5) are responsible for most poisonings. Orellanine is a bipyridine N-oxide that may interfere with protein synthesis in the kidneys causing interstitial nephritis, tubular cell damage, basal cell membrane rupture and, eventually, irreversible fibrosis. Clinical features Orellanine poisoning is the most insidious of all mushroom poison- ings. Occasionally, there may be some mild gastrointestinal symp- toms within a couple of days after the meal, but as these symptoms Group Toxin Commonly implicated species Clinical effect Time of onset 6—Miscellaneous reactions 6A—Shiitake dermatitis Lentinans Lentinola edodes Linear prurigo 1–2 days 6B—Erythromelalgic Acromelic acid Clitocybe acromelalgia/ amoenolens Acromelalgia Hours–days 6C—Paxillus syndrome ? Paxillus involutus Collapse, gastroenteritis, autoimmune haemolysis, AKI, DIC 1–2 h 6D—Encephalopathic syndrome Cyanide Pleurocybella porrigens Cramps, coma (in elderly patients with chronic renal/hepatic disease) Days–weeks Based on the new classification by White J, Weinstein SA, De Haro L, Bédry R, Schaper A, Rumack BH, Zilker T. (2016). Fig. 10.4.3.2 Death cap Amanita phalloides. Courtesy of Hans Marklund. Fig. 10.4.3.3 Destroying angel Amanita virosa. Courtesy of Hans Marklund. Table 10.4.3.1 Continued Fig. 10.4.3.4 Cortinarius rubellus (speciosissimus). Courtesy of Astrid Holmgren.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1824 are both discrete and inconsistent they are easily overlooked. However, usually symptoms do not appear until 4–15 (mean 8) days after the mushroom meal, and, by then, reflect established kidney damage. Symptoms evolve insidiously and are difficult for the patient to interpret—headache, fatigue, intense thirst, chills, muscular discomfort, abdominal, lumbar, and flank pain. After a polyuric phase, oliguria and anuria may follow. Laboratory tests on admission reveal elevated serum creatinine and urea, proteinuria, haematuria, and—characteristically—pyuria. The AKI may resolve or become chronic. Treatment Since patients are normally admitted late, therapeutic interven- tions can neither prevent nor reduce toxic damage. Renal function is monitored. Therapy is

symptomatic with support of renal func- tion and treatment of uraemia, including dialysis while waiting for the kidneys to recover. In case of persistent renal insufficiency, the options are chronic dialysis or transplantation. However, transplant- ation should not be performed too early, as renal recovery may be considerably delayed. Very early suspicion of orellanine poisoning should prompt meas- ures to prevent absorption and promote elimination. Prognosis and comments End-stage renal failure was observed in 11% of Polish, 17% of French, and 40% of Swedish patients. It should be emphasized that treatment measures discussed above are theoretically based and there is so far no clinical support for a rational treatment strategy of this ghostly poisoning, apart from supportive and symptomatic care. Group 2—Neurotoxic mushroom poisoning 2A—Hallucinogenic mushrooms (‘magic mushrooms’) (psilocybin poisoning) Psilocybin and related toxins occur particularly in Psilocybe spe- cies, for example, liberty cap Psilocybe semilanceata (Fig. 10.4.3.6), and Panaeolus, Conocybe, Gymnopilus, Copelandia, Pluteus, and Stropharia species. The toxins—psilocybins, psilocins, and gymnopilins—are tryptamine derivatives that increase sero- tonin levels in the central nervous system and act as potent hal- lucinogens. The effects mimic those of LSD. Ingestion is almost invariably related to abuse as these fungi are sought out for their hallucinogenic properties and can be purchased legally in some countries. Clinical features Within 10–60 min, the patient will experience altered sense of time and space, euphoria, hallucinations, and depersonalization. Less pleasurable symptoms are anxiety, agitation, aggression, bizarre and terrifying hallucinations, tachycardia, mydriasis, headache, and flushing. Symptoms peak at around 2 h after ingestion and start vanishing after 4–6 h. However, symptoms may persist and there may be flashbacks after weeks or months. Organic psychosis is a differential diagnosis. A reliable history may be available only after recovery. Treatment The patient should rest in a quiet environment and be sedated (e.g. with diazepam). If this is inadequate, haloperidol or chlorpro- mazine can be added. 2B—Autonomic-toxicity mushrooms (muscarinic poisoning) Toxic amounts of muscarine occur particularly in certain Inocybe species (e.g. I. patouillardii), Clitocybe species (e.g. C. dealbata, C. rivulosa), Mycena species, and Rubinoboletus species. Muscarine has also been detected in small, mostly insignificant amounts in other genera. Muscarine stimulates cholinergic receptors in the autonomic nervous system. Clinical features Symptoms of parasympathetic stimulation start within 15 minutes to 2 h. Nausea, diarrhoea, diaphoresis, hypersalivation, miosis, brady- cardia, and hypotension are common and rhinorrhoea, lacrimation, chills, tremor, central nervous system depression, bronchorrhoea, bronchospasm, and painful micturition have been reported. The pa- tient is often pale and feels sick and miserable. The clinical features are fairly diagnostic. Fig. 10.4.3.5 A common cause of poisoning by nephrotoxic Cortinarius spp. is confusion of Cortinarius rubellus (the lower three fungi in this picture) and funnel chanterelle Cantharellus tubaeformis. Courtesy of Astrid Holmgren. Fig. 10.4.3.6 Liberty cap/‘magic mushroom’ Psilocybe semilanceata. Courtesy of Hans Marklund.

 Treatment Intravenous atropine (adults 1–2 mg, children 0.02–0.05 mg/kg) effectively counteracts the cholinergic symptoms. Repeated doses may be required. Symptomatic treatment is given as required. 2C—CNS-neuroexcitatory mushrooms (ibotenic acid/muscimol poisoning) Isoxazoles (ibotenic acid, muscimol, and muscazone) occur in certain Amanita species, for example, fly agaric A. muscaria (Figs. 10.4.3.7 and 10.4.3.8), panther cap A. pantherina (Fig. 10.4.3.9), A. strobili- formis, and A. regalis. The toxins act as GABA agonists. Clinical features Symptoms start within 0.5–1.5 h, peak at around 3 h, and vanish gradually over the next 24 h. The symptoms are unpredictable: exhilaration, euphoria, drowsiness, and confusion alternate with anxiety, agitation, delusions, illusions, and hallucinations. Extreme agitation and

violent behaviour may ensue. Occasionally myoclonic jerks, muscle fasciculations, and seizures are ob- served. Tachycardia, mydriasis, and urinary retention may occur. Cholinergic symptoms are attributable to trace amounts of mus- carine in some specimens. Panther cap more often causes central nervous system depression, whereas fly agaric is more likely to trigger excitation and bizarre behaviour. History and symptoms are often diagnostic. However, the his- tory is often obscure until patients are fit enough to tell their story. Differential diagnoses include organic psychosis and central ner- vous system infections. Treatment Treatment is symptomatic and supportive. Intravenous diazepam (adults 5–10 mg, children 0.1–0.2 mg/kg) is given and repeated for sedation. Haloperidol or chlorpromazine may be useful as a complement in delirious and agitated patients. 2D—Morel neurological syndrome (toxin unknown) ‘Morel’ (Morchella species) are highly relished edible mushrooms, but they contain toxic thermolabile hydrazine haemolysins. Ingestion of un/inadequately cooked morels causes acute gastroenteritis (nausea, vomiting, abdominal pain, diarrhoea) after about 5 h. In France and Bavaria, people who ingested morels such as Morchella esculenta and M. conica, even cooked ones, developed neurological symptoms about 12 h later: tremor, dizziness/inebriation, unsteadi- ness/ataxia, visual disturbances, headache, paraesthesiae, trismus or muscle spasms, drowsiness/confusion, and dysarthria. Group 3—Myotoxic mushroom poisoning 3A—Early myotoxicity (cycloprop-2-ene carboxylic acid poisoning) Generalized rhabdomyolysis following ingestion of Russula sub- nigricans (order Russalales), a mushroom that stains red when Fig. 10.4.3.7 Fly agaric Amanita muscaria. Courtesy of Ole Högberg. Fig. 10.4.3.8 Variations in appearance of fly agaric Amanita muscaria—may result in confusion with edible mushrooms. Courtesy of Ole Högberg. Fig. 10.4.3.9 Panther cap Amanita pantherina. Courtesy of Hans Marklund.

 damaged. It was first described in Taiwan in 2001 and subsequently in China, Japan, and Korea. Toxicity is attributable to unstable cycloprop-2-ene carboxylic acid. Poisoning causes self-limiting nausea, vomiting, diarrhoea, and agitation about 2 h after ingestion in most victims, followed a few h later in a minority by generalized myalgia and rhabdomyolysis (serum creatine kinase concentration

> “ 20 000 U/litre), with or without hyperkalaemia, hypocalcaemia, respiratory failure, AKI, pulmonary oedema, hypertension, ven- tricular tachycardia, and circulatory shock. 3B—Late myotoxicity (saponaceolide B and M poisoning) Rhabdomyolysis has been reported in France and Poland, after ingestion of large or repeated meals of ‘man on horseback’ or ‘yellow knight’ (Tricholoma equestre/ flavovirens) that grow under conifers. These puzzling observations, implicating a popular mushroom, have caused considerable attention and concern. Toxic saponaceolides B and M have been found in the related and widely-consumed ‘grey knight’ or ‘dirty tricholoma’ (T. terreum) but not in T. equestre. Clinical features Progressive fatigue, muscle weakness, myalgia especially in the thighs, nausea, sweating, facial erythema, and evidence of generalize rhabdomyolysis develop 1–3 days after the last meal of T. equestre. In severe cases there is progression to fatal acute respiratory failure, cardiac arrhythmias, and cardiovascular collapse. The case fatality in Poland was 20%. Severity correlated with the amount of ingested mushroom. Group 4—Metabolic

toxicity mushroom poisoning 4A—GABA-blocking mushroom poisoning (gyromitrin poisoning) Gyromitrin occurs in fungi of the family Helvellaceae, genus Gyromitra. Most poisonings are caused by the ‘false morel’ or ‘Lorchel’ (Gyromitra esculenta), but the toxin is found also in other Gyromitra species. Gyromitrin decomposes in the stomach to form monomethylhydrazine. This reduces central nervous system pyridoxine and, hence, GABA synthesis. Glutathione depletion in erythrocytes and damage to hepatic macromolecules has also been postulated. Gyromitrin is water-soluble and volatile, and so can be partly removed from the fungus by drying or boiling. Clinical features Systemic symptoms may follow inhalation of vapour, which also irritates eyes and airways. Most common, however, is poisoning by ingestion of false morels that have not been properly pre- pared. Symptoms are delayed 5–8 h. Vomiting and diarrhoea may occur, but more typical features are vertigo, ataxia, nystagmus, diplopia, balance disturbances, diaphoresis, slurred speech, and drowsiness. Rare symptoms are delirium, seizures, and coma. Moderate hepatic damage, haemolysis, and hypoglycaemia have been observed. Treatment If neurological symptoms prevail, it is relevant to give pyridoxine 25 mg/kg as an intravenous bolus infusion over 30 min. Repeated doses may be required. If the patient is convulsing and pyridoxine is not immediately available, diazepam is given initially. It is wise to have a glucose infusion running and maintain an adequate diuresis. 4B—Disulfiram-like mushroom poisoning (coprine poisoning) Antabuse syndrome An ‘antabuse syndrome’ may be induced by ‘common ink cap’ or ‘inky cap’ (Coprinus atramentarius), a few other Coprinus species, Clitocybe clavipes, and Boletus luridus. The toxin (coprine) acts like disulfiram, blocking acetaldehyde dehydrogenase. Consequently, drinking ethanol after eating these mushrooms will cause an antabuse syndrome—flushing, sweating, nausea, anxiety, tachycardia, hypotension, and dyspnoea. The risk persists for about 1 week after the mushroom ingestion. If the mistake is discovered early, decontamination and adminis- tration of activated charcoal may be useful. Otherwise symptomatic and supportive care is given. 4C—Polyporic mushroom poisoning (polyporic acid poisoning) An epiphytic bracket mushroom, ‘tender nesting polypore’, ‘purple dye polypore’, or ‘cinnamon bracket’ (Hapalopilus rutilans) con- tains polyporic acid that can cause gastrointestinal and neuro- logical effects about 12 h after ingestion, followed in severe cases by AKI, mild hepatotoxicity, proteinuria, pyuria, and diagnostic purple/violet coloured urine. 4D—Trichothecene mushroom poisoning
(trichothecene poisoning) Podostroma cornudamae ingestion has caused fatal multisystem poisoning, including AKI, pancytopenia, peeling skin, and alopecia in Japan and Korea attributable to trichothecenes. 4E—Hypoglycaemic mushroom poisoning Deaths of some 400 villagers in Yunnan Province, China over 35 years (‘Yunnan Sudden Unexplained Death’) have been attrib- uted to a previously undescribed species of ‘little white mushroom’, Trogia venenata. It contains γ-guanidinobutyric acid, 2R-amino- 4S-hydroxy-5-hexynoic acid, 2R-amino-5-hexynoic acid which cause profound hypoglycaemia (like hypogycin

> from ackee fruit below). Inhibition of β-oxidation prevents generation of glucose by gluconeogenesis from lipid substrate. 4F—Hyperprocalcitoninaemic mushroom poisoning
> (toxin unknown) Poisoning by Satan's bolete (Rubroboletus/Boletus satanas) in France, associated with high plasma concentrations of procalcitonin and C-reactive protein, caused self-limiting gastrointestinal symptoms and fever. 4G—Pancytopenic mushroom poisoning (toxin unknown) Self-limiting pancytopenia has been described in people taking Ganoderma neojaponicum, a common constituent of herbal medi- cines in China, NE, and SE Asia.
> Group 5—Gastrointestinal irritant mushroom poisoning. Fungi solely causing gastroenteritis form the largest subgroup, comprising species from many genera (e.g. Agaricus, Boletus,

10.4.3 Poisonous fungi 1827 Entoloma, Hebeloma, Lactarius, Ramaria, Russula, and Tricholoma). Many of these genera include delicious, popular, and edible mush- rooms, increasing the risk of confusion. Few toxins in this group are chemically identified. They cause nonspecific irritation of the gastrointestinal mucosae. Clinical features Vomiting and diarrhoea start within a few hours and generally resolve quickly. Intensity and duration may, however, vary. For ex- ample, 'leaden entoloma' (Entoloma sinuatum) may cause intense and long-lasting symptoms. Depending on length and duration of symptoms, fluid and electrolyte imbalance may ensue. Gastrointestinal infection must be considered as a differential diagnosis, together with effects of gorging on large amounts of indi- gestible mushrooms (the death of the Roman Emperor Jovian was attributed to 'a surfeit of mushrooms'). Delayed onset of intense symptoms until 8 to 24 h after the mushroom meal suggests poten- tially dangerous poisoning by amatoxin-containing fungi (see fol- lowing paragraphs). Treatment Admission to hospital is seldom necessary, but if symptoms are more intense fluid and electrolyte replacement may be necessary, espe- cially in children and older people. The 'false parasol' or 'green-spored parasol' (Chlorophyllum molyb- dites or Lepiota molybdites; also Morgan's mushroom, Macrolepiota or Lepiota morganii) is the most commonly ingested poisonous mushroom in North America and Hawai'i. The toxin is irritant and also exerts α-adrenergic blockade and cholinergic effects. Within 30 min to 2 (–4) h, intense, watery, and sometimes bloody diarrhoea begins (also a feature of 'tsukiyotake' —Omphalotus japon- icas/guepiniformis—ingestion mistakenly for shiitake mushrooms in Japan). This may result in dehydration, electrolyte imbalance, shock, and renal impairment. Occasionally miosis, pallor, diaphoresis, and hypotension are observed. Fluid replacement and other symptomatic and supportive care are given as required. Atropine is given in case of cholinergic symptoms.
Group 6—Miscellaneous adverse reactions to mushrooms 6A—Shiitake mushroom dermatitis (lentinan poisoning) Inadequately cooked shiitake mushrooms (Lentinola edodes) that are cultivated in the Far East, can cause 'shiitake dermatitis', a gener- alized, light-sensitive, erythematous, micro-papular, linear, pruritic, urticarial rash that appears 24 hours after ingestion and that persists for 3–21 days. It is attributed to the thermolabile polysaccharide, lentina. 6B—Erythromelalgic mushroom poisoning (acromelic acid poisoning) Consumption of 'paralysis funnel' or 'poison dwarf bamboo mush- room' (Clitocybe acromelalgia/amoenolens) can cause persisting acromelalgia, attributed to acromelic acid. 6C—Paxillus syndrome (toxin unknown) After repeated ingestion of the 'roll-rim cap' or 'poison pax' (Paxillus involutus), its antigens may induce a Paxillus syndrome: severe gastroenteritis, haemolysis, and subsequent renal impairment. High

plasma concentrations of bilirubin and aminotransferases due to haemolysis may suggest amatoxin poisoning. Symptomatic and supportive care includes fluid replacement, maintenance of adequate diuresis, and blood transfusions. 6D—Encephalopathic syndrome (possibly cyanide poisoning) ‘Angel wing’ (Pleurocybella gyrometrinporrigens), ‘king trumpet mushroom’ (Pleurotus eryngii) and several other species of mush- rooms long considered safe for eating have been responsible for delayed encephalopathic poisoning in Japan in elderly people often with chronic renal or hepatic disease. Cyanide has been implicated. FURTHER READING Bédry R, et al. (2001). Wild-mushroom intoxication as a cause of rhabdomyolysis. N Engl J Med, 345, 798–802. Bresinsky A, Besl H (1990). A colour atlas of poisonous fungi. A hand- book for pharmacists, doctors, and biologists. Wolfe Publishing, London. Cooper MR, Johnson AW (1998). Poisonous plants and fungi in Britain. Animal and human poisoning, 2nd edition. The Stationery Office, London. Dinis-Oliveira RJ, et al. (2016). Human and experimental toxicology of orellanine. Hum Exp Toxicol, 35, 1016–29. Enjalbert F, et al. (2002). Treatment of amatoxin poisoning: 20-year retrospective analysis. J Toxicol Clin Toxicol, 40, 715–57. Garcia J, et al. (2015). A breakthrough on Amanita phalloides poi- soning: an effective antidotal effect by polymyxin B. Arch Toxicol, 89, 2305–23. Garcia J, et al. (2015). Amanita phalloides poisoning: mechanisms of toxicity and treatment. Food Chem Toxicol, 86, 41–55. Graeme KA (2014). Mycetism: a review of the recent literature. J Med Toxicol, 10, 173–89. Holmdahl J, Blohmé I (1995). Renal transplantation after Cortinarius speciosissimus poisoning. Nephrol Dial Transplant, 10, 1920–2. Karlson-Stiber C, Persson H (2003). Cytotoxic fungi—an overview. Toxicon, 42, 339–49. Lee PT, et al. (2001). Rhabdomyolysis: an unusual feature with mush- room poisoning. Am J Kidney Dis, 38, E17. Saviuc P, et al. (2010). Can morels (Morchella sp.) induce a toxic neuro- logical syndrome? Clin Toxicol (Phila), 48, 365–72. Wasson RG (1972). The death of Claudius or mushrooms for
murderers. Botanical Museum Leaflets Harvard University, 23, 101–28. White J, et al. (2016). Mushroom poisoning: a proposed new
clinical classification. (in press). Presented at The 18th World Congress of the International Society on Toxinology, Oxford, UK, 25–30 September 2015: abstract 143. Toxicon 103 Supplement (2015), 85–6. Yin X, et al. (2014). Chemical and toxicological investigations of a pre- viously unknown poisonous European mushroom Tricholoma ter- reum. Chemistry, 20, 7001–9.1 Zhou ZY, et al. (2012). Evidence for the natural toxins from the mushroom Trogia venenata as a cause of sudden unexpected death in Yunnan Province, China. Angew Chem Int Ed Engl, 51, 2368–70. Mushroom identification app: http://rogersmushroomsapp.com/

Revision #1
Created 2026-01-22 16:37:17 UTC by Omar Ayman
Updated 2026-01-22 16:37:17 UTC by Omar Ayman