What the Primary Care Pediatrician Should Know about Syndromes Associated with Exposures to Mycotoxins

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Abstract

Disease associated with exposure to mycotoxins is known as the "Great Masquerader" of the 21st century because of its complex natural history involving different tissues and resembling different diseases at each stage in its evolution. It can present with a variety of nonspecific clinical signs and symptoms such as rash, conjunctivitis, epistaxis, apnea, cough, wheezing, nausea, and vomiting. Some cases of vomiting illness, bone marrow failure, acute pulmonary hemorrhage, and recurrent apnea and/or "pneumonia" are associated with exposure to mycotoxins. Familiarity with the symptoms of exposure to the major classes of mycotoxins enables the clinician to ask pertinent questions about possible fungal exposures and to remove the infant or child from the source of exposure, which could be contaminated food(s), clothing and furniture, or the indoor air of the home. Failure to prevent recurrent exposure often results in recurrent illness. A variety of other conditions, including hepatocellular and esophageal cancer and neural tube defects, are associated with consumption of foods contaminated with mycotoxins. Awareness of the short- and long-term consequences of exposures to these natural toxins helps pediatricians to serve as better advocates for children and families.

Introduction

During the past decade, a paradigm shift has taken place with respect to pediatricians' understanding of the links between exposures to fungi and health problems. Once considered to be an issue of concern only for immunocompromised children or those living in developing countries in Africa and Asia, a growing body of evidence now documents that immunocompetent children in the United States and other industrialized countries can experience symptoms secondary to the allergic properties of fungi and/or the toxic properties of mycotoxins. Pediatricians have long been aware of the importance of preventing invasive fungal infections among children with immune compromise and they are very familiar with handling allergies to fungi. Primary care pediatricians are less aware of the toxic properties of fungi and many find themselves confused and somewhat puzzled by the often contradictory messages currently flooding the media.

This article will highlight some of the acute presentations that should prompt a clinician to consider exposure to mycotoxins in the differential diagnosis. Currently there are four pediatric syndromes that can be associated with exposures to mycotoxins. These typically have been characterized as "idiopathic" but in fact the possibility of an etiologic link to fungi and mycotoxins has rarely been considered. For each syndrome, this article will describe possible mycotoxins to consider, a diagnostic approach, and when evidence is available, possible interventions. In a busy practice, the clinician must act before all of the research questions have been definitively answered. Therefore a preventive approach is recommended in keeping with the Hippocratic injunction to do no harm.

The article will then describe some of the long-term health effects associated with mycotoxins. Because of their long latency periods, the pediatrician will rarely see patients with mycotoxin-associated cancers but should nonetheless be able to provide guidance to

Table 1. Selected mycotoxin-producing fungi of relevance to children's health

Fungus	Mycotoxins	Associated health effects
Aspergillus flavus	Aflatoxins	Vomiting, hepatitis
Aspergillus parasiticus		Liver cancer
Fusarium verticillioides	Fumonisins	Vomiting
Fusarium proliferatum		Neural tube defects
Aspergillus ochraceus		Esophageal cancer
	Trichothecenes, Nonmacrocyclic	
Fusarium culmorum	Deoxynivalenol	Vomiting
Fusarium graminearum		
Fusarium cerealis		
Fusarium sporotrichiodes	T-2 toxin	Alimentary toxic aleukia
		Vomiting, hemorrhage
	Trichothecenes, Macrocyclic	
Stachybotrys chartarum	Satratoxins	Protein synthesis inhibition
Trichoderma viridi		Hemorrhage
Trichothecium roseum		
Aspergillus ochraceus	Ochratoxins	Balkan nephropathy
Aspergillus niger		Renal cancer
Aspergillus alliaceus		
Penicillium verrucosum		
Penicillium expansum	Patulin	Vomiting, cancer (suspect)
Fusarium graminearum	Zearalenone	Estrogenic effects, cervical cancer (suspect)
Claviceps purpurea	Ergot alkaloids	Ergotism

concerned parents. The literature on the toxic effects of fungi is expanding rapidly and additional information will soon be available for the clinician.

Fungi are omnipresent in our environment. They grow on foods routinely consumed by animals and humans. Fungi also are plentiful in the outdoor air. The concentrations of fungi in the outdoor air vary according to season and weather conditions.[1] In subarctic climates, outdoor concentrations of fungi are usually highest in spring and autumn.[2] Fungi are also present in most indoor environments; they enter homes through doorways, windows, and heating and air conditioning systems. The most common fungi found indoors are *Cladosporium*, *Penicillium*, *Aspergillus*, and *Alternaria*.[3,4] Fungi require water and nutrients to grow. Problems may develop indoors when the presence of standing water leads to excessive growth of fungi.[5-7] Water may come into a home from leaks in roofs and walls, or from flooding.[8-10] Nutrients required by fungi often come from cellulose items in the home, such as wallpaper, wood, or cardboard.

Certain fungi such as *Stachybotrys chartarum* (previously and commonly known as *Stachybotrys atra*) and *Trichoderma* species require chronically water-damaged environments to grow.[11] Because of this requirement, they tend to be found indoors less frequently than *Cladosporium*, *Penicillium*, *Aspergillus*, and *Alternaria*.

Indoors, when fungi are disturbed, they can disseminate spores into the confined space of a building.

Under some circumstances, fungi produce toxins.[12-14] Mycotoxins on the fungal spores are easily absorbed by the airways, intestinal lining, and skin.[15] The word mycotoxin is derived from "myco" meaning fungus and "toxin" meaning naturally produced poison. Fungi probably developed toxins to serve as a chemical defense against insects, microorganisms, nematodes, grazing animals, and humans.[16] About 400 mycotoxins have been identified, and there are probably many more. The name of a mycotoxin is usually derived from the fungus producing it. Aflatoxin, the toxin from *Aspergillus flavus*, gets its first letter "A" from the genus *Aspergillus*, "fla" from the species *flavus* appended with "toxin." Some mycotoxins are known by a chemical name (eg, deoxynivalenol) or by a toxic manifestation (eg, vomitoxin).

Certain mycotoxins are beneficial to children and adolescents. They are used as antibiotics (penicillin), immunosuppressants (cyclosporine A), and for the abortive treatment of migraine headaches (ergotamine). Mycotoxins also can be harmful to children and adolescents, even in the absence of viable fungi. Table 1 lists fungi that produce the mycotoxins of primary importance to children's health (aflatoxins, fumonisins, trichothecenes, och-

Table 2. Clinical presentations of mycotoxin-associated diseases among infants and children

Vomiting illness
Bone marrow failure
Acute pulmonary hemorrhage
Recurrent apnea and/or "pneumonia"

ratoxins, patulin, zearalenone, ergot alkaloids) and identifies some of their associated health effects.[16]

Diseases associated with exposures to mycotoxins can present with a variety of nonspecific clinical signs and symptoms in infants and children such as rash, conjunctivitis, epistaxis, apnea, cough, wheezing, nausea, and vomiting. A century ago, syphilis was called the "Great Masquerader" because of its complex natural history involving different tissues and resembling different diseases at each stage in its evolution. In the 21st century the "Great Masquerader" is disease caused by mycotoxins. Because of the variety of ways that mycotoxin-related diseases manifest clinically, the chance of confusing them with other diseases is great. Moreover, many pediatricians have little experience detecting or even suspecting that mycotoxins might be involved in pediatric diseases. The symptoms can easily be mistaken for those of other illnesses such as pneumonia or influenza. Further complicating the picture is the fact that the diverse clinical manifestations associated with exposures to mycotoxins may not be readily identifiable as a single clinical entity. The reason that the clinician should consider exposure to mycotoxins in the differential diagnosis of puzzling and recurrent symptoms is that effective treatment involves removing the infant or child from the source of exposure. Just as a child with carbon monoxide poisoning will continue to be symptomatic (and could die) if he returns to a home with an elevated carbon monoxide level, so the child with symptoms related to a specific fungal exposure will likely become symptomatic again on returning to a home with high levels of certain fungal spores or spore fragments in the air. Unless the clinician considers this potential etiology and asks questions about exposure to moldy items and environments, the opportunity to prevent further harm will be missed.

Mycotoxins can have protean manifestations; the symptoms depend on the specific toxin or mixture of toxins, the age, sex, and diet of the child, the dose, and whether exposure is by ingestion, inhalation, skin and mucosal exposure, or a combination of two or more of these routes.[14,17] The most well-characterized presentations among infants and children are summarized in Table 2 under four headings: vomiting illness, bone

marrow failure, acute pulmonary hemorrhage, and recurrent episodes of apnea and/or "pneumonia."

Acute Clinical Presentations

Vomiting Illnesses

> ***Illustrative Case History 1.*** A previously healthy 12-year-old boy presented to the clinic with the chief complaint of abdominal cramps, vomiting, headache, and dizziness that began about 15 minutes after eating lunch at the school cafeteria. He denied diarrhea, diplopia, blurred vision, flushing, or paresthesias. Three hours earlier he ate three beef burritos made from wheat flour tortillas. Several other classmates became ill at the same time. On examination the boy was well-hydrated, afebrile, and acyanotic. Results of the physical examination were unremarkable. His carboxyhemoglobin level was 0.5%.

This case history presents a scenario that should prompt the alert clinician to investigate the possibility of food poisoning from preformed toxins such as mycotoxins. Mycotoxin ingestion should be considered in a previously healthy child who develops vomiting within minutes to 8 hours after eating. The physical examination is within normal limits. Acute vomiting secondary to ingestion of mycotoxin-contaminated food usually is self-limiting and the symptoms resolve within a few hours. Children present with predominant nausea and vomiting; fever is typically absent. The vomiting may be accompanied by headache and dizziness, but rarely is diarrhea a predominant symptom. If present, it is watery and fecal leukocytes are absent. A thorough history can offer important clues to diagnosis. The history should emphasize the number of minutes after eating that the vomiting started, occurrence of similar symptoms in siblings or classmates, and occurrence in animals or pets after eating leftover food.[18] The differential diagnosis of headache, dizziness, nausea, and vomiting should include carbon monoxide poisoning. Other preformed toxins that can cause vomiting include *Staphylococcus aureus* toxins and *Bacillus cereus* toxins. Heavy metals that can cause vomiting include copper, tin, cadmium, and zinc.[19]

Mycotoxins that Should be Considered. Four groups of mycotoxins merit consideration when a child presents with a vomiting illness within hours of eating: trichothecenes, especially deoxynivalenol (also

Table 3. Clinical features of vomiting illness from exposure to mycotoxins

Toxin	Latent period	Clinical features	Foods associated
Vomitoxin	3-15 min	Vomiting Nausea Headache Abdominal cramps Prompt resolution No sequelae	Food made from wheat and corn (eg, burritos)
T-2	5 min-1 h	Nausea Vomiting Diarrhea (bloody) Abdominal pain Dizziness "Burning" in mouth Symptoms improve in 3-9 days	Food made with wheat, rice, millet, or corn
Aflatoxins	~8 h	Vomiting Diarrhea Abdominal pain Dizziness Seizures Fever Hepatic toxicity can occur in weeks	Peanuts, maize, soybeans, cassava
Fumonisins	N/A	Nausea Vomiting	Food made from corn
Patulin	N/A	Nausea Vomiting	Apple juice, other nonfermented apple products

known as vomitoxin) and T-2 toxin, fumonisins, aflatoxins, and patulin. Table 3 lists the major clinical features of each, which will be described separately below.

Trichothecenes. The first group of mycotoxins that can cause vomiting among children is the trichothecene mycotoxins, including vomitoxin and T-2. Produced by species of *Fusarium*, these nonmacrocyclic trichothecenes can contaminate grain products and retain their toxicity even after the grain is baked or cooked. Ingestion of heavily contaminated food results in vomiting within hours.[20]

Vomitoxin, one of the most common mycotoxins causing vomiting among children, frequently contaminates wheat and corn. The estimated tolerable daily intake of vomitoxin is 1.5 μg/kg body weight and 3.0 μg/kg body weight for infants and adults, respectively.[21] Multiple outbreaks of vomiting illness during 1961 to 1985 in China were linked to consumption of foods made with grain contaminated with vomitoxin.[22] In 1987, nearly 100 persons in India became ill after they consumed wheat products from which vomitoxin and other trichothecene mycotoxins were recovered.[18] In 1997 and 1998, approximately 1700 school children in the United States developed vomiting, nausea, headache, and abdominal cramps after

eating burritos.[23] Vomitoxin was identified as a contaminant in the burritos and might have caused the outbreaks, which subsided within 24 hours of onset.[23]

Aflatoxins. A second group of mycotoxins that can cause vomiting among children is the aflatoxins. Produced by *A. flavus* and *A. parasiticus*, these mycotoxins commonly contaminate peanuts, maize, soybeans, and cassava, especially in tropical areas. Massive aflatoxin ingestion can result in acute aflatoxicosis with vomiting, abdominal pain, hepatitis, and sometimes death. The acute lethal dose for adults is 10 to 20 mg, whereas the acute lethal dose for children is estimated to be about 3 mg.[24] In developing countries, epidemics have been reported following ingestion of food heavily contaminated with *A. flavus*.[24-30] One of the largest reported outbreaks of aflatoxin poisoning occurred in Kenya in 2004.[28-30] Three hundred seventeen people became ill and 125 died.[29] About 22% of the patients were aged < 5 years and 29% were aged 5 to 14 years.[28] Diet clearly affects the toxicity of aflatoxins. In animal studies, rats deficient in B vitamins and fed aflatoxins showed signs of aflatoxicosis; rats with adequate B vitamins did not show signs of aflatoxicosis.[31,32]

Fumonisins. A third group of mycotoxins that can cause vomiting among children is the fumonisins.

Table 4. Interaction of fungal toxins and risk factors in the development of food-borne disease outbreaks

Geographic region/ country	Age-standardized incidence (No. of cases per 100,000)	Fungal infection of major dietary staples	Mycotoxin contamination	Dietary and other risk factors
Southern India	Deccan Plateau; gastrointestinal disease[35-37]	Moldy sorghum and maize *Fusarium, Aspergillus, Alternaria* spp.[35,38]	Sorghum: fumonisin B_1 (0.14-7.8 mg/kg); aflatoxin B_1 (trace-0.08 mg/kg)	Low socioeconomic status; lack of access to other foods such as rice[35]
			Maize: fumonisin B_1 (0.25-65 mg/kg); aflatoxin B_1 (0.05-0.93 mg/kg)	
Eastern and Central Kenya	Makueni 16.7 Thika 1.9[30]	Maize *Aspergillus* spp.[30]	Maize: total aflatoxin in Makueni (27.19-103.21 μg/kg); in Thika 3.83-14.78 μg/kg)[30]	Hepatitis B surface antigen positivity[29]

Adapted from: Joint Expert Committee on Food Additives. Safety evaluation of certain mycotoxins in food. Geneva: World Health Organization; 2001:151-5. Reproduced by permission.

Table 5. Questions to consider in the history if ingestion of mycotoxins is suspected

Have other persons who ate the same food become ill?
Did the symptoms begin within minutes to 3 hours of eating?
Did any pets or animals eat the same food and become sick?
Was diarrhea absent or a minor part of the illness?

Fumonisins are universally present in corn and corn-based products.[33] They are produced by *Fusarium verticillioides*, *Fusarium proliferatum*, and *Aspergillus ochraceus*. Both fumonisin exposure and aflatoxin exposure are epidemiologically associated with food-borne disease outbreaks.[33-38] Because contamination with more than one fungus is a common occurrence, it is likely that interaction between toxins is a key factor determining the severity of the child's symptoms. Table 4 lists the interactions of fungal toxins and other risk factors in the development of food-borne disease outbreaks.

Patulin. A fourth mycotoxin that can cause vomiting among children is patulin. Patulin comes from a number of fungal species, including *Penicillium*, *Aspergillus*, and *Byssochlamys*. The apple-rotting fungus *Penicillium expansum* is the most commonly encountered producer of patulin. Apple juice and other apple products can contain patulin when rotten apples have been processed.[39] Alcoholic fermentation of fruit juices destroys patulin; fermented products such as cider do not usually contain patulin.[40] Symptoms in humans reportedly due to patulin toxicosis are nausea, vomiting, and gastrointestinal disturbances, although published literature on the occurrence of these symptoms among children is sparse.[41,42] No reports of outbreaks have been published.

Diagnostic Approach. If acute ingestion of mycotoxins is a concern, the clinician should consider the questions in Table 5. There are no definitive diagnostic tests to confirm that a child's illness is associated with consumption of mycotoxins in food. Neither hospital laboratories nor public health laboratories in the United States routinely perform testing for mycotoxins. Identifying the etiologic agent is therefore difficult. If multiple people in the same family or group develop symptoms of nausea and vomiting without diarrhea or fever after eating together, a sample of the suspected food(s) should be obtained for possible analysis. In food-borne illness outbreaks, the local health department should be consulted to assist in determining whether and where the food samples should be analyzed because the specialized analyses for mycotoxins are usually only conducted in national laboratories of the US Food and Drug Administration and the US Department of Agriculture.

Intervention. Mycotoxin contamination in food is greatest during years of extreme drought.[43] Fungi usually are unable to penetrate intact seed kernels but drought conditions can weaken the plant and allow penetration to occur. Severe rain and flooding can also increase mycotoxin contamination of crops; intense rain events have increased 20% in the last century.[44,45] Thus both drought and flooding can contribute to mycotoxin contamination of food. Visibly moldy foods should not be eaten. Contamination with lower levels of mycotoxins, however, cannot be detected by sight, smell, or taste. Few food items undergo any testing to detect mycotoxins. The US Food and Drug Administration establishes action levels for aflatoxins in food, but these informal guidelines are not binding.

The US Food and Drug Administration sets advisory levels for vomitoxin, but no established action levels. The Food and Drug Administration has a draft guidance document for industry on fumonisin levels in human foods and animal feeds,[46] but no advisory levels or action levels for fumonisin have been set.

Case 1 Follow-Up. The 12-year-old boy recovered completely within 2 hours. A cafeteria worker saved a sample of the beef burritos that had been served for lunch on the day the children became ill and it was sent to the US Food and Drug Administration. The level of vomitoxin detected in the burrito was 0.3 milligrams per kilogram, lower than the advisory level (1 milligram per kilogram) set by the US Food and Drug Administration. Vomitoxin could not, however, be ruled out as a possibility because this advisory level does not account for the special vulnerabilities of children.

Bone Marrow Failure

Illustrative Case History 2. An 8-month-old white Hispanic male was brought to the clinic with a fever of 102.4°F and neutropenia. Six days earlier during a clinic visit for diarrhea, irritability, and rash he was noted to have mouth sores and a 3-mm pustule on his back. At that time his white blood cell count was 5500 per cubic millimeter with a differential count of 1% polymorphonuclear forms, 68% lymphocytes, 29% monocytes, 2% eosinophils, and adequate platelets. The pediatrician instructed the parents to return if the infant developed a fever.

The infant was admitted directly from the clinic to the hospital. Examination revealed a well-hydrated healthy-appearing infant in no acute distress with a very mild papular rash. No hyperpigmentation, café-au-lait spots, or Mees lines were seen. Palpebral conjunctiva were injected. His heart sounds were normal and his chest was clear to auscultation. Neurologic examination was entirely normal. The abdomen was soft and nontender. The spleen was palpable three finger-breaths below the left costal margin. Results of the physical examination were otherwise unremarkable.

His white blood cell count was 7000 per cubic millimeter with a differential count of 3% poly-

morphonuclear forms, 77% lymphocytes, 13% monocytes, 7% eosinophils, and 206,000 platelets. His hemoglobin was 12.4 g/dL, hematocrit was 36.6%, and reticulocytes were 0.14%. Blood chemistry results showed a glucose of 84 mg/dL, urea nitrogen 9 mg/dL, creatinine 0.3 mg/dL, sodium 138 mmol/L, potassium 4.9 mmol/L, chloride 104 mmol/L, CO_2 21 mmol/L, alanine aminotransferase 61 U/L, alkaline phosphatase 291 U/L, aspartate aminotransferase 69 U/L, total bilirubin 0.2, and erythrocyte sedimentation rate 27. Urine analysis was normal. Direct antibody test (DAT), Anti-IgG was positive. Nonspecific cold antibodies were found.

His past history revealed that he had been healthy until about 6 weeks before admission when he developed "itchy eyes." Three weeks before admission he developed a cough and a fever of 102 to 103°F. Radiograph of the chest showed patchy hilar and infrahilar infiltrates bilaterally. He was given a presumptive diagnosis of pneumonia and treated with azithromycin. No blood tests were taken.

The initial hospital evaluation included a bone marrow biopsy that showed dilute bone marrow with erythroid hypoplasia and paucity of mature red cell precursors. There was slight myeloid hyperplasia with a maturation block at the band stage. No evidence of leukemia or myelodysplastic syndrome was found. He had a normal male karyotype with no numerical or structural chromosome aberrations. He received granulocyte colony-stimulating factor 50 μg subcutaneously; the following day his white blood cell count was 6300 per cubic millimeter with 16% neutrophils. Six days later his absolute neutrophil count rose to 15,200 cells per cubic millimeter and the granulocyte colony-stimulating factor treatments were discontinued. Cultures of blood and urine showed no growth of bacteria and he was discharged from the hospital.

Over the next month, the hemoglobin dropped progressively to 5.7 g/dL. Iron was 96 μg/dL, ferritin was 72.3, iron saturation was 41, total iron-binding capacity was 232, and the erythropoietin level was 1060 mIU/mL (normal < 19 mIU/mL). The platelet count was 150,000. He had a normal partial thromboplastin time, prothrombin time, and international normalized ra-

Hgb, Platelets, and WBC by Date
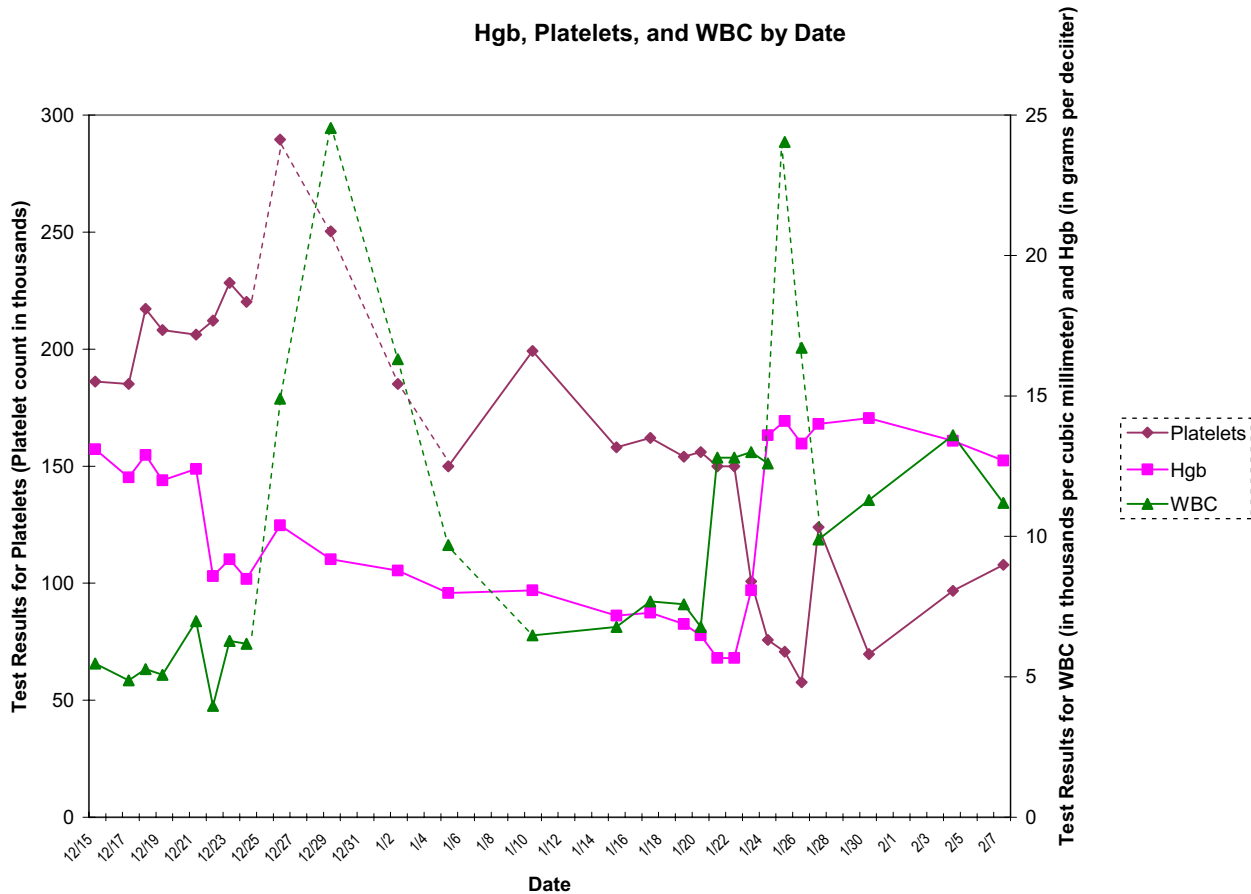
FIG 1. Hemoglobin, platelets, and white blood cell count by date. Dotted lines indicate results following platelet and blood transfusions. (Color version of figure is available online.)

tio. He underwent the first of several blood transfusions. A repeat bone marrow at age 10 months was dilute but showed a decreased number of red cell precursors and no mature red cell precursors. His platelets dropped to 57,000 and he received platelet transfusions, cefepime, and granulocyte colony-stimulating factor. A week later the hemoglobin was 13.4 g/dL, the hematocrit 36.9%, mean corpuscular volume 84.4 fL, mean corpuscular hemoglobin 30.7 pg, and mean corpuscular hemoglobin concentration 36.3 g/dL. The platelet count was 97,000. Immunologic testing for hepatitis B and C, cytomegalovirus, Epstein–Barr virus, and mycoplasma was negative. Figure 1 shows the time sequence of this illness; neutropenia was the first manifestation, followed by anemia, and then thrombocytopenia.

Mycotoxins that Should be Considered. This case history of neutropenia of unknown etiology should prompt the alert clinician to investigate the possibility of exposure to toxic agents including trichothecene mycotoxins.

Trichothecenes. Ingestion of foods heavily contaminated with trichothecene mycotoxins is well recognized as a cause of neutropenia. This has, however, rarely been described outside of Russia, where it was originally named alimentary toxic aleukia. Affected patients progress to develop pancytopenia.[47] When the platelet count drops below 5000 per millimeter, patients develop necrotic ulcers in the nose, mouth, throat, stomach, and intestines and begin bleeding from the nose, mouth, and gastrointestinal tract. At this stage fatalities are common. The disease was first documented in 1913 in far Eastern Siberia and was reportedly responsible for the death of at least 100,000 Russian people between 1942 and 1948.[48] During that period, alimentary toxic
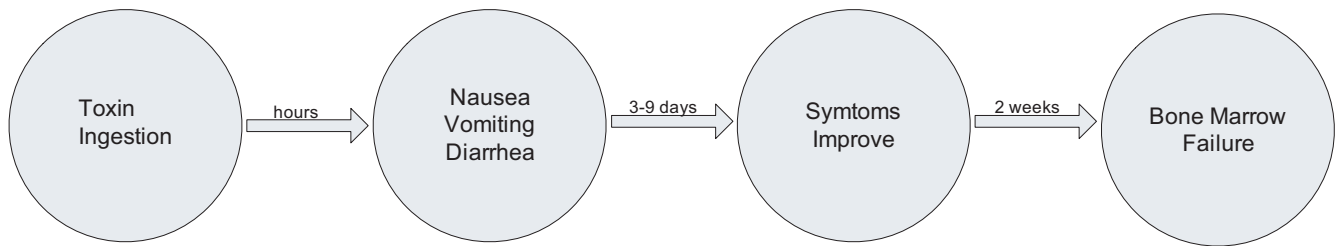
FIG 2. Time course of adverse events preceding bone marrow failure. (Color version of figure is available online.)

aleukia was linked with consumption of grains (including wheat, millet, and corn) that had been covered with snow during winter and were contaminated with *Fusarium* and *Stachybotrys* fungi.

Although this disease is unfamiliar to most primary care pediatricians, it is well known to large animal veterinarians. The fact that trichothecenes cause disease when ingested by farm animals is extensively documented in the veterinary literature.[49-52]

Skin and mucous membrane exposure to the trichothecene mycotoxins can cause a severe skin rash with which clinicians are rarely familiar. The dermatitis, first described among workers handling fodder and those who used infected straw for fuel or slept on mattresses made of infected straw, is characterized by hyperemia, encrustations, and necrosis.[53] Young children may present with a maculopapular rash and numerous painful oral ulcers that make it difficult to eat. An erythematous, indurated lesion was described in an 11-year-old male with severe aplastic anemia; cultures of the lesion revealed *Trichoderma longibrachiatum*.[54]

Diagnostic Approach. A bone marrow biopsy is required to make the diagnosis. In the differential diagnosis, other causes of neutropenia should be considered, including exposure to radiation, leukemia, Fanconi's anemia, cyclic neutropenia, chronic benign neutropenia, and severe chronic neutropenia. To test for Fanconi's anemia, an autosomal-recessive disease, chromosome breakage in peripheral blood lymphocytes should be evaluated.

The evaluation should include a thorough history of exposure to toxic agents such as radiation, chemotherapy, or other drugs or chemicals. Hospital laboratories in the US do not routinely test for trichothecene mycotoxins in human tissue. Identifying the etiologic agent is therefore difficult. The classic history includes diarrhea and rash that persist for about a week before symptomatic improve-

ment. As shown in Figure 2, bone marrow failure follows about 2 weeks later.

Intervention. Therapy is supportive. If exposure to trichothecene mycotoxins is being considered as a possible etiology, the mainstay of treatment is to remove the child from any chronically water-damaged environments to prevent recurrences.

Case 2 Follow-Up. The infant's parents reported that there was a longstanding ongoing toilet leak in the master bedroom of their house. They saw aquatic midges (small winged insects) coming out of the ventilation ducts. The area behind the toilet was chronically wet and black mold was present. An air sample collected in the wall cavity of the master bathroom showed 1932 colony-forming units (CFU) per cubic meter of *Penicillium* species. *Stachybotrys* species was identified microscopically from a sample of the bathroom drywall.

Following an extensive hematologic evaluation, no etiology could be identified and the physician concluded that the infant's bone marrow failure was likely secondary to the fungal exposure in the house. The child improved dramatically after his parents vacated that house and has since been in good health.

Acute Pulmonary Hemorrhage

Although ingestion is the most widely documented route of exposure to mycotoxins, inhalation is increasingly being recognized as an important route.[55] Unlike the gastrointestinal effects secondary to ingestion of mycotoxins, the effects of inhalation of mycotoxins are different for children at different ages of exposure. This may be because the respiratory tract is still developing during the first year

of life, and some mycotoxins have an affinity for rapidly dividing cells.[56]

Illustrative Case History 3. An 8-month-old black male was brought to the emergency room because of cyanosis, tachypnea, and grunting. Mother reported an episode of epistaxis 2 days before admission. The infant had been delivered by cesarean delivery at 37 weeks and had an uneventful neonatal course. He had six previous hospital admissions for afebrile episodes in which he became apneic, limp, and cyanotic and the mother noted frothy blood coming out of the mouth. On each admission he required mechanical ventilation and radiographs of the chest showed bilateral alveolar infiltrates.

Physical examination revealed an agitated infant with a temperature of 36.5°C, pulse of 140 beats per minute, and respirations of 60 per minute with grunting and rib retractions. Blood pressure was 103/70 mm Hg. His skin was cyanotic but without bruises, petechiae, or rashes. There were lacy reticular plaques on the buccal mucosa and the posterior pharynx. The heart sounds were normal. Chest auscultation revealed rales bilaterally. Abdomen was soft and nontender. Twelve hours after admission he developed pulmonary failure and was placed on mechanical ventilation. Bright red blood was noted in the endotracheal tube after atraumatic intubation. Hemoglobin was 7.8 g/dL, and hematocrit was 26.6% with 10.10% reticulocytes. Analysis of the urine showed hemoglobinuria. The infant died on the first day of hospitalization.

Mycotoxins that Should be Considered. This case history of massive pulmonary hemorrhage of unknown etiology should prompt the alert clinician to investigate the possibility of exposure to toxigenic fungi including trichothecene mycotoxins. The link between exposure to fungi in the home environment and acute pulmonary hemorrhage was discovered in 1994 when a case-control study found that 10 infants with life-threatening acute pulmonary bleeding who were admitted to a children's hospital were more likely than a matched group of 30 comparison infants to live in severely water-damaged homes with *Stachybotrys* and other fungi in the indoor air.[57] Exposure to *Stachybotrys* and other toxigenic fungi, including *Trichoderma*, has subsequently been associated with acute pulmonary hemorrhage among infants in other areas of the United States[58-63] and New Zealand.[64] The rapidly growing lungs of infants under 1 year of age appear to be especially vulnerable to the effects of the trichothecene mycotoxins produced by *Stachybotrys* and *Trichoderma*.[65] These mycotoxins are lipid-soluble and readily absorbed by the airways.[65] They are among the most potent protein synthesis inhibitors known.[66] The effects of the trichothecene mycotoxins are more than 10 times greater via inhalation than via intravenous exposure.[65] *Stachybotrys* also produces a hemolysin and several proteinases which can degrade vascular collagen.[67]

There have been a number of studies in animal models that document pulmonary hemorrhage following exposure to the spores of toxigenic fungi. It appears that the effects are more serious for the infant than for the adult animal. Yike and colleagues instilled conidia of *S. chartarum* directly into the tracheas of 4-day-old rat pups. The pups suffered fatal pulmonary hemorrhage.[68] Among adult mice, however, intranasal exposure to *Stachybotrys* spores resulted in severe alveolar and interstitial inflammation with hemorrhagic exudate in the alveoli, but no overt hemorrhage.[69]

Apnea also has been documented following exposure to fungal spores. One day after Yike instilled spores in the tracheas of the rat pups, 28% of them experienced apnea more than 3 seconds in duration.[68] Yike showed that when a dose of 4×10^5 spores per gram was instilled in the trachea of infant rat pups, 73% of the pups suffered fatal pulmonary hemorrhage; when the dose was increased to 8×10^5 spores per gram, 83% of the pups suffered fatal pulmonary hemorrhage.[68] This suggested a dose-response relationship in infant animals between increased exposure to *Stachybotrys* and pulmonary hemorrhage.

Like any new discovery, the findings linking *Stachybotrys* and other fungi to acute pulmonary hemorrhage have undergone careful scrutiny. Analysts not involved in the original study reanalyzed the data employing different assumptions and found that the relationship between *S. chartarum* and infant pulmonary hemorrhage remained statistically significant.[70] Additional studies are needed to determine whether the association between infant pulmonary hemorrhage and exposure to toxigenic fungi is causal.[71,72]

Diagnostic Approach. The causes of acute pulmonary hemorrhage in a previously healthy infant can include trauma, foreign body, infection, and suffo-

cation. The evaluation should include a careful history and physical examination. Laboratory tests include a complete blood count with differential, reticulocyte count and platelet count, manual review of the peripheral smear for evidence of hemolysis, partial thromboplastin time, prothrombin time, and bleeding time, renal function tests, and analysis of urine. The key to acute management of acute pulmonary hemorrhage is endoscopic evaluation of the airway to determine the area of bleeding and possibly the specific site or lesion responsible.[73] Bronchoalveolar lavage should be done to look for hemosiderin-laden macrophages. A finding of more than 50% of the macrophages containing hemosiderin is pathognomonic of pulmonary hemosiderosis. Lack of hemosiderin-laden macrophages may indicate that the infant is experiencing the first occurrence of alveolar bleeding. It takes approximately 50 to 70 hours for hemosiderin-laden macrophages to appear after acute pulmonary hemorrhage.[74] Endoscopy may be indicated to evaluate gastrointestinal bleeding with aspiration, and an electrocardiogram and echocardiogram to look for cardiac disease. The mortality from acute pulmonary hemorrhage in children is 21% despite prompt and thorough evaluation and treatment.[73]

Intervention. Although no randomized controlled trials have yet been performed, it may be helpful to treat infants with acute pulmonary hemorrhage with methylprednisolone (1 mg/kg every 6 hours while intubated and 1 mg/kg/d after extubation).[75,76]

To prevent recurrence, the American Academy of Pediatrics suggests that infants with acute pulmonary hemorrhage not be returned to moldy home environments.[11,77] A significant reduction in recurrent pulmonary hemorrhage was documented following the recommendation that each infant with acute pulmonary hemorrhage be removed from the residence in which the infant was living when the pulmonary hemorrhage occurred.[75] Before routine recommendations to move, five of seven infants had recurrent pulmonary hemorrhage; after the recommendation to move, 1 of 21 had recurrent pulmonary hemorrhage. The Center for Indoor Environments and Health at the University of Connecticut has published guidance for clinicians on the recognition and management of health effects related to mold exposure indoors.[78] Figure 3 shows that infants exposed to extensive indoor fungal

contamination can present with an acute life-threatening event.

> *Case 3 Follow-Up.* Post-mortem examination of the 8-month-old male showed extensive alveolar and interstitial hemosiderosis with pulmonary arterial and right ventricular hypertrophy. Home evaluation after the infant's death revealed a chronically water damaged environment with evidence of toxigenic fungi on walls and other surfaces.

Recurrent Apnea and/or "Pneumonia"

> *Illustrative Case History 4.* A 10-month-old Alaska Native male was brought to the emergency room with the chief complaints of cough, fever, and decreased appetite. The mother reported that the infant had approximately seven "spells" of coughing and not being able to breathe. On arrival the infant's rectal temperature was 105.7°F, the pulse was 144, and the respirations were 44 per minute. He was noted to have retractions and audible wheezes. A radiograph showed active infiltrates in the right upper lobe. He was admitted to the hospital with a presumptive diagnosis of pneumonia and reactive airways disease.
>
> A complete blood count showed a white blood cell count of 10,200 with a differential count of 45% polymorphonuclear forms, 14% band forms, 39% lymphocytes, 2% monocytes, and adequate platelets. The hemoglobin was 10.8 g/dL and hematocrit was 32.1%. Blood chemistry results showed a glucose of 128 mg/dL, urea nitrogen 6 mg/dL, creatinine 0.2 mg/dL, sodium 139 mmol/L, potassium 3.9 mmol/L, chloride 101 mmol/L, and CO_2 23 mmol/L.
>
> The infant was treated with intravenous ceftriaxone and albuterol by nebulizer. After less than 24 hours in the hospital the infant improved and the mother asked that he be discharged. He was discharged home on amoxicillin-clavulinic acid suspension.
>
> Within 3 hours of discharge, the infant was brought back to the emergency room by his mother because he started coughing hard. The infant's temperature was 98.4°F; his pulse was 176 and his respirations were 68 per minute. He was readmitted to the hospital. The past history
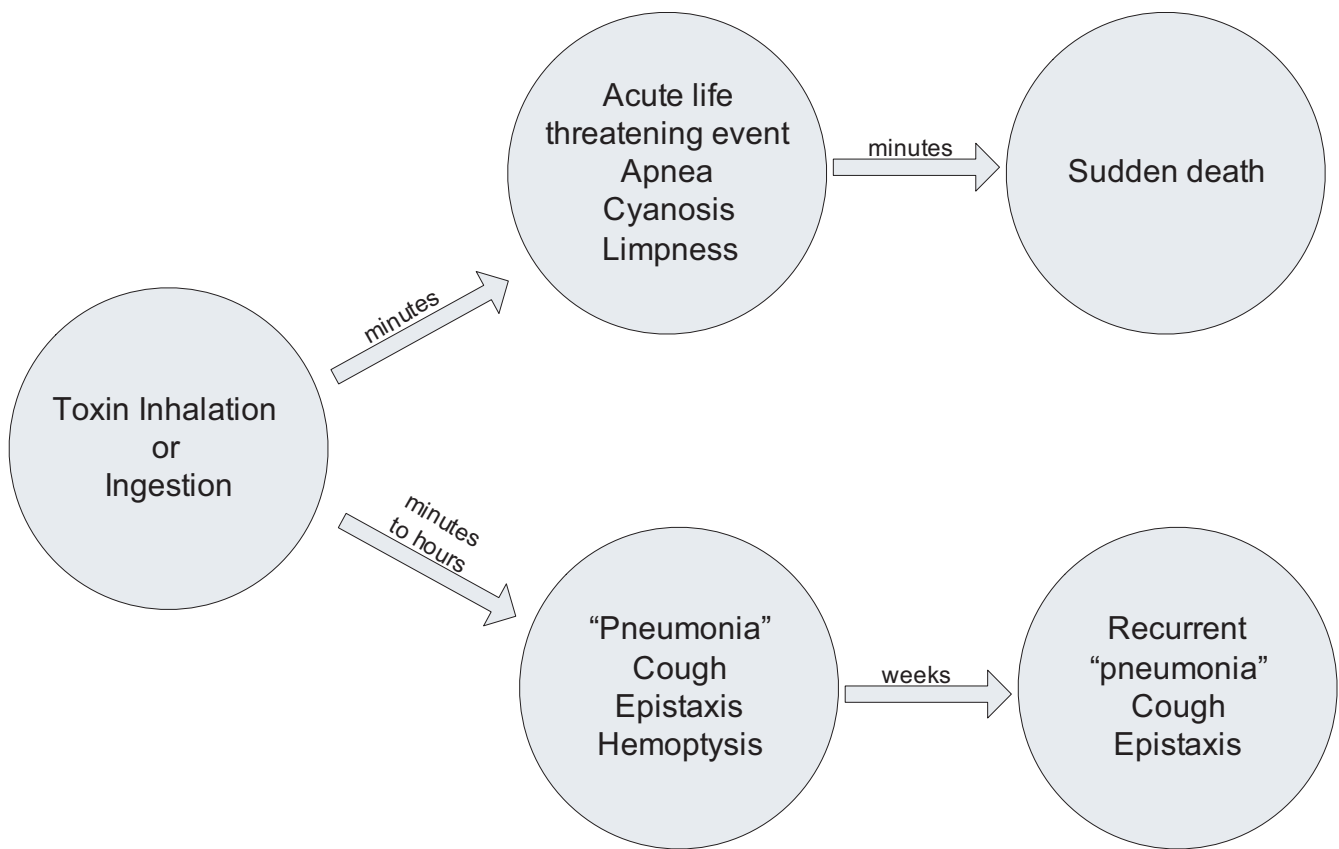
FIG 3. Time course of adverse events preceding sudden death or recurrent "pneumonia." (Color version of figure is available online.)

revealed that the infant was the 6 pound 15.4 ounce product of a full-term pregnancy and spontaneous vaginal delivery. At 2 weeks of age the infant was admitted to the hospital with "concern of not breathing." The mother reported a 2-day history of cough and four cyanotic episodes. After 1 day of observation the infant was breathing well and was discharged home. The infant was diagnosed with "pneumonia" at age 2 months and again at age 5 months; each time he was brought to the emergency room with cough and dyspnea and fleeting infiltrates were seen on chest radiographs. He was treated presumptively with antibiotics. Blood cultures showed no growth of bacteria.

Mycotoxins that Should be Considered. This case history of recurrent apnea, cyanotic episodes, cough, and "pneumonia" in an anemic infant should prompt the alert clinician to investigate the possibility of recurrent pulmonary hemorrhage. The pathologic find-ing after pulmonary hemorrhage is pulmonary hemosiderosis. Infants with pulmonary hemosiderosis have anemia and recurrent or chronic cough, dyspnea, wheezing, and often cyanosis.[77] Unlike older children, hemoptysis may be absent in infants. Pulmonary hemosiderosis in infants has been epidemiologically linked to exposure to toxigenic molds in the home.[57] A pertinent feature is prompt deterioration after returning home from the hospital and subsequent rehospitalization only hours later. One published case study found an association between pulmonary hemosiderosis and exposure to fungi in the indoor environment.[79] *Stachybotrys* was cultured from the bronchoalveolar lavage fluid of a 7-year-old child with pulmonary hemosiderosis in Houston, Texas.[79]

Diagnostic Approach. The evaluation of infants with recurrent apnea and/or "pneumonia" should include a careful history and physical examination. The differential diagnosis can include trauma, foreign body, suffocation, pneumonia, and Heiner's syndrome. Heiner's syndrome is a diagnosis that has been

Table 6. Questions to consider in the history if inhalation of fungi and mycotoxins is suspected

Has the house or apartment been flooded?
Is there any water-damaged wood or cardboard in the house?
Has there been a roof or plumbing leak?
Have occupants seen any mold?
Have occupants noticed a musty smell?

Table 7. Rules of thumb for fungi in the indoor air

Low	<100 CFU/m^3
Medium	101 to 300 CFU/m^3
High	301 to 1000 CFU/m^3
Very high	1001 to 5000 CFU/m^3
Extremely high	>5000 CFU/m^3

CFU, colony-forming units.

applied in children with pulmonary infiltrates, gastrointestinal bleeding, iron-deficiency anemia, peripheral eosinophilia, and failure to thrive[80]; its association with milk is uncertain.

A complete blood count with differential, reticulocyte count, and platelet count should be ordered. Coagulation studies, metabolic panel, cultures of blood and urine, skeletal survey, electroencephalogram, and an endoscopic evaluation of the airway with bronchoalveolar lavage are suggested. If abundant hemosiderin-laden macrophages are found and inhalation of fungal spores is a possible concern, the clinician should consider the questions in Table 6. It is not necessary to measure the quantity of mold spores in the air of an infant's home. If mold is detectable by sight or smell, the parents or guardians should determine the water source and fix it. Fungi cannot grow without water. Evaluation of the types and quantities of fungi in the indoor air of a home is not usually recommended, but may occasionally be done for research purposes. The parents should be advised to consult a certified industrial hygienist with experience in bioaerosol measurements in the indoor air. Infants should not be permitted to remain in the home while testing is done.

If bioaerosol measurements are taken, they may be difficult for the clinician to interpret. Table 7 lists values that can be used as "rules of thumb" for assessing the number of fungal spores found in the indoor air. Mean levels of culturable fungal counts are categorized into five groups (group 1: low < 100 CFU/m^3; group 2: medium 101 to 300 CFU/m^3; group 3: high 301 to 1000 CFU/m^3; group 4: very high 1001 to 5000 CFU/m^3; group 5: extremely high > 5000

CFU/m^3).[81] Concentrations of 100 *Alternaria* conidia/m^3 and 3000 *Cladosporium* conidia/m^3 are levels that may induce respiratory symptoms.[82] Although no indoor guidelines have been set in the United States, experts have suggested that even 150 CFU/m^3 is considered to be high if there are dominant species of fungi along with a few other species.[4,83] The acceptable levels for airborne fungi are in the 200 CFU/m^3 range.[84] This is exclusive of the toxigenic fungi, which are considered unacceptable in indoor air.[6]

Intervention. To prevent growth of molds, parents should be advised to mop up water and remove all water-damaged items (including carpets) within 24 hours of a flood or leak. If this is done, toxigenic fungi will not have the opportunity to grow. If some mold is already present, the affected area needs to be washed with soap and water, followed with a solution of one part bleach to four parts water. Protective gloves and respiratory protection should be worn during clean up.[85] Most importantly, infants and children should be removed from the house until the cleanup is completed. If exposures to fungal toxins were responsible for an infant's symptoms, the infant will usually improve quickly once he is out of the contaminated environment.

> *Case 4 Follow-Up.* The infant's mother raised the issue of inadequate housing; the family of six lived in a one-bedroom trailer with a significant roof leak for the past year and water damage to the interior that had not been remediated. The mother stated that she did not feel comfortable taking the recovering infant back there because of the mold. She relocated to another trailer without water damage and the infant's symptoms disappeared.

Diseases with Long Latency Periods

The pediatrician will only rarely encounter conditions linked to chronic ingestion of fungi and mycotoxins because they may take years to develop. Nonetheless, a familiarity with some of the chronic effects will prepare the pediatrician to answer questions from families and communities. The most serious chronic health effect associated with ingestion of mycotoxins is cancer. The specific mycotoxins consumed will determine the type of cancer.
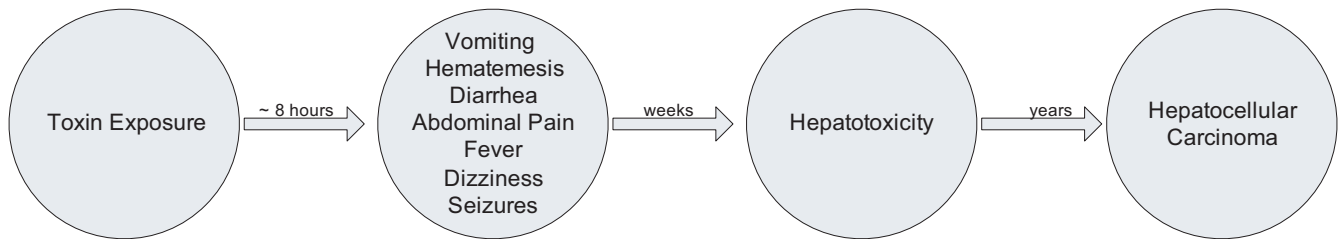
FIG 4. Time course of adverse events preceding hepatocellular carcinoma. (Color version of figure is available online.)

Hepatocellular Carcinoma

The most extensively documented mycotoxin-associated cancer is hepatocellular carcinoma.[86] In the 1960s the aflatoxins were discovered to be potent carcinogens in laboratory animals.[87] In 1993 the International Agency for Research on Cancer determined that aflatoxin B_1 (the most potent of the aflatoxins) was a human carcinogen.[88] Epidemiologic studies clearly document that ingestion of aflatoxin B_1 is a risk factor for hepatocellular carcinoma in humans.[31] Figure 4 shows that hepatocellular cancer follows many years after the acute symptoms of aflatoxin ingestion (vomiting, abdominal pain, hemetemesis, fever, diarrhea, dizziness, and seizures) have occurred. Persons who have both hepatitis B infection and aflatoxin B_1 exposure have a higher risk for hepatocellular cancer than those who have only hepatitis B infection or only aflatoxin exposure.[89] Persons with hepatocellular carcinoma who have been heavily exposed to aflatoxins have more p53 mutations at codon 249 than do those with little exposure to aflatoxins.[90-97] Hepatocellular cancer is rarely diagnosed in persons younger than 20 years of age born in the United States[89] except among Alaska Native children.[98] In hyperendemic areas (such as Taiwan) the mean age at which hepatocellular carcinoma occurs in children is 10.6 years.[99]

Intervention. Recent studies demonstrate that primary prevention of hepatocellular cancer in children is possible. Universal immunization programs for hepatitis B have been shown to reduce the incidence of hepatocellular carcinoma in children in Taiwan[100] and Alaska.[98] Although universal vaccination is the most crucial step, efforts also are underway to reduce children's exposures to aflatoxins. In Qidong, Jiangsu Province, China (where hepatocellular carcinoma is the leading cause of cancer deaths and exposure to dietary aflatoxins is widespread) ongoing clinical trials have documented that oltipraz, an antishistosomal

drug, can lower the biologically effective dose of aflatoxins by decreasing the metabolism of aflatoxin B_1 to its carcinogenic form and increasing the detoxification pathways of its metabolites.[101] In high-risk regions intervention with drugs such as oltipraz and improved storage conditions of staple foods are measures being investigated to reduce the incidence of hepatocellular carcinoma.[102] Table 8 shows that dietary factors, including nutritional deficiencies, appear to increase the risk.[103-114]

Esophageal Cancer

Fumonisins. The fumonisins were discovered in 1988 following an outbreak of equine leukoencephalomalacia in South Africa in 1970.[115] Extensive investigations document that consumption of corn and corn-based products contaminated with fumonisin B_1 causes fatal diseases in farm animals including leukoencephalomalacia in horses and pulmonary edema in pigs.[33] In 1989 and 1990 corn grown in the United States had high levels of fumonisins; fatal outbreaks of equine leukomalacia and porcine prenatal and neonatal mortality and pulmonary edema occurred.[116-118] Epidemiologic studies suggest a link between exposure to fumonisin B_1 and esophageal cancer.[33] Table 9 shows evidence from studies in South Africa, China, Iran, Italy, Kenya, Zimbabwe, Brazil, and the United States linking esophageal cancer to ingestion of fumonisin-contaminated foods.[33,119-167]

Renal Cancer

Ochratoxin A. Tumors of the upper urinary tract have been associated with exposure to ochratoxin A, the most toxic of the ochratoxins.[34] Ochratoxins are produced by *Aspergillus ochraceus*, *Aspergillus alliaceus*, and *Penicillium verrucosum* growing on cereal grains (barley, oats, rye, corn, and wheat) and other items including coffee, milk powder, wine, and beer. The ochratoxins were the first group of mycotoxins to be found after the discovery of the aflatoxins.[168] The

Table 8. Interaction of fungal toxins and risk factors in the development of liver cancer

Geographic region/country	Age-standardized incidence (No. of cases per 100,000)	Fungal infection of major dietary staples	Mycotoxin contamination	Dietary and other risk factors
Jiangsu County, China	Haimen: 52-65 (mortality rate)[103,104]	No studies	Maize: Fumonisin B (0.16-26 mg/kg) Aflatoxin B_1 ($\leq$31 μg/kg) Deoxynivalenol (0.89 mg/kg)[104]	Microcystins[103]
Transkei, South Africa	Kentani: 2.4-7.7 Lusikisiki: 13[105,106]	Maize-based food and home-grown maize[107-109]	Aflatoxin B_1 (16 ng/kg body weight) Healthy maize: fumonisin B (2.0-2.1 mg/kg)	Low socioeconomic status; nutritional deficiencies[110-114]
			Moldy maize: fumonisin B (32-67 mg/kg) Deoxynivalenol (2.9 mg/kg), nivalenol (4.6 mg/kg), zearalenone (1.4 mg/kg), aflatoxin B_1 (0.66 μg/kg), moniliformin (3.5 mg/kg)	

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International Agency for Research on Cancer has determined that there is sufficient evidence in experimental animals for the carcinogenicity of ochratoxin A.[169] Ochratoxin A is categorized as possibly carcinogenic to humans (group 2B).[169]

Balkan Nephropathy

Ochratoxin A is also a potent nephrotoxin. Outbreaks of Balkan nephropathy, a fatal, chronic renal disease occurring in limited areas of Bulgaria, the former Yugoslavia, and Romania, have been associated with ochratoxin A.[170,171] Levels of ochratoxin A are higher in the blood of patients with Balkan nephropathy than in the blood of unaffected people.[169]

Intervention. Investigations are underway to explore the use of aspartame, a structural analog of ochratoxin A and phenylalanine, in preventing the nephrotoxic effects of ochratoxin A exposure.[172] Aspartame competitively prevents the binding of ochratoxin to serum albumin. Investigations are also being conducted to explore ways to reduce the genotoxic effects of ochratoxin. The quantity of DNA adducts that are induced by ochratoxin A in animals can be reduced dramatically by pretreatment of the animals with aspirin and indomethicin, which inhibit prostaglandin H synthase.[173]

Other Associations of Mycotoxins with Health Effects

The associations between liver cancer and aflatoxins and esophageal cancer and fumonisins have been shown in numerous epidemiologic studies. Scientists speculate that other cancers, such as testicular cancer

and cervical cancer, could possibly be associated with mycotoxin exposure; these associations are considered speculative. Further evaluation is merited to reach a definitive conclusion.

Suspected Testicular Cancer

Some researchers speculate that ochratoxin A may be linked to testicular cancer. Epidemiologic information suggests a carcinogenic exposure in early life may play a role in the development of this cancer.[174] Testicular cancer has a peak in occurrence at age 25 to 34 years and is rare among elderly men. It is plausible that exposures to ochratoxin A in early life might induce lesions in testicular DNA. Testicular growth at puberty may promote these lesions to testicular cancer.[174] In humans, ochratoxin A levels were twice as high in umbilical cord blood as in maternal blood at the time of delivery,[175] suggesting that active placental transfer may be occurring.

In experimental studies, in utero transfer of ochratoxin A has been documented in mice,[176] rats,[177] and humans.[178] The hypothesis that ochratoxin A is associated with testicular cancer is consistent with evidence from animal studies showing that the risk of cancer increases if exposure to a carcinogen occurs in utero or in infancy rather than in adult life.[179]

Estrogenic Effects

Zearalenone. Estrogenic effects have been associated with eating foods contaminated with zearalenone, a mycotoxin produced by *Fusarium graminearum* and other *Fusarium* species. Found in corn, wheat, barley, oats, sorghum, sesame, and hay, it was isolated in the

Table 9. Interaction of fumonisins and other fungal toxins and risk factors in the development of esophageal cancer

Geographic region/ country	Age-standardized incidence (No. of cases per 100,000)	Fungal infection of major dietary staples	Mycotoxin contamination	Dietary and other risk factors
Transkei, Southern Africa (rural)	Males: Lusikisiki, 51; Bizana, 37; Butterworth, 43; Centane, 56[106]	Maize: *F. verticillioides* and *F. graminearum*[107-109,119-122]	Healthy maize: fumonisin B (2.0-2.1 mg/kg) Moldy maize: fumonisin B (32-67 mg/kg) Deoxynivalenol (2.9 mg/kg), nivalenol (4.6 mg/kg), zearalenone (1.3 mg/kg), aflatoxin B_1 (0.66 μg/kg), moniliformin (3.5 mg/kg)	Vitamin A, E, and B_{12}, folate, selenium deficiencies[105,111,113,114] Smoking: some relationship Alcohol: some relationship[110,123,124]
Henan, Hebai, Linxian, and Shanxi provinces, northern China	Yancheng, 135; Hebei, 140; Linxian, 108[125]	Wheat, maize, dried sweet potato, rice, soya bean; *Penicillium* spp., *Aspergillus* spp., *F. verticillioides* predominant fungi[126-131]	Healthy maize: fumonisin B_1 (0.7-3.5 mg/kg). One study: fumonisin B_1 (35 mg/kg) Moldy maize: fumonisin B_1 (74 mg/kg) Aflatoxin B_1 (8.6-10 μg/kg), type A (630 μg/kg) and B (2400 μg/kg); trichothecenes, deoxynivalenol (0.02-3.5 mg/kg), nivalenol (0.05-09 mg/kg), zearalenone (0.06 mg/kg)	Low intake of vitamins A and C. Inverse relationship with molybdenum, manganese, zinc; no relationship with pickled vegetables Alcohol intake: no association; smoking: mild risk factor Nitrosamines: Bread inoculated with fungi and tumor induction in rat esophagus[125,132-135]
Mazandaran, Province, Gonbad region, Caspian littoral of Iran	Females: 262 Males: 206[136,137]	*Aspergillus, Fusarium, Penicillium* spp. on maize. *F. verticillioides* and *F. proliferatum* important spp. *Alternaria alternata*[136-140]	Healthy maize: fumonisin B (1.6-6.1 mg/kg) Aflatoxins, polycyclic aromatic hydrocarbons, nitrosamines	Micronutrient deficiencies: iron, manganese, copper, zinc, vitamins A, C riboflavin. Nonsignificant roles for alcohol and tobacco smoking (women). Nass, mixture of opium, lime, and ash, risk factor in men. Thermal irritation with hot tea, bread contaminated with silica, fiber, consumption of sour pomegranate seeds, black pepper, and garlic[136,141-144]
Fruili-Venezia Giullia, northeast Italy	Pordenone Province Males: 17[145]	Fumonisin-producing *Fusarium* species (ref [146])	Fumonisins: fumonisin B_1 (0.15-0.38 mg/kg), fumonisin B_2 (0.06-0.91 mg/kg)	Consumption of polenta. Low intake of micronutrients such as riboflavin and niacin; interactive role of alcohol[145,147]
Western and central Kenya	45% of cases[148]	Maize: *F. verticillioides*[149-151]	Healthy maize: fumonisin B (0.06-1.0 mg/kg) Poor quality maize: fumonisin B_1 (3.6-12 mg/kg)	Dietary patterns and tribal customs vary; alcohol consumption; geographical and ethnic variations[148]
Zimbabwe	Males: Harare: 30 Bulawayo: 59[152]	No studies	Breakfast cereals: total fumonisin B (4.9 mg/kg)[153]	No studies
Charleston County, South Carolina, USA	Black males, 170 (death rate)[154-156]	No studies	Maize-based human foods Fumonisin B_1 (0.1-1.9 mg/kg) Fumonisin B_2 (0.07-0.46 mg/kg)[157]	Low socioeconomic status, tobacco and alcohol ("moonshine" distilled from fermented maize meal); low intake of fresh fruits[154,156]

Table 9. Interaction of fumonisins and other fungal toxins and risk factors in the development of esophageal cancer

Geographic region/ country	Age-standardized incidence (No. of cases per 100,000)	Fungal infection of major dietary staples	Mycotoxin contamination	Dietary and other risk factors
Southern Brazil	Santa Catarina, Parana, Rio Grande do Sul Males: 18[158]	Maize: *F. verticillioides, A. flavus*[159-165]	Animal mycotoxicosis: Fumonisin B_1 (38 mg/kg); Fumonisin B_2 (12 mg/kg) Maize samples: Fumonisin B_1 (2.7-11 mg/kg) Fumonisin B_2 (2.3-10 mg/kg) Maize-based food: Fumonisin B_1 (0.04-12 mg/kg) Fumonisin B_2 (0.01-10 mg/kg) Markets and supermarkets: Fumonisin B_1 (< 32 mg/kg)	Farm workers, smoking and drinking: regional variation; hot beverages (maté and chimarrao)[161,162,166,167]

Adapted from: Joint Expert Committee on Food Additives. Safety evaluation of certain mycotoxins in food. Geneva: World Health Organization; 2001;151-5. Reproduced by permission.

early 1960s after an unusually high incidence of estrogenic signs occurred in swine.[180] Metabolites of zearalenone cause infertility in both males and females.[181,182] It is the only mycotoxin whose known effect is primarily an estrogenic one.[183,184] Also, zearalenone is the only mycotoxin that is useful in commercial agriculture; its derivatives, such as zearalenol, give enhanced growth rates in cattle when used at the proper time and in the proper amounts.[185] Its estrogenic properties make exposure a concern for human health. Although studies are ongoing, researchers speculate that the mycotoxin may be associated with precocious puberty and possibly cervical cancer.[186] It can adopt a conformation resembling 17-beta-estradiol that allows it to bind to the estrogen receptor in target cells.[187]

Zearalenone has been implicated in several incidents of precocious pubertal changes in children.[188] For example, zearalenone was found in the blood of children in Puerto Rico with precocious puberty.[189] It is under investigation as a possible etiology for an increase in premature telarche in the southeast part of Hungary since 1989.[190] Further investigation will be needed before these associations are fully understood.[191]

Ergotism

Ergotism was the first chronic condition associated with ingesting mycotoxins. During the 9th to the 14th century the ergot alkaloids, produced by *Claviceps purpura*, were recognized to cause epidemic disease in persons who consumed moldy rye grain.[192] The first

symptom was a prickly sensation in the limbs, following which the limbs became swollen, inflamed, and subject to sensations of intense heat and cold. Peripheral vasoconstriction resulted in gangrene and limb loss. During the late 16th to the late 19th century, a convulsive form of ergotism involving the nervous system occurred in Europe and the United States.[193]

Ergotism following ingestion of contaminated food is very rare today. It is important for clinicians to recognize the symptoms because they may occur as side effects following therapeutic administration of ergot alkaloids.[194,195]

Patulin

Patulin is suspected to have carcinogenic properties, although the International Agency for Research on Cancer concluded that no evaluation could be made of the carcinogenicity of patulin to humans and that there was inadequate evidence in experimental animals.[196] A study of the combined effects of patulin on reproduction, long-term toxicity, and carcinogenicity suggested a harmless intake of 43 μg/kg body weight per day. On the basis of this work and using a safety factor of 100, the Joint Food and Agriculture Organization /World Health Organization Expert Committee on Food Additives set a provisional tolerable daily intake of 0.4 μg/kg body weight in 1995.[197] A child weighing 10 kg would reach the provisional tolerable daily intake of 4 μg by drinking 80 mL of apple juice, while a 20 kg child would reach the provisional tolerable

Table 10. Interaction of fungal toxins and risk factors in the development of neural tube defects

Geographic region/country	Age-standardized incidence (No. of cases per 100,000)	Fungal infection of major dietary staples	Mycotoxin contamination	Dietary and other risk factors
Southern Texas, USA	Lower Rio Grande valley: 27/10,000[199,201,203]	Case-control study, 1995-1999, Texas Health Department No data on fungal contamination	Maize-based foods: 1.2 mg/kg[156] 1997-1998 study of maize meal: degermed, 0.15 mg/kg; whole 1.2 mg/kg	Tortillas; sphingonine: sphingasine ratio in serum; protective effect of folate supplementation[201,203]
China	Hebei and Shanxi Provinces: 60/10,000[205]	*Penicillium, Aspergillus* spp., *F. verticillioides* in wheat, maize[126,128,129]	Healthy maize: fumonisin B_1 (0.7-3.5 mg/kg); one study 35 mg/kg Moldy maize: fumonisin B_1 (74 mg/kg)	Low socioeconomic status; nutritional deficiencies[125]
Transkei and Mpumulanga South Africa	Umzimkulu: 38/10,000 Mpumulanga: 3.6/10,000[206,207]	*F. verticillioides, F. proliferatum, F. graminearum, F. subglutinans*[109]	Healthy maize: fumonisin B_1 (0.3-0.6 mg/kg) Moldy maize: fumonisin B_1 (5-9 mg/kg)	Low socioeconomic status; nutritional deficiencies[105,110,111,113,114]

Adapted from: Joint Expert Committee on Food Additives. Safety evaluation of certain mycotoxins in food. Geneva: World Health Organization; 2001:151-5. Reproduced by permission.

daily intake of 8 μg by drinking 160 mL of apple juice. Because infants and children consume far more apple juice, kilogram per kilogram, than adults, patulin's potential association with human cancer should be followed closely.[198]

Neural Tube Defects

Fumonisins. Neural tube defects are associated with excessive consumption of foods contaminated with fumonisins. A cluster of neural tube defects that occurred in South Texas in 1990 generated the hypothesis that ingestion of high levels of fumonisins in corn-based products was linked to birth defects such as anencephaly and spina bifida in humans.[199-203] Mexican Americans have neural tube defect rates that are much higher than those of non-Hispanic whites.[200] During the period when the cluster of affected pregnancies occurred, US corn-based products had relatively high levels of fumonisins (two to three times higher than normal). Mexican American women in Texas, unlike their non-Hispanic counterparts, usually eat a lot of corn, in the form of tortillas (90 g per day versus 17 g per day).[199] A case-control study showed that increasing levels of the postpartum sphinganine-to-sphingosine ratio (a biomarker for fumonisin exposure) were associated with an increased odds ratio for neural tube defects.[203] Fumonisins interfere with cellular folate uptake.[204] Studies in China and South Africa lend support to this association (Table 10).[205-207]

The fumonisins can disrupt sphingolipid metabolism.[208] Sphingolipids play a role in membrane and lipoprotein structure and in cell regulation as second messengers for growth factors, differentiation factors, and cytokines.[208] Additional research is being conducted to identify how disruption of sphingolipid metabolism may affect the development of the human nervous system.

Summary and Importance to the Clinician

Pediatricians should be able to recognize that some cases of vomiting illnesses, bone marrow failure, acute pulmonary hemorrhage, and recurrent apnea and/or "pneumonia" may be caused by mycotoxins. Diseases caused by mycotoxins are great masqueraders. Familiarity with the symptoms of exposure to the major classes of mycotoxins mentioned in this review will enable the clinician to ask pertinent questions about possible fungal exposures and to remove the infant or child from the source of the exposure, which could be contaminated food(s), clothing, and furniture, or indoor air. Failure to prevent recurrent exposure often results in recurrent illness. Table 11 lists warning signs that should prompt the primary care pediatrician to ask questions about exposures to fungi.

Pediatricians also should recognize that other conditions, including hepatocellular and esophageal cancer and neural tube defects, although less well-researched, are associated with consumption of foods contaminated with mycotoxins. Pediatricians can serve as better advocates for children and families if they are

Table 11. Clues for the pediatrician

Two or more of the following in infants under 1 year should prompt the primary care pediatrician to ask questions about exposures to fungi and mycotoxins
1. Recurrent afebrile "pneumonias"
2. Recurrent "thrush" or painful sores in mouth
3. Persistent maculopapular rash
4. Normocytic anemia
5. Epistaxis
6. Recurrent apnea
7. Hematemesis
8. Hemoptysis

aware of the short- and long-term consequences of exposures to natural toxins.

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