

Yeast and Mould Infections in Neutropenic Patients and HSCT Recipients

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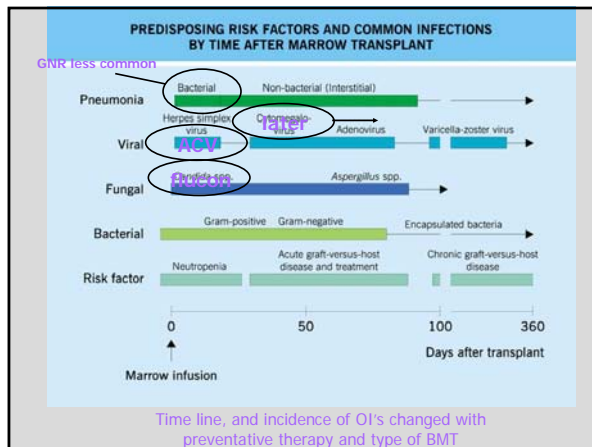
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Issues

- Diseases
- Current epidemiology of infection
 - Incidence and Outcomes
- Diagnosis
- Therapies



Diseases



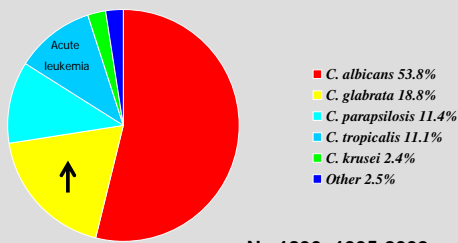
- Candidemia
- Deep-tissue infection
 - Acute invasive candidiasis
 - Abscess formation in the presence of hematogenous spread
 - Multiple organs may be involved
 - Endocarditis
 - Abscesses
 - Chorioretinitis
 - 30-40% attributable mortality

Hepatosplenic Candidiasis



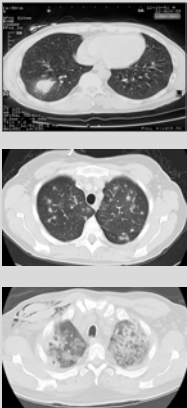
- Neutropenic - HSCT
- Typically does NOT present during neutropenia, although may develop
- Mucosal breakdown with invasion into portal vasculature
 - Clinical presentation largely secondary to inflammatory response to lesions
 - After engraftment: abdominal pain, increased LFTs (alk phosph), fever, leg / flank pain (?)
- Diagnosis may require invasive procedure
 - Differential: other fungi, bacteria, lymphoma
- Radiographic changes may get worse before better
- *C. albicans* most common (hyphal formation)

Distribution of *Candida* species: U.S. Hospitals



Wisplinghoff CID 2004;39:307-19


Mould Infections: Primary Pulmonary Disease



- Nodule +/- halo: typical presentation in neutropenics; evolves to cavitation
- More variability in non-neutropenic patients¹
 - Nodular disease
 - Bronchopneumonia
- Multiple microbial causes of disease
 - Aspergillus species
 - Zygomycetes
 - Other filamentous organisms

Kojima et al. BBMT 11(7): 506-11 (2005)

Angioinvasion



Multiple organisms disseminate to skin, brain, other organs

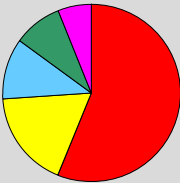
- Differentiate syndromes caused by organisms that "sporulate" in vivo

Fig. 71.1. Cutaneous manifestations of disseminated fungal infections in leukemic patients. (A) Aspergillus niger, (B) Candida tropicalis, (C) Aspergillus, (D) Paracoccidioides brasiliensis, (E) Aspergillus.

From: Marchetti and Calandra, Cohen and Powderly 2nd ed (in press)

Diseases Caused by Aspergillus species

- Invasive pulmonary aspergillosis
- Genus Aspergillus > 250 different species
- *A. fumigatus* historically considered to be most common cause of disease



Species	Percentage
<i>A. fumigatus</i>	56%
Other	18%
<i>A. flavus</i>	11%
<i>A. niger</i>	9%
<i>A. terreus</i>	6%

TRANSNET Preliminary data.
Baddley, JW, et al. Poster Presentation at the 42nd Annual Meeting of IDSA, 2004. Abstract 673.

Aspergillus fumigatus "group"

- Isolates identified as *A. fumigatus* are heterogeneous- small phenotypic differences
- Different species suggested by polyphasic taxonomy definition
 - Multiple closely related and "new" species
 - *Aspergillus lentulus*
 - *Aspergillus fumisynnematus*
 - *Aspergillus udagawae*
 - *Neosartorya pseudofischeri*
 - ◆ Variable susceptibilities to antifungal drugs in vitro

Other Sections

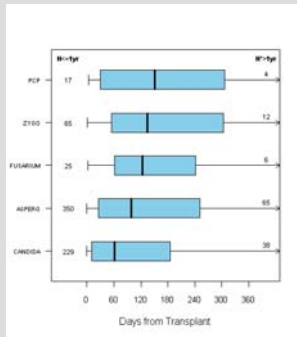
- *Aspergillus ustus*
 - *A. ustus*
 - *A. pseudodeflectus*
 - *A. calidoustus*
 - High MICs to AmB, all azoles
- *Aspergillus terreus*
 - *A. terreus*
 - *A. alabamensis*
 - High MICs to AmB

Varga et al. Euk Cell 2008
7(4): 630 – 38
Balajee et al. Euk Cell 2009
8(5): 713 – 22

Epidemiology Update: Multicenter Surveillance Networks

- TRANSNET
 - 23 US centers, 2001 – 2006
 - SOT, HCT, with denominator data
- PATH Alliance
 - 16 US centers, 2004 - 2007
 - Diagnosed in hospital

TRANSNET BMT



Kontoyiannis et al. Clin Infect Dis, in press

■ 25% survival after IA

Take-home points

- Variable incidence of IFI- especially IA, *even within transplant types* reported across centers
 - Diagnostic differences
 - Differences in follow up of transplant recipients
 - Variable case - mix
 - Type of transplants performed across centers
 - Type of patients, regimens within transplant types

Take-home points

- Variable incidence, *even within transplant types* reported across centers
- Better outcomes of IA compared to prior years
 - Historical death rates reported 60 - 80% 3 mo. - 1 year



(1-3)- β -D-Glucan Detection

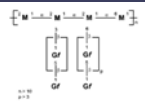
- 279 patients with variable diagnoses
- Case control design with variable control groups

Parameter*	IFI patient groups and subgroup/control groups			
	Total IFI patients/ blood donors	Total IFI patients/ patients at risk	Pulmonary aspergillus/ corresponding patients at risk	Bloodstream infections/ corresponding patients at risk
No. of patients	117/40	117/22	70/100	27/101
No. of patients with a BD ≥ 80 pg/ml	91/3	91/36	48/77	23/36
Sensitivity (95% CI)	77.8 (70.2-85.3)	77.8 (70.2-85.3)	68.6 (57.7-79.5)	85.2 (71.8-98.6)
Specificity (95% CI)	92.5 (84.3-1.0)	70.5 (62.4-78.6)	73.0 (64.3-81.7)	64.4 (55.0-73.7)
LR+ (95% CI)	10.4 (3.5-30.9)	2.64 (1.07-3.53)	2.06 (1.09-3.91)	4.07 (2.06-8.07)
LR- (95% CI)	0.24 (0.17-0.34)	0.32 (0.22-0.45)	0.43 (0.30-0.62)	0.23 (0.09-0.57)
Yule Q	0.95	0.79	0.71	0.82

Persat et al. J Clin Microbiol 46(3): 1009-13

Galactomannan

- Linear core of mannan with α 1,2 and α 1,6 linkages
- Antigenic side chain of β 1,5 galactofuranosyl target of Eba2 Ab
- Double sandwich ELISA



Mennink-Kersten et al Lancet Infect Dis 2004 4 349

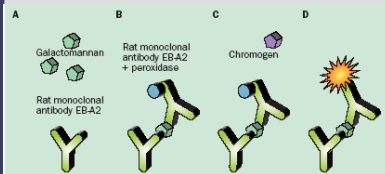


Table 2. Five-year summary of published studies investigating performance of the galactomannan EIA used for diagnosis with serum.

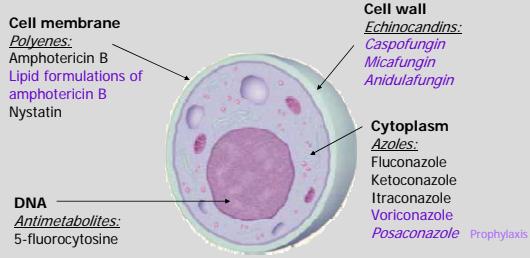
Study	Population	Sample size, no. of patients	Sensitivity, %	Specificity, %
Kawanura et al. [14]	Variable	94	100	100
Maertens et al. [15]	Hematologic malignancies	186	92.6	95.4
Ulasakarya et al. [16]	Hematologic malignancies	135	69	96
Sakonen et al. [17]	Hematologic malignancies	105	77	NA
Fortun et al. [18]	Liver transplant	240	56	94
Kami et al. [19]	Hematologic malignancies	122	58	97
Siemann and Koch-Dorfler [20]	Pulmonary diseases	52	100	23
Maertens et al. [21]	Hematologic malignancies, HCT	294	90	98
Sulahan et al. [22]	Hematologic malignancies, HCT (many children)	797	91	94
Maertens et al. [23]	HCT	97	94	99
Herbrecht et al. [24]	Hematologic malignancies	797 ^a	65	95
Rimek and Kappe [25]	Variable	90	59	NA
Pinel et al. [26]	Variable	807	50	100
Becker et al. [27]	Hematologic malignancies	160	47	93
Buchheid et al. [28]	Hematologic malignancies	165	33	99
Kwak et al. [29]	Liver transplant	154	NA	87
Husain et al. [30]	Lung transplant	70	30	93
Rovira et al. [31]	HCT	74	75	100
Marr et al. [4]	HCT	67	82	75

NOTE. HCT, hematopoietic cell transplantation; NA, not available.

^a Denotes number of episodes, not number of patients.

Marr and Leisenring Clin Infect Dis 2005; 41:S381

Antifungals: Filamentous Fungal Infections

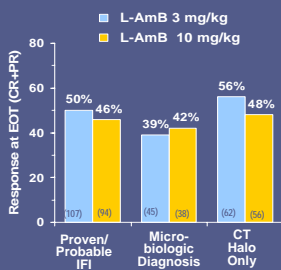


Voriconazole

- Voriconazole vs. AmB-d
 - Global, randomized, double-blind trial: Primary therapy of IA
 - Voriconazole – better responses, better survival
 - Voriconazole issues: dosing, need for therapeutic level monitoring
- Prophylaxis in allogeneic HSCT
 - Voriconazole vs. fluconazole
 - No difference in fungal free survival
 - Fewer IFI

Herbrecht et al. New Eng J Med 347: 408 (2002)
 Wingard et al. Amer Society Hematology 2008

Efficacy of Liposomal AmB (L-AmB) in Invasive Mycoses: AmBiLoad Trial



14-day loading dose of L-AmB 3 or 10 mg/kg/d followed by L-AmB 3 mg/kg/d

	L-AmB	
	3 mg/kg/d	10 mg/kg/d
IPA	96%	97%
CT Halo	58	60
Allo-SCT	16	19
Neutropenia	71	76
Survival	72	59
Toxicity	20	32

L-AmB = liposomal amphotericin B; CR+PR = complete and partial responses; EOT = End of Therapy; IPA = invasive pulmonary aspergillosis; Allo-SCT = allogeneic stem cell transplant
 Connelly D, et al. Clin Infect Dis. 2007;44:1289-97.

Conclusions

- Fungal infections- especially filamentous organisms account for large morbidity in patients with hematologic malignancies
- Reported incidence varies
- Outcomes of IA improved in many centers
- New diagnostics, new therapies
- Many controversies
