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REVIEW

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Fungi associated with drug recalls and rare disease outbreaks

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Abstract Fungi rarely cause disease outbreaks associated with use of microbe-contaminated drugs. These rare episodes typically involve a restricted spectrum of common environmental species with relatively low virulence, rather than classical pathogens. Review of data involving over-the-counter contact lens solutions and prescription drug-related recalls revealed six episodes during the past decade with significant adverse health and financial impact (including loss of vision and death). Contaminations involved fungi mostly identified with the genera *Aspergillus, Exserohilum, Fusarium, Paecilomyces*, and *Rhizopus.* These organisms are noted for their capacity to produce resistant morphotypes (chlamydoconidia, ascospores) under various adverse conditions, generally with temperature survival/tolerances markedly in excess of maximal growth temperatures. High constituent levels of melanin, trehalose and heat-shock proteins facilitate differential survival of morphotypes following exposures to toxic chemicals and temperatures above 80 °C. Adverse environmental factors that induce resistant morphotypes are suggested to occur more readily in situ than during in vitro testing. Rare unexplained, sporadic drug contamination episodes with select thermotolerant fungi may relate, in part, to resistant dormant stages.

Keywords Fungal drug contaminants · FDA recalls · Contact lens solutions · Temperature tolerances

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Introduction

Over the past decade, disease episodes caused by eukaryotic microorganisms associated with contaminated pharmaceuticals and Food and Drug Association (FDA)-motivated product recalls have been infrequent and related to microorganisms that seldom cause disease in normal individuals [14–16, 70]. The recalls, which have involved both over-the-counter (OTC) and prescription drugs, were mostly of FDA Class 2 category, i.e., exposure to or use of the violative product may cause temporary or medically reversible health consequences, but the probability of a serious health effect is remote [27]. Data on the episodes of drug contamination by fungi are not readily apparent from the information available from drug recalls [26, 61, 66, 71]. We have extrapolated from these available data, particularly the FDA safety alerts/recalls, eukaryotic episodes: single or reoccurring events at a manufacturing or processing site involving one or more products (Table 1). We estimated that about 1 % or less of the microbial-related drug recalls (often only identified under "lack of sterility assurance" or "particulate") over the past decade involved eukaryotic microorganisms associated with disease outbreaks. With two exceptions [15, 69, 70], these disease episodes involved prescription drugs and a limited spectrum of fungi [10, 13, 14, 16, 26, 45] (Tables 2, 3). The involved fungi are ubiquitous species complexes in association with plants and soils and relatively rare causes of infections of immune-competent individuals. Aside from *Exserohilum rostratum*, these or closely related species are known to colonize indoor surfaces, particularly those involved with water sources and food preparation and storage [3, 6, 20, 34, 40, 44, 56, 57, 64, 76] (Table 4).

Table 1 Estimated drug contamination episodes involving eukaryotic microorganisms eventuating FDA drug alerts and recalls (2004–2013)

Year	Episodes[a]	Total recalls
2004–2010	23	~1,750
2011	2	~440
2012	4	~365
2013	2[b]	>250[c]

Selected references: (Chang et al. [15], Verani et al. [70], CDC 2012 [14], CDC 2013 [13], FDA 2013 [26], Staes et al. [61], Sutton and Jimenez [66], Wang et al. [71], Yoder et al. [75])

[a] Exclusive of microbial episodes with biologics and supplements

[b] As of 8/30/2013, one episode with an inferred indolent infection and 26 patients in question

[c] As of 6/30/2013, the final numbers to be determined

Table 2 Incidences of documented over-the-counter contact lens solution-associated microbial keratitis (USA 2004–2007)

Eukaryotic keratitis	Incidences per 10,000 CLS per year[a]
Fusarium spp. [165]	0.5–0.8 (ReNu with MoistureLoc)
Acanthamoeba spp. [145]	0.001–0.2 (Complete Moisture Plus)

Individual cases documented during outbreak studies. Selected references: (Chang et al. [15], Verani et al. [70], CDC 2012 [14], Tu and Joslin [69], Stapleton and Carnt [62])

[a] 1–4 (20 per overnight–extended)

OTC drug-related outbreaks and recalls

Sutton and Jiminez [66] noted that 23 of 142 microbial-related OTC recalls between 2004 and 2011 involved yeasts and molds. Of these, one involved an OTC contact lens disinfection solution with worldwide distribution of millions of units [15, 69, 70]. Disproportionate incidences of rare *Fusarium* keratitis (FK) with ReNu with MoistureLoc (B&L Rochester NY) were associated with extrinsic contamination during use (Table 2). Worldwide product recalls resulted in a reduction of FK to pre-outbreak levels [62, 75]. In contrast, an outbreak of *Acanthamoeba* keratitis (AK) linked to the use of Complete MoisturePlus (AMO Santa Ana CA) was reduced by only 10–25 % from the outbreak peak upon recall [62, 75]. These two outbreaks overlapped in time and in control groups used for the statistical analyses, but were essentially discrete in their capacities for extrinsic contamination of contact lens cases [1, 78]. *Fusarium* and *Acanthamoeba* in drains may be repeatedly exposed to heat shock and disinfectant chemicals known to select for survival of resistant morphotypes [1, 15, 62, 75, 76]. Mutualistic survival enhancement may occur in such environmental niches. Loss of preservative activity through its uptake by the hydrogel contact lens, or from evaporation and drying of these formulations coupled with inappropriate hygiene practices of the user [e.g., reuse of solution (i.e., the topping-off of solution in the case) and failure to replace or sterilize cases regularly] were considered risk factors for the contamination of the solutions that potentiated keratitis [1, 15, 25, 35, 69, 73, 78].

The contact lens solutions initially contained preservatives sufficient to meet extant antimicrobial challenge requirements. Unfortunately, the standard tests were insufficient for predicting the unique and adverse interactions of select formulations and selective effects of consumer use, particular poor hygienic practices, for protection against eukaryotic microorganisms [15, 69, 70]. The standard challenge tests are currently undergoing re-evaluations [25, 55,

Table 3 Molds associated with infection outbreaks and drug recalls: multiple countries 2009–2013

	Main species complex	Product	Patients	Disease	References
A	*Rhizopus microsporus*	Allopurinol tablets	12	Intestinal zygomycosis	Cheng et al. 2009 [16]
B	*Fusarium solani*	Cefuroxime basic salt solution	9	Endophthalmitis	Cakir et al. 2009 [10]
C	*F. incarnatum–equiseti* *Bipolaris hawaiiensis*	Brilliant Blue Green dye	21	Endophthalmitis	CDC 2012 [14] Mikosz et al. 2014 [11]
		Triamcinolone	~26		
	Exserohilum rostratum	Methylprednisolone acetate	~100	Meningitis	CDC 2012–2013 [13]
C	*Aspergillus fumigatus*		1	Meningitis	
	Mixed species? (*Paecilomyces formosus*)		~650*	Spinal epidural abscesses–meningitis	
C	*Aspergillus* (*Alternaria, Cladosporium Penicillium*)	Methylprednisolone acetate	1, ~26?	Skin abscesses	FDA 2013 [26] CDC 2013 [13]

() poor or negligible growth at 37 °C in vitro, but associated with rare infections. Of the referenced "outbreaks" alert recalls, including the two OTC contact lens solutions, the contamination was extrinsic to the initial production. The *Rhizopus* exposures were both intrinsic and extrinsic

A both intrinsic and extrinsic contamination possible, ***B*** geographically restricted clinic-surgery events, ***C*** outbreaks associated with compounding pharmacies

[a] Approximately, 650 additional patients with meningitis and/or epidural abscesses, etc. mostly associated with *E. rostratum* and at least 22 additional fungi and bacteria

Table 4 Indoor habitats of molds associated with disease outbreaks and drug recalls

Species complex	Representative sub-strata
Aspergillus fumigatus	Rubberized incubator seals, cellulosic wall boards behind incubators and refrigerators
Bipolaris hawaiiensis	Indoor plants
Paecilomyces formosus	Indoor plants
Paecilomyces variotii	Moist surfaces (wood, cosmetics, drugs), food items
Exophiala dermatitidis	Warm water seals, dishwashers
Fusarium solani [a]*F. petroliphilum* [a]*F. keratoplasticum*	Showers and drains, rubber seals, tile grout, cosmetics
F. oxysporum *F. incarnatum–equiseti*	Food products, potted plants
Rhizopus microsporus	Food products
Exserohilum rostratum	(Plants?)

Selected references: (Anaissie et al. [3], Mehl and Epstein [44], Short et al. [56, 57], Houbraken et al. [34], Lian and Hoog [40], Summerbell et al. [64], Zalar et al. [76], Samson et al. [52], Mehl and Epstein [43])

[a] These are molecular-based species in the *F. solani* complex identified with drains

68]. OTC formulations, particularly those that may involve the eye area, need efficacy against fungi as well as bacteria for the intended period of use.

From 2009 to 2011, there were several Class 2 recalls of popular OTC drugs (e.g., acetaminophen, ibuprofen, and calcium carbonate/magnesium hydroxide tablets) because of unacceptable musty odors [53]. Disease outbreaks and direct microbial contamination of the OTC formulations did not occur, but nausea, diarrhea, or the organoleptic rejection of the needed medications was discussed as a need for the manufacturers' recalls. An extensive consortium investigation found that trace levels (parts per trillion) of volatile 2, 4, 6-tribromoanisole (TBA) had been released from fungicide-treated wood pallets with uptake of the volatile TBA by polyethylene-based plastic containers and subsequent taint of their contents [53]. The wood pallets treated with 2, 4, 6-tribromophenol (TBP) in South America presumptively were colonized with *Paecilomyces variotii*, a species complex recognized for the production of musty odors via active haloanisole metabolism [72]. This common species complex has been identified with cork odor in wine, musty food spoilage, contamination of multiple commercial products including pharmaceuticals, and as a rare opportunistic pathogen [33, 34, 52]. We noted recalls of preserved hydrocortisone creams contaminated during manufacturing or processing by *P. variotii* during this study, but without details of adverse consequences to users [30]. In 2013, through December, recalls of bevacizumab (processed by a compounding pharmacy) and a preserved OTC carboxymethylcellulose-based eyedrop (subject to spoilage during use), and injectable saline formulations were recalled because of potential fungal contaminants [26]. Information on adverse health events and involved species is currently sparse and incomplete.

Recently, the mold contaminants from four lots of intravenous magnesium sulfate solution and one lot of dexamethasone sodium phosphate solution, produced by a compounding pharmacy, were identified and characterized by genotype [8, 26]. The sulfate solution yielded *Hamigera insecticola* (*Paecilomyces*-like anamorph), *Neosartorya hiratsukae* (*Aspergillus*-like anomorph) and isolates of the *Penicillium chrysogenum–P. rubens* complex. *Penicillium rubens* was obtained from the phosphate solution. These two species of *Penicillium* have distinct genotypes, but similar and overlapping phenotypes with a complex that encompass a number of cryptic species [9, 31]. Genotype analyses have demonstrated that both species in nature seem heterothallic for the mating type genes at a near 1:1 ratio. All of the taxa identified with the mold-contaminated solutions from this compounding pharmacy have the potential for producing stress-resistant stages including ascospores [7, 54]. With the exception of *P. chrysogenum*, these taxa have no history of involvement in rare opportunistic infections. Rare opportunistic disease potential, including keratitis, has been indicated for *P. chrysogenum*, but prior to the recognition that the taxon was a complex of cryptic species. In the extensive and expensive (costs over $800 K) follow-up of 1309 patients potentially exposed to contaminated salines, Boyce and collaborators [8] did not identify any associated mold disease.

The recent multistate fungal meningitis outbreak associated with three lots of methylprednisolone acetate (MPA) with sporadic fungal incidence from a single compounding pharmacy has accentuated the potential of certain environmental molds for adventitious pathogenicity. *Exserohilum rostratum*, previously recognized as a rare cause of sinusitis and keratitis [50], is presently involved with near 14,000 individuals potentially exposed to three lots of contaminated steroids [5]. More than 750 infections and at least 64 deaths have been investigated and implicated [4, 13, 18, 28, 37, 38, 41, 49, 58].

Resistant stages

Fusarium spp., the complex of molds generally identified as the contaminants in drug-associated episodes, as well as *Acanthamoeba* spp. are known to produce discrete morphotypes with varying degrees of resistance to environmental stresses such as heat, desiccation, starvation, and toxic chemicals [2, 36] (Table 5).

Table 5 Characteristics of eukaryotic species complexes facilitating contamination of drugs; properties favoring persistence in adverse environments

Species complex	Zygospore (Z) Ascospore (A)	Sclerotia	Chlamydo-conidia	Thermotolerant (hsp-trehalose)[a]	Hsp-trehalose
Rhizopus microsporus	**Z**	–	+	+	+
Paecilomyces variotii	**A**	+	+	+	+
Fusarium solani-oxysporum complexes	**A**	+	+	–	+
F. incarnatum-equiseti	**(A?)**	+	+	–	+
Aspergillus fumigatus	**A**	–	+	+	+
Exserohilum rostratum	**A**	–	+	+	+
Acanthamoeba spp.	_	Cell clusters	Pre-cysts, cysts	(+)	+

[a] Hsp: Heat-shock proteins (ranges extrapolated to encompass data in complexes with cryptic species)

The rate and extent of the development of these resistant morphotypes as well as their degree of resistance to environmental stress appear to vary by strain. In part, these phenotypic variations reflect constituent levels and complex interactions of polyols (e.g., mannitol), trehalose, melanin, various shock proteins, and associated enzymes in a given cell at the time of stress [17, 50, 51, 59, 60]. Such constitutive protection may allow certain morphotypes (e.g., *Fusarium*) to survive under conditions that normally result in loss of viability [2, 36]. During drug processing, microorganisms in excipients and those found in the general environment are exposed to a variety of adverse stresses, particularly temperature shifts, known to reduce their viability and recoveries [21, 22]. In rare instances, however, resistant fungal morphotypes may persist when a final sterilization step is lacking. Houbraken et al. [33] implicated the sexual stage of *P. variotii* as one of the causes of heat-resistant food spoilage. Sporadic and latent mold spoilage of OTC drugs during storage or use may occur after mild disinfection procedures, particularly if preservatives are lacking.

In compost and hot springs, natural environments for many *Aspergillus*, *Curvularia*, *Exserohilum* and *Fusarium* strains may persist in metabolically active states at temperatures in excess of the 62–65 °C recorded in vitro for maximal growth of thermophilic fungi [42, 47]. *Exserohilum rostratum* may produce chlamydoconidia and ascospores and is recognized as thermotolerant, but a role for these morphotypes in the epidemiology of the meningitis outbreak (although possible) is unknown to us. The three contaminated lots of methylprednisolone yielded a variety of bacteria and fungi usually susceptible to routine disinfection and sterility procedures. This suggests a failure or lack of sterility and quality control procedures. Routine quality control protocols may not be sufficient for detection of resistant morphotypes with sanitize–disinfection procedures used with heat-sensitive formulations.

Exophiala dermatitidis, a thermotolerant rare opportunistic pathogen (maximal growth in vitro, 42–47 °C), was identified as the cause of meningitis in five patients receiving injectable MPA from a compounding pharmacy [12, 77]. This species, only sporadically isolated as an aerial contaminant or in general environmental sampling, is a profuse colonizer of steam baths and dishwashers and is capable of surviving repeated exposures to 60–80 °C [74, 76]. Moreover, dried fungal morphotypes, including conidia and mycelia of various genera, may demonstrate prolonged temperature/survival tolerances up to and exceeding 100 °C [11, 65].

Temperature influences

Most fungi recovered in culture are mesophiles with optimal growth temperatures below 30 °C, maximal temperatures below 40 °C and short-term biocidal temperatures for aqueous suspensions in the range of 55–65 °C. Some strains may grow near 0 °C. Thermophilous fungi in the mycology literature encompass both thermotolerant and the less common thermophilic strains. Thermotolerant fungi have been considered in various studies as those with growth below 20 °C, nearly equivalent growth in the mid-20 °C with 37 °C, or nearly equivalent growth at 34 and 45 °C (maximal about 48 °C) [43, 46]. Thermophilic fungi have been categorized as strains with maximal growth near or above 50 °C (max about 62 °C in vitro) and no growth below or near 20 °C, whereas thermotolerant strains grow below 20 °C with maximal growth near 45 °C [19, 32, 46, 48]. In clinical medicine, visually detectable "good" growth at 37 °C has often earned a thermotolerant categorization. These temperature categories have been reproducible in general for active growth in vitro for many species and given strains, but variation within a species complex is not uncommon. Data on temperature survival/tolerances or heat resistance of fungi are infrequently provided or emphasized in sources other than the food-related literature [6].

Table 6 Potential and possible thermotolerances (°C) among fungal species identified with recalls of contaminated pharmaceuticals

Fungal species complex		Tolerances °C[a]	
Anamorph	Teleomorph	Anamorph	Teleomorph
Aspergillus fumigatus	Eurotiales *Neosartorya*	60–70	70–90+
Paecilomyces variotii–fumosus complexes	Talaromyces *Byssochlamys*	65–85	90–100+
Fusarium solani–oxysporum complexes	Hyocreales *Necteria*	50–55	65–70
F. incarnatum–equiseti complexes	Hypocreales polyphyletic	42–55	(70)
Exserohilum rostratum	Pleosporales *Setospheria*	45–50	65
Rhizopus microporus	Zygopora *Mucorales*	55–60	90

Selected references: (Beuchat and Pitt [6], Houbraken et al. [33], Samson et al. [52], Suryanarayanan et al. [65], Swilaiman et al. [67], Leach and Cowen [39], Delgado et al. [23])

[a] Survival tolerances of varied inocula with possible inclusion of resistant morphotypes in moist suspension for at least 10–90 min; survival tolerances may be increased for dry heat exposures and in the presence of increased organics (implied presence)

Various thermophilic, thermotolerant, and mesophilic strains reviewed in this report had been identified on the basis of phenotype similarities. Molecular sequencing studies, particularly those within the species complexes with histories of uncommon infections (*Aspergillus fumigatus*, *Fusarium solani*, *Paecilomyces variotii*) [32, 34, 56, 63, 67], have shown the presence of discrete cryptic species. The temperature tolerances of the ascospores of cryptic species, regardless of the mesophilic or thermophilous nature of growth ranges, may be in excess of 80 °C [67]. The temperature/survival tolerances for complexes associated with contaminated drugs are presented in Table 6. These in vitro temperature parameters are approximate for maximal growth with varied enrichment media, whereas temperature survival/tolerances (Table 6) apply to moist mixed morphotype suspensions, mostly in saline. The actual parameters for any given propagule(s) in situ would be subject to its physiological state, densities, degree of aggregation (particulates), and environment. Constitutive adaptation to higher growth temperatures by several degrees may occur [17, 39]. Fungal propagules initiating the rare contaminations of finished drugs prior to retail are not limited to active colonization–biofilm formation niches within or near a processing facility. Resistant and dormant morphotypes, (potential precursors for recurrent contaminations), albeit in low numbers, may be present also in many laminated cardboard materials, cellulosic packaging fillers, hospital linens, and paperboard for aseptic packaging [23, 24, 34].

Conclusions

In summary, eukaryotic microbes with the potential for growth and survival in drugs are not uncommon in drug excipients and the processing environment, but rarely present in the final drug [3, 6, 10, 13, 21, 26, 44, 45, 56, 57, 61, 66, 69, 71]. Those sparse fungi present in drugs from all processing facilities even more rarely associate with disease outbreaks. Our estimations of outbreak incidences were problematic, partially because of broad geographical distribution and sporadic contaminations of the varied drugs, the indolent nature of many of the infections, and the relatively low incidence of disease. Host disposition can be the overriding factor in the fate of an infection with fungi of low virulence; exposure seldom leads to disease [29, 50].

The rare episodes that have occurred with devastating health and financial impact typically have been associated with thermotolerant species that have a prior history of adventitious pathogenicity. Also, the reviewed "outbreak" episodes were associated mostly with ocular products and injectable drugs, with the latter having been secondarily processed in compounding pharmacies or isolated clinics.

The capacities of select environmental fungi to differentiate to stress-resistant morphotypes following exposure to sublethal temperatures or chemical stress would make them suspect contaminants to survive some current drug-processing protocols. However, when the fungal taxon has no molecular documented disease history, it appears highly unlikely to associate with a disease episode. Genotype characterization of isolates in the future should clarify possible environmental origins and potential for involvement in the infection–disease process.

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