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MEDICAL MYCOLOGY TRAINING NETWORK

Prevention and control of nosocomial fungal infections

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Prevention and Control of Nosocomial Fungal Infections

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Contents

- Fungal diseases occur beyond expectation
- Emerging challenges
- Fungi, human and environment
- Infection prevention and control

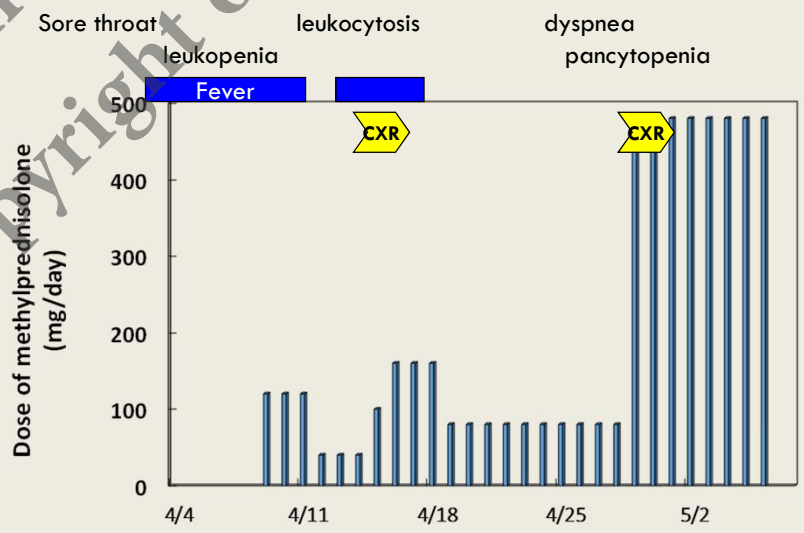
Who is responsible the occurrence of invasive fungal diseases? (multiple choices)

1. Hospitals
2. Healthcare personnel
3. Patients and/or their main care givers
4. Others

Fungal diseases occur beyond expectation

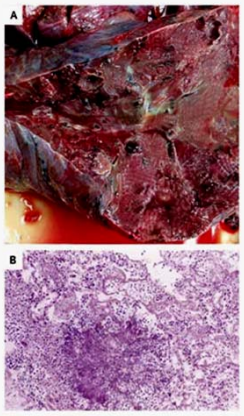
Case 1

A 39-year-old physician with SARS



Wang et al. NEJM 349:507; July 2003

Fatal aspergillosis in a 39-year-old male with SARS who was treated with corticosteroids



Autopsy showed SARS-associated pathologic changes

Dissemination aspergillosis: multiple lung abscesses containing aspergillus; cerebral edema, diffuse cerebral hemorrhage, aspergillus meningitis, and multiple brain abscesses containing aspergillus; multiple abscesses containing aspergillus in the heart, liver, kidney, spleen, stomach, pancreas, and adrenal glands.

A. Cut surface of a lung.
B. Extensive hyaline membranes, desquamated epithelial cells, and exuded monocytes in alveoli (HE stain, x100).
Aspergillus mycelia were observed on microscopical examination of the abscess and were isolated by culture as well.

Wang et al. NEJM 2003;349:507

Doubling time for
Aspergillus: 48 hr
E. coli: 20 min
M. tuberculosis: 24 hr

Denning et al. Microbiology 1994;140; Michail et al. Lancet 2003;362:1828

Increasing growth rate of *Aspergillus* in the presence of steroids

Invasive fungal tracheobronchitis in mechanically ventilated critically ill patients

- A retrospective multicenter study, Taiwan
- 31 patients with proven/probable IFD
- DM 58%
- Chronic lung disease 39%
- Systemic steroid use 55%
- pH1N1 10%

Variable	No. of patients (%)
Pathogen	
Aspergillus spp.	19 (61.3)
Aspergillus fumigatus	11 (35.4)
Aspergillus flavus	2 (6.5)
Aspergillus terrus	1 (3.2)
Undifferentiated *Aspergillus* species	5 (16.1)
Mucorales	8 (25.8)
Candida spp.	2 (6.5)
Undifferentiated mold	2 (6.5)

Lin et al. Ann Intensive Care 2017;7:9

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Case 2

A 45-year-old woman with post-traumatic intracranial hemorrhage

- Endotracheal intubation (emergent operation, comatous)
- Steroid for increased intracranial pressure
- Acute renal failure
- Stress ulcer with bleeding, proton pump inhibitor, central line, parenteral hyperalimentation
- Suspect lower respiratory tract infection, treated with antibacterials
- Persistent fungemia due to *Candida krusei* despite of removal of central line and CT showed IVC thrombosis

Pan SC.....Chen YC. Septic *Candida krusei* thrombophlebitis of inferior vena cava with persistent fungemia successfully treated by new antifungal agents. Med Mycol 2005;43:731

A block of fresh yeast

Pichia kudriavzevii

Pichia kudriavzevii, Issatchenkia orientalis & *Candida glycerinogenes*,
used for industrial-scale production of glycerol and succinate, also used to make some fermented foods.

Population genomics shows no distinction between *Candida krusei* and *Pichia kudriavzevii*:
One species, four names

Douglass AP, et al. PLoS Pathog 14(7): e1007138

Saccharomyces fungaemia related to use of probiotics

- A multicenter study in Belgium showed 21 *Saccharomyces cerevisiae* (65.6%) were the most common isolates in non-*Candida* yeasts in blood specimens.
- Seven patients with *S. cerevisiae* fungaemia were reported at two hospitals in India between July 2014 and September 2015.
- Fluorescent amplified fragment length polymorphism (FAFLP).
- Of the three AFLP types (group I, II, II) identified, all the probiotic isolates clustered in group I (major cluster) including majority of the blood isolates.
- The isolates were susceptible to all antifungal agents tested.

Swinne D, et al. Epidemiol Infect 2009;137:1037; Roy U, …Chakrabarti A. Mycoses 2017;60:375

Emerging issues related to yeasts

- *Candida auris* [1]
- *Candida dubliniensis*[5]
- *Candida guilliermondii* [6]
- *Candida kefyr* [1,7]
- *Candida krusei* [2]
- *Candida lusitaniae*[4]
- *Candida nivariensis* [8]
- *Candida norvegensis*
- *Candida pelliculosa* [1]
- *Candida rugosa* [3]
- *Candida tropicalis* [11]
- *Cryptococcus humicolus*
- *Cryptococcus uniguttulatus*
- *Geotrichum capitatum* [9]
- *Hansenula*
- *Saccharomyces cerevisiae*[10]

1. Multidrug resistance, outbreak, misidentification
2. Intrinsic resistance to fluconazole, susceptible to voriconazole; fermented foods
3. Cross resistance to fluconazole and voriconazole
4. Can develop secondary resistance to amphotericin B
5. Can develop stable fluconazole resistance, especially in patients with HIV/AIDS
6. Potential for decreased susceptibility to polyenes, azoles, flucytosine, and echinocandins
7. Dairy products
8. Gardens or potted plants
9. Presence of blastoconidia with hyphae differentiates *Trichosporon* from *Geotrichum*, predominantly in Italy.
10. Probiotics
11. Emergence of azole resistance, fruits and other environment source

Modified from: Lancet Infect Dis 2011;11: 142–51

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Case 3

Aspergillus meningitis after the administration of spinal anesthesia for cesarean section

Characteristic or Test	Patient No.				
	1	2	3	4	5
Clinical features					
Age — yr	26	21	27	29	38
Date of exposure	June 21	June 22	June 20	June 22	July 17
Date of onset of symptoms	July 3	July 2	July 5	July 3	July 25
Neck stiffness and Kernig's sign†	Absent	+++	++	+	+
Lateral rectus palsy	Absent	Absent	Bilateral	Bilateral	Absent
Stroke	Thalamic infarction on July 9	Thalamic infarction on July 31	Absent	Absent	Ventricular hemorrhage on Aug. 10
Complications	Partial seizures, diabetes insipidus	Partial seizures	Deep-vein thrombosis	Papilledema, hydrocephalus	Coagulopathy, polyuria
Laboratory results					
Random blood glucose — mg/dl	115	90	133	120	109
Cerebrospinal fluid					
Protein — mg/dl	68	49	134	33	28
Glucose — mg/dl	56	25	21	45	61
Neutrophils — no. per mm³	300	400	20	572	0
Lymphocytes — no. per mm³	2	175	700	858	225
Gram's stain	Negative	Negative		Negative	Negative
Cytologic findings	Negative	Negative	Positive for fungal spores	Negative	Negative
Fungal culture of cerebrospinal fluid	Negative	Negative	Negative	*Aspergillus fumigatus*	Negative
Postmortem fungal culture of brain specimen	*A. fumigatus*	*A. fumigatus*			*A. fumigatus*

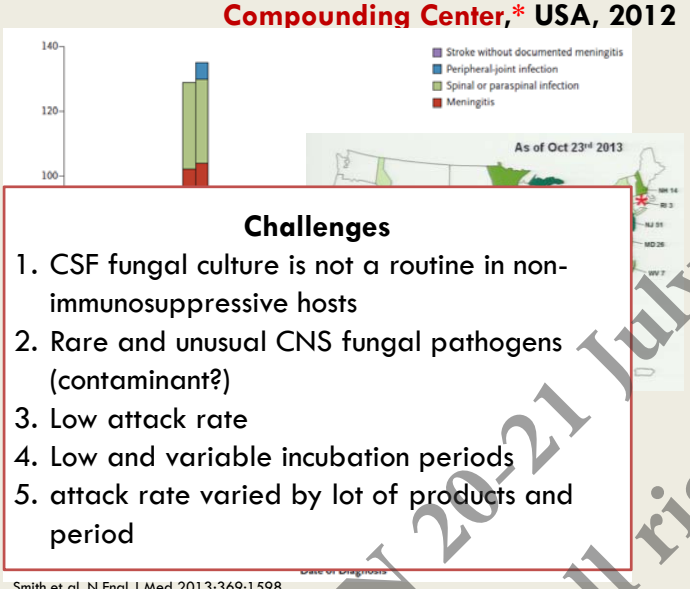
Gunaratne PS, et al. Aspergillus meningitis in Sri Lanka--a post-tsunami effect? N Engl J Med. 2007;356:754

Rare fungi in unusual anatomic sites!
Maintain high index of suspicion of unexpected findings

Variable	First Admission	Second Admission				
		Day 1	Day 6	Day 11	Day 13	Day 15
Cerebrospinal fluid						
Source of sample	L4–L5	L3–L4	L3–L4	EVD	EVD	EVD
Opening pressure (cm of water)		33	24	>30		
Protein (mg/dl)†	147	319	247	193	93	80
Glucose (mg/dl)‡	31	2	1	63	50	59
White cells (per mm³)	2304	4422	5863	14	27	341
Polymorphonuclear cells (%)	72	89	92	71	90	97
Lymphocytes (%)	23	4	2	21	4	2
Red cells (per mm³)	3	34	21	2225	2850	14,700
Gram's staining	No bacteria	No bacteria	No bacteria	No bacteria	No bacteria	No bacteria
Bacterial culture	No growth	No growth	No growth	No growth	No growth	No growth
Fungal culture	Not performed	*Aspergillus fumigatus*§	No growth to date	No growth to date		No growth to date
Aspergillus antigen index	9.14¶	9.52¶	9.51¶			9.65
Serum						
Glucose (mg/dl)	108	109	107	147	127	139
Aspergillus antigen index			0.23‖			

Pettit et al. N Engl J Med 2012;367:2119

Exserohilum rostratum outbreak linked to contaminated methylprednisolone injections produced by the New England Compounding Center,* USA, 2012



Challenges

1. CSF fungal culture is not a routine in non-immunosuppressive hosts
2. Rare and unusual CNS fungal pathogens (contaminant?)
3. Low attack rate
4. Low and variable incubation periods
5. attack rate varied by lot of products and period

751 (5.36%) of 14,000 potentially exposed persons has developed clinically apparent disease in 20 states, with 64 deaths (8.5%).
http://www.cdc.gov/ (accessed Nov 2013)

Smith et al. N Engl J Med 2013;369:1598

Case 4

Outbreak of bloodstream infection with the *Phialemonium* among patients receiving dialysis, 2002

DESIGN:

- Environmental assessment
- Case-control study

CONCLUSION:

- Possible healthcare-related environmental reservoirs: heating, ventilation, and air-conditioning (HVAC) systems
- Suboptimal contact time with antiseptic agents used to prepare dialysis access sites.

Clark T, et al. Infect Control Hosp Epidemiol 2006;27:1164

Specimen, by location	Proportion positive for *Phialemonium* species
New hemodialysis unit	
Environmental surfaces[a]	0/11[b]
HVAC system and ducts	0/4
Water, processed	0/7
Water, unprocessed	0/10
Dialysate	0/2
Old hemodialysis unit	
Environmental surfaces[a]	0/3
HVAC system vents	0/3
Inpatient unit	
Environmental surfaces	0/8
HVAC system vents	0/3
Water, processed	0/2
Water, unprocessed	0/1
Hospital building	
Standing water from HVAC drip pans	2/3[c]

NOTE. HVAC, heating, ventilation, air-conditioning.
[a] Specimens were obtained in October.
[b] *Cladosporium*, *Pithomyces*, *Aureobasidium*, and *Fusarium* species and many different *Aspergillus* species were recovered.
[c] Specimens from 2 of 3 HVAC units were culture positive for *Phialemonium* species.

Contaminated product water as the source of *Phialemonium curvatum* bloodstream infection among patients undergoing hemodialysis

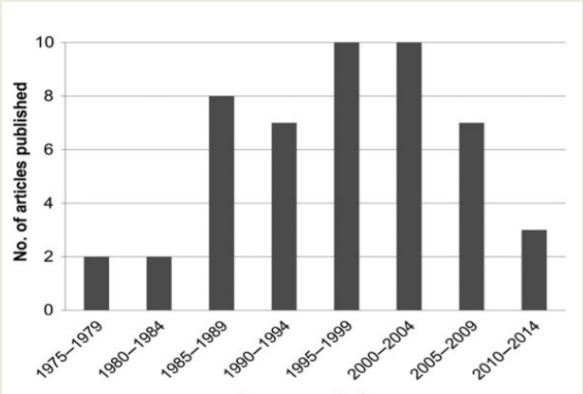
Culture Yielding Molds and Yeasts from Environmental Samples in the Hemodialysis Unit and in the Building Ventilation System, 2005

Air handling units	Dec 12	8	Dry swab	All samples with hyaline nonsporulating molds; yeasts; *Aspergillus*, *Penicillium*, and/or *Cladosporium* species
Drain from water tap 3	Dec 12	2	Dry swab	2 samples with *Fusarium solani* species
Air handling units from on-site long-term care unit	Dec 16	2	Wet swab	*Alternaria*, *Epicoccum nigrum*, *Trichoderma*, and/or *Cladosporium* species; 7 hyaline nonsporulating molds
Unit air filters from dialysis unit	Dec 16	5	Wet swab	Hyaline nonsporulating molds; *Alternaria*, *Penicillium*, and/or *Cladosporium* species
Machine 14 waste handling option port (implicated dialysis machine)	Dec 12	7	Wet swab	2 samples with *Candida tropicalis* in the new waste handling option port tubing; all other samples negative for fungi
Water room (after final filtration)	Dec 12 and 21	2	Water	No mold growth detected
Municipal water from on-site long-term care unit	Dec 16	2	Water	No mold growth detected
Water tap 3A (implicated treatment station)	Dec 12	1	Water	*Phialemonium curvatum*, nonsporulating molds, and *Cladosporium* species
All water taps	Dec 21	18	Water	Molds recovered from water taps 1A, 1B, 2A, 2B, 4A, 4B, 5A, 12, 15, 16, 17, 18, and 19 (hyaline nonsporulating molds and unidentified pigmented molds); *P. curvatum* recovered from water tap 2B and *F. solani* recovered from water tap 16
Water room (recirculated water)	Dec 21	1	Water	Hyaline molds detected in recirculated water returning to water treatment room
Water taps	Dec 29	5	Water	All samples negative for molds after disinfection of water distribution system on Dec 22

Rao et al. Infect Control Hosp Epidemiol 2009;30:840

Fungal outbreaks and infections associated with construction, renovation, and demolition

These activities are an ever-constant phenomenon in healthcare facilities, causing dust contamination and possible dispersal of fungal spores.



Kanamori H et al. Review of fungal outbreaks and infection prevention in healthcare settings during construction and renovation. Clin Infect Dis 2015;61(3):433

Fungal Infections During Construction, Renovation, or Demolition

The causative pathogens of these outbreaks were usually *Aspergillus* species, but Zygomycetes and other fungi

	Underlying Diseases	No. of Patients Infected	No. of Patients Died	Mortality, No.[a] (%)
26	Hematologic malignancies or bone marrow transplant	414	148	131/288 (45.5)
13	Other malignancies, transplant, and/or immunosuppressed patients	105	38	38/60 (63.3)
3	Patients in intensive care unit	8	2	2/4 (50)
2	Rheumatology patients	6	4	4/6 (66.7)
2	After surgery	8	1	1/8 (12.5)
2	Premature infant	3	2	2/3 (66.7)
1	Nephrology and dialysis patients	3	2	2/3 (66.7)
49	Total	547	197	180/372 (48.4)

Numbers of articles published

Kanamori H et al. Review of fungal outbreaks and infection prevention in healthcare settings during construction and renovation. Clin Infect Dis 2015;61(3):433

Healthcare-associated vs. community-acquired invasive aspergillosis

Healthcare-associated	Community-acquired
• Due to break in, or contamination of hospital water system • Due to break in HEPA filtration system • Due to construction or demolition work in the hospital	• Due to housing quality • Due to occupational activities • Due to construction, etc. • Due to leisure activities Due to exposure to *Aspergillus* spores (minimum effective dose not known)

Praz-Christinaz et al. Transplant Infect Dis 2007; 9: 175-181

Emerging challenges

Case 5

27-year-old man with cutaneous T cell lymphoma with acute leukemic change

8/27 Doxorubicin HCl, liposomal 20mg
8/28 Fever → Cefepime
9/1 Blood (port-A) culture report: MSSA
9/2 BiCNU 100 mg
9/9 NEC (Mitoxantrone, Etoposide, Cytarabine)
9/15 Febrile neutropenia → Imipenem, G-CSF
9/17 Fever subsided
9/18 Fever (Nadir D8) → Add teicoplanin and fluconazole
9/20 Blood culture and urine culture: no growth
Multiple painful nodules over the four extremities & trunk, multiple oral ulcers with whitish exudates

Liu JY.....Chen YC. Med Mycol. 2011;49:872

Cutaneous T cell lymphoma with acute leukemic change

Liu JY…. Chen YC. Combination Antifungal Therapy for Disseminated Fusariosis in Immunocompromised Patients: A Case Report and Literature Review. Med Mycol. 2011;49:872

Call for Action

Clinical Infectious Diseases
VIEWPOINTS
2018; **66**: 140-148

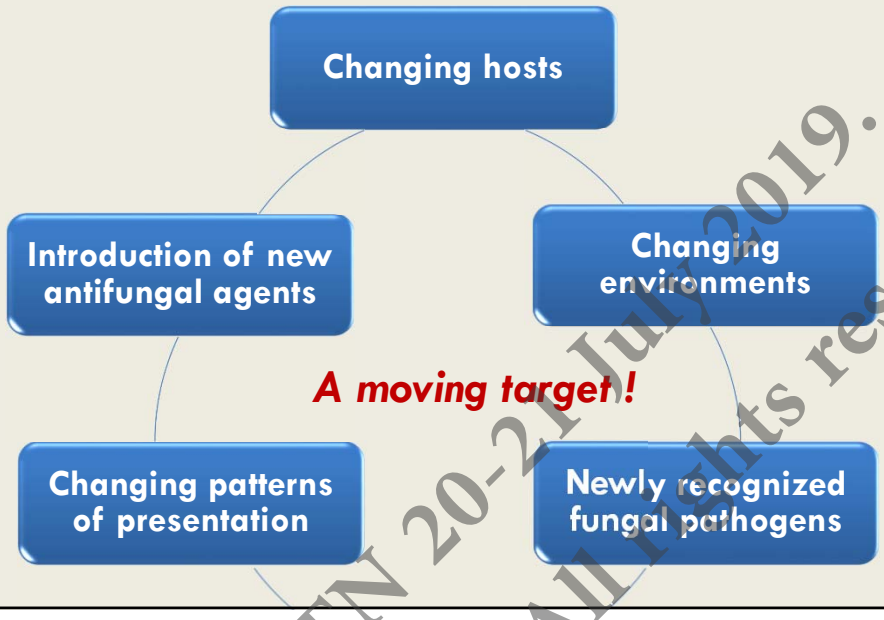
Call for Action: Invasive Fungal Infections Associated With Ibrutinib and Other Small Molecule Kinase Inhibitors Targeting Immune Signaling Pathways

Georgios Chamilos,[1,2] Michail S. Lionakis,[3] and Dimitrios P. Kontoyiannis[4]

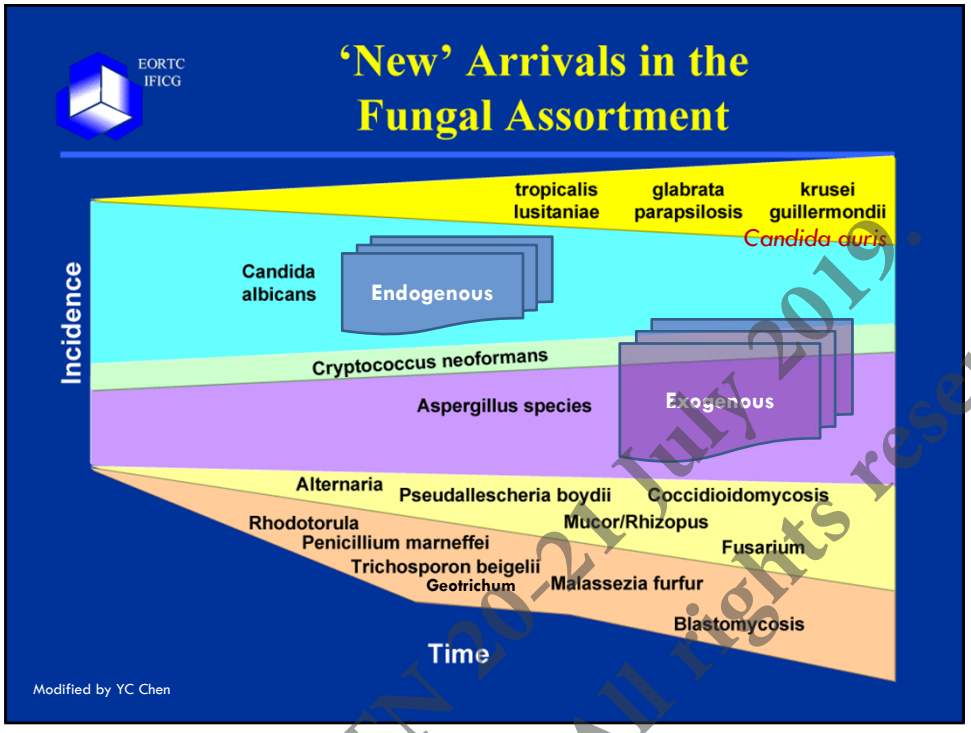
[1]Department of Clinical Microbiology and Microbial Pathogenesis, University of Crete, and [2]Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, Crete, Greece; [3]Fungal Pathogenesis Unit, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and [4]Department of Infectious Diseases, The University of Texas MD Anderson Cancer Center, Houston

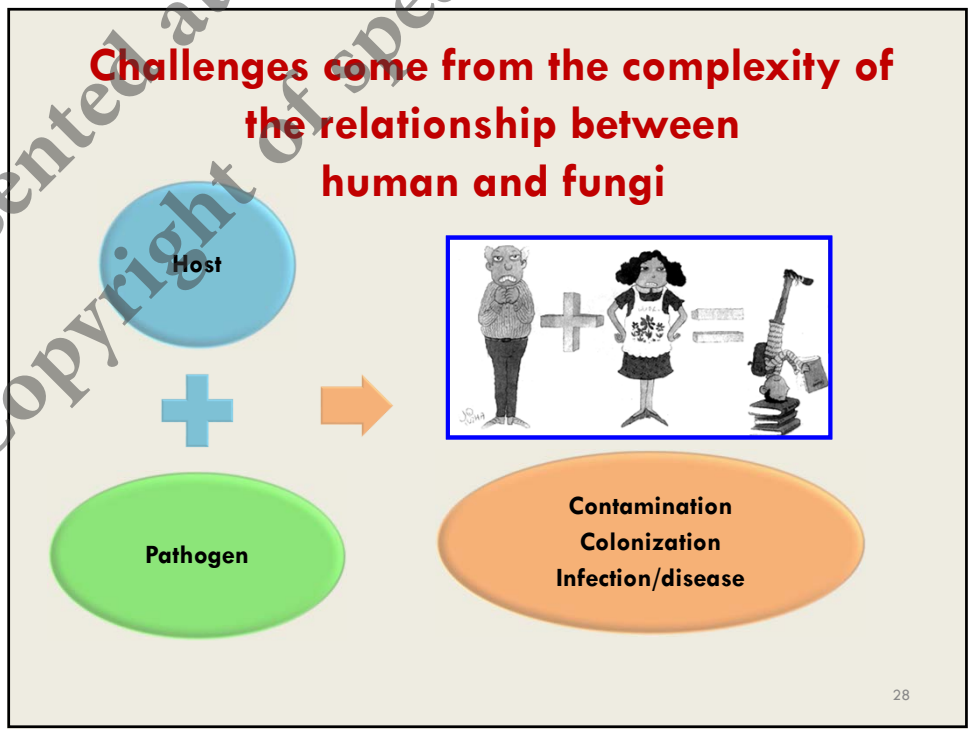
Opportunistic infections caused by *Pneumocystis jirovecii*, *Cryptococcus neoformans*, and ubiquitous airborne filamentous fungi have been recently reported in patients with hematological cancers historically considered at low risk for invasive fungal infections (IFIs), after receipt of the Bruton tyrosine kinase inhibitor ibrutinib. The spectrum and severity of IFIs often observed in these patients implies the presence of a complex immunodeficiency that may not be solely attributed to mere inhibition of Bruton tyrosine kinase. In view of the surge in development of small molecule kinase inhibitors for treatment of malignant and autoimmune diseases, it is possible that there would be an emergence of IFIs associated with the effects of these molecules on the immune system. Preclinical assessment of the immunosuppressive effects of kinase inhibitors and human studies aimed at improving patient risk stratification for development of IFIs could lead to prevention, earlier diagnosis, and better outcomes in affected patients.

Epidemiology of invasive fungal infections



Fungi, human and environment

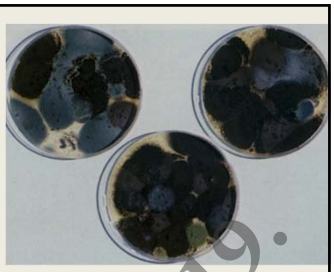




Aspergillus

are found in :

- Soil
- Air; spores may be inhaled
- Food
- Compost and decaying vegetation
- Water/storage tanks in hospitals, etc
- Ventilation and air conditioning systems
- Fire proofing materials, bedding, pillows, computer fans



***A. niger* & *A. fumigatus* growing from tea bag s of Darjeeling tea**

***Aspergillus* keratitis**

***Aspergillus* can be both colonizers and pathogens, and even laboratory contamination**

Infection prevention and control

Prevention and control of healthcare-associated fungal infections

Hospitals	Healthcare personnel
Patients and their care givers	Government or third parties

Prevention and control of healthcare-associated fungal infections

Hospitals

- Environment control: water, air, food
- Environmental control during renovation/construction
- Quality control of medical products and supplies, etc.
- Patient allocation (protective isolation; contact precaution)

Healthcare personnel

- Standard precaution: hand hygiene, etc.; care bundle
- Rationale use of immunosuppressive agents, invasive procedures (and antimicrobial agents)

Patients and their care givers

- Hand hygiene, personal hygiene
- Avoid exposure: food safety, etc.

Risk assessment
Patient education

Environmental risk factors for mould-related diseases in immunocom-promised patients

Pagano et al. J Antimicrob Chemother 2011; 66 Suppl 1: i5

Seasonal incidence

Weather variation
- temperature
- rainfall
- humidity
- wind speed

Personal habits
- smoking
- living in countryside
- fungus exposure
- type of work (e.g. farmer, agriculture)

Exposure outside
- pets
- dusty household
- construction work

Exposure inside
- potted plants
- absence of HEPA-filtered rooms
- water

HEPA, high-efficiency particulate air.

Preventing Filamentous Fungal Infections Associated With Renovation/Construction Activities

- ICP should be notified by plant engineering prior to any RCA in the healthcare facility
- Conduct an ICRA for all RCA and implement prevention strategies accordingly
- Focus on control of airborne dissemination of fungal spores (e.g., barriers, containment, air handling, portable HEPA filters).
- Maintain surveillance for healthcare-associated filamentous fungal infections during RC. Investigate any cases to see if they are related to RC and determine if prevention efforts need to be revised.
- Visit RC sites regularly to assure compliance with prevention activities.

Adapted from the Centers for Disease Control and Prevention. Guidelines for Environmental Infection Control in Health-Care Facilities. http://www.cdc.gov/hicpac/pdf/guidelines/eic_in_HCF_03.pdf.
Abbreviations: RCA, renovation/construction activities; ICP, Infection control personnel; HEPA, high-efficiency particulate air; ICRA, infection control risk assessment.