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Invasive Fungal Infections Acquired from Contaminated Food or Nutritional Supplements: A Review of the Literature

Kaitlin Benedict, **Tom M. Chiller**, and **Rajal K. Mody**

Mycotic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract

Fungi are an integral part of the natural environment and, therefore, play many roles in relation to food: some fungi are used in food production, some are food sources themselves, and some are agents of food spoilage. Some fungi that contaminate food can also be harmful to human health. The harmful but noninfectious health consequences of mycotoxins have been well-characterized, but the extent to which fungi in food pose a risk for invasive infections is unknown. We conducted a literature review to identify cases of invasive fungal infections (IFIs) believed to have resulted from ingestion or inhalation of food, beverages, or dietary supplements (excluding *Saccharomyces* infections). We identified 11 publications describing cases or small outbreaks of IFIs related to foods or beverages and three describing IFIs related to dietary supplements. These food-associated IFIs were predominantly mold infections, and the few yeast infections were associated with dairy products. Suspected foodborne IFIs appear to be rare, but are increasingly described in the electronically searchable literature. They are associated with a variety of foods, are due to a variety of fungal pathogens, and primarily occur in persons with immunosuppressive conditions or other predisposing factors. Various guidelines for high-risk patients recommend avoidance of certain food products that may contain high levels of fungi, but further work is needed to evaluate the effectiveness of these restrictive diets in preventing fungal infections. The relationships between food spoilage, food insecurity, and IFI risk are another area that may warrant further exploration.

Introduction

Fungi are diverse organisms that serve countless roles in the Earth's ecosystems and are abundant throughout the environment (Buckley, 2008). Many fungi are essential to the biotechnology field and have industrial applications in the production of certain medications, foods, and beverages. The yeast *Saccharomyces cerevisiae* is perhaps the most widely recognized example for its role in baking and brewing. Other foods made with fungi include soy sauce and other fermented soybean products and several types of cheese. Some fungi, such as truffles, other mushrooms, and corn smuts, are food sources on their own.

Address correspondence to: Kaitlin Benedict, MPH, Mycotic Diseases Branch, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop C-09, Atlanta, GA 30033, jsy8@cdc.gov.

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Disclosure Statement

No competing financial interests exist.

In contrast, some fungi are harmful to human health. Approximately 300 of the estimated 1.5 million fungal species on Earth are known to cause illnesses ranging from allergic reactions to life-threatening invasive infections (Hawksworth, 2001). Many fungi also synthesize secondary metabolites, some of which can be harmful. Mycotoxins, for example, are major contaminants of crops such as maize, wheat, rice, and numerous other foods (Marroquin-Cardona *et al.*, 2014). Although several health consequences of mycotoxins have been relatively well described (e.g., acute poisoning, cancer, liver disease, and neural tube defects), the global disease burden associated with mycotoxin exposure is unknown (Marroquin-Cardona *et al.*, 2014). Worldwide, an estimated 600 million foodborne diseases occur yearly (WHO, 2015). Some food-borne illnesses could be due to fungi or their byproducts, such as poisoning by mushrooms or mycotoxins. Some fungi that contaminate or spoil food are known pathogens, such as *Alternaria*, *Aspergillus*, *Candida*, *Fusarium*, and mucormycetes (Tomsikova, 2002; Brenier-Pinchart *et al.*, 2006; Pitt and Hocking, 2009). These pathogens primarily infect immunocompromised persons. In general, invasive fungal infections (IFIs) cause devastating illnesses and can result in considerable mortality, yet quantifying their public health burden is challenging (Vallabhaneni *et al.*, 2015a). Similarly, the true risk and frequency of foodborne IFIs are unknown. We review the documented instances of IFIs potentially acquired from exposure to food, beverages, and dietary supplements and describe their common features to inform improved detection and prevention of these often severe infections.

Methods

We searched the biomedical literature databases PubMed and Embase in February 2015 with no date or language restrictions for case reports and outbreaks using the search term “mycoses” and various terms related to food, beverages, and dietary supplements (Technical Appendix). Scopus and Google Scholar were also searched with similar terms, yet no additional publications for inclusion were found. We also reviewed references of relevant articles found during the initial search. We included publications in which the authors suspected a food, beverage, or dietary supplement as the source of an IFI. Numerous reports of *Saccharomyces* infection associated with probiotics are not included in the results because they have been previously reviewed elsewhere; however, the topic is addressed in the discussion.

Results

IFIs from foods or beverages

We identified 11 publications about IFIs believed to be related to a specific food or beverage (Table 1). Eight articles described mold infections (five of which involved mucormycetes), and three described yeast infections.

Mold infections

The most recently reported case occurred in a man with a history of poorly controlled diabetes, acute myelogenous leukemia, and prolonged neutropenia who presented with a unilateral headache, fever, nausea, and vomiting (Lazar *et al.*, 2014). A sinus culture yielded

Mucor circinelloides, and the suspected source of infection was potentially contaminated commercially-produced and widely distributed Greek yogurt, which he consumed several days before developing symptoms (Lazar *et al.*, 2014). This infection occurred during a large recall of the Greek yogurt. The manufacturer publicly announced a quality issue with its yogurts in late August 2013 and voluntarily recalled their products in early September, shortly before *M. circinelloides* was identified as the cause of contamination (FDA, 2013). More than 300 persons who consumed the contaminated yogurt reported illnesses (primarily nausea, vomiting, and diarrhea) to the U.S. Food and Drug Administration (FDA), but there was no evidence that the illnesses were linked to the yogurt (Cadotte, 2013). *M. circinelloides* is not known to cause acute gastrointestinal illness, and it is an extremely rare agent of infection in immunocompromised persons. Some molecular evidence suggests that *M. circinelloides* contains genes potentially involved with secondary metabolite production, so it may be capable of producing toxins (Lee *et al.*, 2014).

Other food- or beverage-associated mucormycotic cases have manifested as gastrointestinal or disseminated infections. In one case, a man from Australia developed acute abdominal pain, diarrhea, and fever 3 h after eating a meal that had been unrefrigerated for a day (Aboltins *et al.*, 2006). The patient's blood and feces cultures grew *Mucor indicus*, and he was successfully treated with 6 weeks of amphotericin B lipid preparations. Due to the unusually rapid symptom onset, it is reasonable to suspect that a toxin may also have played a role in his illness. Another case occurred in a man in South Africa who was hospitalized for acute abdominal pain, septic shock, and organ dysfunction due to an invasive intestinal infection with *Rhizopus* species (Martinello *et al.*, 2012). The report's authors speculated that the source of his infection was home-brewed beer and that his history of alcohol misuse, irritable bowel syndrome, and recent *Salmonella enterica* serotype Typhimurium enteritis predisposed him to the infection. Another report describes a similar infectious source for a man who was ill with pneumonia and occasional abdominal pain for 3 weeks (Sutherland and Jones, 1960). The patient died on the third day of hospitalization. An autopsy revealed that the cause of death was likely pneumonia, but histopathology of the stomach tissue also revealed mucormycosis and a possible gastric ulcer. The localized gastric mucormycosis was suspected to be related to the frequent ingestion of a fermented corn beverage.

The only documented outbreak of potentially foodborne mold infection occurred among hematological oncology unit inpatients in Hong Kong (Cheng *et al.*, 2009). Five patients had culture and histopathology-proven invasive intestinal *Rhizopus microsporus* infection causing abdominal symptoms, and seven additional patients (two with abdominal symptoms and five asymptomatic) had positive stool cultures for *R. microsporus*. The outbreak source was either contaminated cornstarch used to manufacture allopurinol tablets or contaminated prepackaged ready-to-eat food, fungal isolates recovered from both of which were identical to patient isolates by DNA sequencing (Cheng *et al.*, 2009).

Several infections with nonmucormycete molds have also been suspected to be acquired through food, including a case of disseminated *Fusarium moniliforme* infection in a man with acute lymphoblastic leukemia whose diet was entirely based on cereals (Karam *et al.*, 2005). A man from French Guiana who had gastric cancer developed a gastric infection with *Monascus ruber* after consuming dried salted fish; cultures of the remaining fish were also

positive for *M. ruber* (Iriart *et al.*, 2010). Finally, in a sterile hospital unit in France, cooked rice dishes were suspected to have caused three sporadic cases of pulmonary *Aspergillus fumigatus* infection (Vermorel-Faure *et al.*, 1993).

Yeast infections

Invasive yeast infections associated with food were less common in the literature than foodborne mold infections, and all were linked to dairy products. For example, a pregnant woman who frequently consumed organic dairy products developed a bloodstream infection with *Candida kefyr* that was transmitted through the placenta to her premature twin infants (Pineda *et al.*, 2012). Whether any of the dairy products implicated in the report were unpasteurized was unknown. *C. kefyr* is commonly found in raw fermented dairy products, and it is also able to grow in ultra-pasteurized cow's milk (Gadaga *et al.*, 2001; Pineda *et al.*, 2012). Like *C. kefyr*, *Candida catenulata* is naturally present in some dairy products and is an extremely uncommon cause of human infection (Pineda *et al.*, 2012). One case of *C. catenulata* fungemia in a patient with gastric cancer was believed to have resulted from frequent cheese consumption (Radosavljevic *et al.*, 1999). In another publication, a small outbreak of *Blastoschizomyces capitatus* (now *Saprochaete capitata*) infection occurred in 2001–2002 in four patients hospitalized in a hematology ward in Spain (Gurgui *et al.*, 2011). Two patients had fatal disseminated infection, and two had oropharyngeal colonization. The source was vacuum flasks containing milk; *B. capitatus* isolates from the flasks and patient isolates were identical by various molecular typing techniques.

Fungal infections from dietary supplements

Excluding *Saccharomyces* infections, our literature search identified three publications about dietary supplements as the likely source of IFI. One publication describes a bone marrow transplant recipient who began taking multiple oral naturopathic supplements 5 months post transplant and developed hepatic mucormycosis 2 months later (Oliver *et al.*, 1996). Fungi, including *Aspergillus*, *Rhizopus*, and *Mucor*, were identified in 4 of 10 different supplements consumed by the patient. *Mucor indicus* strains from the patient's liver aspirate and from one of the supplements were genetically identical by DNA sequencing. In another report, a 10-year-old girl developed appendicitis and multiple liver abscesses 4 months after starting chemotherapy for a relapse of acute lymphatic leukemia (Bellete *et al.*, 2006). Histopathological examination of the appendix and liver abscess revealed mucormycetes, which DNA sequencing identified from the liver abscess as *Absidia corymbifera* (reclassified as *Lichtheimia corymbifera*). The same fungus isolated from a sample of the probiotic used in the preceding weeks was more than 98% similar to the clinical strain (Bellete *et al.*, 2006). Finally, a fatal case of gastrointestinal mucormycosis occurred in a premature neonate given a dietary supplement to aid in the prevention of necrotizing enterocolitis (Vallabhaneni *et al.*, 2015b). DNA sequencing identified *Rhizopus oryzae* in a tissue sample from the neonate's cecum and from a sample from an unopened bottle of the dietary supplement (Vallabhaneni *et al.*, 2015b).

Discussion

IFIs associated with food, beverages, or dietary supplements appear to be rare, but may be increasingly observed, as 10 of the 14 reports reviewed in this study were published in the last 10 years; this may be due to increased testing for fungal pathogens. In general, IFIs are less common in otherwise healthy persons than in those with immunosuppression or other medical risk factors, and this also appears to be true for suspected foodborne IFIs. In immunosuppressed populations, *Aspergillus* and *Candida*, which most commonly infect the respiratory system and the bloodstream, respectively, are the most common causes of IFIs, whereas the IFIs in this review were primarily due to non-*Aspergillus* molds and generally affected the gastrointestinal tract. Although non-*Aspergillus* mold infections such as mucormycosis can result in substantial morbidity and mortality, the gastrointestinal tract is typically an uncommon site of infection (Roden *et al.*, 2005). Fungal gastrointestinal infections such as aspergillosis may initiate in the lungs; isolated gastrointestinal infection is less common and although it can result from ingestion, the possibility that it may have spread from another site of infection can be difficult to exclude (Eggimann *et al.*, 2006; Kazan *et al.*, 2011). Consistent with the high mortality rates seen with many IFIs (Pfaller *et al.*, 2006), 11 of 20 patients in this review with a known outcome died; however, determining IFI-attributable mortality is often difficult because persons with IFI typically also have other life-threatening comorbidities.

The manifestations and outcomes of food-associated IFIs likely depend on the fungus and host factors. These infections' apparent rarity could be due to the fundamental difficulties associated with diagnosing IFIs, particularly gastrointestinal IFIs. Diagnosis requires a keen clinical sense of suspicion; in several reports, diagnosis occurred after death (Sutherland and Jones, 1960; Vallabhaneni *et al.*, 2015b). In a large study of IFIs identified at autopsy among patients with hematological malignancies, gastrointestinal tract involvement was detected in 35% of *Candida* infections and in 15% of *Aspergillus* infections, indicating that the gastrointestinal tract may be an overlooked site of IFI (Lewis *et al.*, 2013). Food-associated IFIs may also be underdetected due to the challenges of implicating a specific food source given the ubiquitous nature of environmental fungi. This is particularly true for sporadic cases (i.e., not part of an outbreak). Food contaminated with fungi may also appear less likely to cause outbreaks than other more common foodborne pathogens because the clinical manifestations of IFIs strongly depend on host factors. In several cases, patients had a disruption in their intestinal mucosal barrier. The gastrointestinal microbiome is likely an additional factor that may influence an immunosuppressed host's susceptibility to IFIs. Fungi such as *Candida,* among hundreds of others, are an integral part of the normal gastrointestinal flora, but the relationships between these commensal fungi, potentially pathogenic exogenous fungi, and digestive disease pathogenesis are complex and deserve future study (Wang *et al.*, 2014; Gouba and Drancourt, 2015).

Efforts to prevent foodborne infections in high-risk patients focus on restricting or eliminating intake of foods that could contain pathogens. These diets are called "low-microbial," "low-bacterial," or "neutropenic" diets and are typically recommended for hematopoietic stem cell transplant (HSCT) recipients; however, there is little evidence to demonstrate their effectiveness (Tomblyn *et al.*, 2009; van Dalen *et al.*, 2012). In addition,

specific recommendations vary among institutions regarding which patients should be placed on a restrictive diet, when to initiate and discontinue the diet, and which foods should be restricted (Smith and Besser, 2000; van Dalen *et al.*, 2012).

Comprehensive guidelines for preventing infectious complications among HSCT recipients, cosponsored by the U.S. Centers for Disease Control and Prevention and nine other American, Canadian, and European agencies, were published in 2009 (Tomblyn *et al.*, 2009). Their specific recommended food safety practices include avoiding raw or undercooked meat, eggs, or seafood and avoiding certain fresh fruits and vegetables, particularly those that cannot be washed or peeled. Recommendations particularly relevant for preventing IFIs include avoiding nonpasteurized milk products, cheeses with molds (e.g., blue cheese and gorgonzola), uncooked brewer's yeast, maté tea, (Vieira *et al.*, 2010) and herbal and nutritional supplements (Tomblyn *et al.*, 2009). Surveys to evaluate the presence and diversity of fungi in hospital food products show that fungal contamination with potential human pathogens such as mucormycetes and *Aspergillus* does occur, particularly in pepper, teas, and fruits, suggesting that these foods may pose a risk for immunocompromised patients (De Bock *et al.*, 1989; Bouakline *et al.*, 2000; Brenier-Pinchart *et al.*, 2006); however, the associated infectious risk remains largely unknown and likely depends on many other environmental, host, and pathogen factors. Future work to assess the role of a restrictive diet in preventing infections in immunosuppressed patients is needed.

Three of the cases reviewed in this study were associated with dietary supplements not intended to contain fungi (Oliver *et al.*, 1996; Bellete *et al.*, 2006; Vallabhaneni *et al.*, 2015b). Because dietary supplements are regulated as foods rather than as drugs, the FDA does not require premarket review or demonstration of safety and effectiveness for these products. Some dietary supplements intentionally contain *Saccharomyces cerevisiae* and have been used for decades as probiotics to promote intestinal health and to treat some diarrheal illnesses (Venugopalan *et al.*, 2010). These are sometimes given to prevent *Clostridium difficile* infection and other gastrointestinal conditions in critically ill patients, but their effectiveness is unclear, and poses a risk of *Saccharomyces* bloodstream infection in this population (Cohen *et al.*, 2010; Venugopalan *et al.*, 2010; Allen, 2015). However, clinicians should weigh the potential benefits of probiotics against the risk of IFI. We did not include cases of invasive *Saccharomyces* infection associated with probiotics in our review as the topic is comprehensively reviewed elsewhere (Enache-Angoulvant and Hennequin, 2005; Munoz *et al.*, 2005).

Food contamination with pathogens can occur at any point in the production chain. A few reports in this review suggest that the IFIs were likely attributable to fungal contamination during processing (Lazar *et al.*, 2014; Vallabhaneni *et al.*, 2015b), whereas others may have been related to fungi intrinsically present in certain products (Sutherland and Jones, 1960; Radosavljevic *et al.*, 1999) or to improper storage (Aboltins *et al.*, 2006; Gurgui *et al.*, 2011). Fungal food spoilage accounts for the loss of an estimated 5 to 10% of all food production (Pitt and Hocking, 2009) and is a particularly relevant topic for consumers. Chemical preservatives are commonly added to foods to prevent bacterial and fungal growth, but consumer preference for minimally-processed foods (Nielsen Global Health and Wellness

Survey, 2015) has prompted the food industry to explore new methods for processing and preservation. Whether these trends will influence risk for negative health effects from fungi in foods is unclear.

If fungal spoilage presents a risk for IFI, food insecurity could be an additional risk factor through its influence on a person's likelihood of consuming spoiled foods. For example, during focus groups with resource-limited individuals in New Jersey, reported food management practices included removing mold from cheese and grains and removing spoiled parts of fruits and vegetables (Kempson *et al.*, 2003), although the U. S. Department of Agriculture (USDA) advises discarding bread, baked goods, soft fruits and vegetables, and soft cheeses containing visible mold (USDA, 2013). In contrast, a nationwide survey of Special Supplemental Nutrition Program for Women, Infants, and Children participants found that 94% would throw away an entire package of cream cheese or cottage cheese if mold was present (Kwon *et al.*, 2008). Elderly persons may be especially vulnerable to food insecurity due to economic factors, which is concerning because immunecompromising conditions are more common in this population; a systematic review of studies from developed countries found some evidence that food expenditures and intake decreased as individuals transitioned from employment to retirement (Conklin *et al.*, 2013). Avoiding mold spoilage may be even more difficult in developing countries where food insecurity is an even more widespread problem.

Conclusions

IFIs associated with food, beverages, and dietary supplements are associated with various fungi and primarily affect the gastrointestinal tract in persons with immunosuppressive conditions. Disruption of the intestinal mucosal barrier may also be a contributing factor. Although these infections appear to be very rare based on the number of documented cases, they can lead to considerable morbidity and mortality. They can also be challenging to diagnose and potentially difficult to definitively attribute to a specific food, particularly for cases that are not part of an outbreak. Various food products have been implicated, including dietary supplements. Additional work is needed to assess the role of restrictive diets in preventing foodborne fungal infections in high-risk patients and to better understand consumers' knowledge and practices related to fungal food spoilage.

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Technical Appendix: Search Terms

PubMed

(((“Mycoses”[Majr]) AND ((((food*[tiab] OR eating[tiab] OR ate[tiab] OR eat[tiab] OR eats[tiab] OR ingest*[tiab] OR consumption[tiab] OR consume[tiab] OR consumes[tiab] OR consumed[tiab] OR consuming[tiab] OR edible*[tiab] OR swallow*[tiab] OR drink*[tiab] OR beverage*[tiab] OR probiotic*[tiab] OR dietary supplement*[tiab] OR herbal supplement*[tiab])) OR “Food”[Mesh]))) AND ((“Case Reports” [Publication Type]) OR “Disease Outbreaks”[Mesh])

Embase

Search string ID No.	Search string
1	*mycosis/or exp *candidiasis/or *chytridiomycosis/or exp *dermatomycosis/or exp *dimorphic fungal infection/or exp *eumycetoma/or exp *fungal endocarditis/or exp *fungal eye infection/or *fungal genital infection/or exp *fungal meningitis/or *fungal sinusitis/or exp *fungus ball/or *geotrichosis/or exp *hyalohyphomycosis/or exp *lung mycosis/or exp *microsporidiosis/or exp *mycosis by basidiomycetes/or *mycotic aneurysm/or exp *oomycosis/or *otomycosis/or *perianal mycosis/or exp *phaeohyphomycosis/or exp *pneumocystosis/or *subcutaneous mycosis/or exp *systemic mycosis/or exp *vagina mycosis/or exp *zygomycosis/
2	exp food/or food contamination/or food additive/or food composition/
3	(food$ or eating or ate or eat or eats or ingest$ or consumption or consume or consumes or consumed or consuming or edible$ or swallow$ or drink$ or beverage$ or probiotic$ or dietary supplement$ or herbal supplement$).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4	2 or 3
5	case report/
6	epidemic/
7	5 or 6
8	1 and 4 and 7

Table 1

Invasive Fungal Infections Resulting from Exposure to Foods, Beverages, or Dietary Supplements

Author and publication year	Country	Patient population or predisposing factors (*n*)	Site or type of infection (*n*)	Suspected source	Fungus	Outcome (*n*)
Mold infections						
Sutherland and Jones (1960)	South Africa	Unknown medical history, but possible gastric ulcer (1)	Stomach	Fermented corn beverage	Unspecified mucormycete	Died
Vermorel-Faure *et al.* (1993)	France	Patients in a sterile hospital unit (3)	Pulmonary	Cooked rice	*Aspergillus fumigatus*	Unknown
Oliver *et al.* (1996)	United States	Bone marrow transplant (1)	Liver	Naturopathic medicine	*Mucor indicus*	Survived
Karam *et al.* (2005)	France	Leukemia (1)	Disseminated to skin	Cereal	*Fusarium moniliforme*	Survived
Aboltins *et al.* (2006)	Australia	History of intravenous drug use (1)	Fungemia	Unrefrigerated meal	*Mucor indicus*	Survived
Bellete *et al.* (2006)	France	Leukemia (1)	Appendix, liver	Probiotic	*Absidia corymbifera*	Survived
Cheng *et al.* (2009)	China	Hematology/oncology unit (5 invasive infections, 2 mucosal infections, 5 colonized)	Intestine	Prepackaged food or allopurinol tablets	*Rhizopus microsporus*	4/5 invasive, 1/2 mucosal, 0/5 colonized died
Iriart *et al.* (2010)	French Guiana	Gastric cancer (1)	Stomach	Dried salted fish	*Monascus ruber*	Died
Martinello *et al.* (2012)	Australia	Alcohol misuse, irritable bowel syndrome, and *Salmonella* Typhimurium enteritis (1)	Intestine	Home-brewed beer	*Rhizopus* sp.	Survived
Lazar *et al.* (2014)	United States	Diabetes, leukemia, and neutropenia (1)	Rhinocerebral	Yogurt	*Mucor circinelloides*	Died[a]
Vallabhaneni (2015b)	United States	Premature infant (1)	Intestine	Dietary supplement	*Rhizopus oryzae*	Died
Yeast infections						
Radosavljevic *et al.* (1999)	France	Gastric cancer (1)	Fungemia	Cheese	*Candida catenulata*	Died[a]
Gurgui *et al.* (2011)	Spain	Hematology unit (2 infected, 2 colonized)	Disseminated (2), oropharyngeal colonization (2)	Vacuum flasks of milk	*Blastoschizomyces capitatus*	Died (2), survived (2)
Pineda *et al.* (2012)	United States	Pregnant woman (1), premature infants (2)	Fungemia and chorioamnionitis	Organic dairy products	*Candida kefyr*	Survived

Excluding cases of *Saccharomyces* infection related to probiotics.

[a]Due to underlying condition.

n, number of persons.