Defining the Spectrum of (IFI) Invasive Fungal Infections in Canada

SHARIQ HAIDER

MD, FRCPC, FACP, CCST(UK)

PROFESSOR MEDICINE

McMaster University

Disclosures

Advisory Board:

- Pfizer, Merck Pharmaceuticals & Astellas Pharmaceuticals

Clinical Trial participation:

- Merck Pharmaceuticals

UNMET NEEDS IN IFI(Invasive Fungal Infection) EPIDEMIOLOGY IN CANADA

1. Invasive Candidiasis- single center and multicenter sentinel surveillance studies, and a single population based study reported a rate of 2.9/100,000 persons (2.8/100,000 persons for Candidemia)
2. Rates of Invasive Candidiasis much lower then in US Population based studies 4-6/100,000 persons.

Laupland K et al.Invasive *Candida* species infections: a 5 year population based assessment. JAC(2005) 56, 532-537

UNMET NEEDS IN IFI (Invasive Fungal Infection) EPIDEMIOLOGY IN CANADA

Table 2. *Candida* species causing invasive disease in the Calgary Health Region

Candida species	Number of cases (age < 20)	Number of cases (age ≥ 20)	Total number of cases	Incidence per 100 000
C. albicans	21	86	107	1.5
C. glabrata	1	44	45	0.7
C. parapsilosis	5	8	13	0.2
C. tropicalis	1	11	12	0.2
C. krusei	2	8	10	0.1
Other[a]	2	20	22	–

[a]Other includes two *Candida guillermondii* (one patient, age <20 years), one *Candida lusitaniae*, and 19 non-albicans *Candida* species (one patient, age <20 years).

Laupland K et al.Invasive *Candida* species infections: a 5 year population based assessment. JAC(2005) 56, 532-537

	Yamamura CMAJ 1999 (92-94) N=415	Hoban ICAAC 2002 (98-02) N=1730
Species	%	%
C. albicans	68.9	55.5
C. glabrata	8.2	14.5
C. parapsilosis	10.4	13
C. tropicalis	6.5	9
C. krusei	1	4.3

UNMET NEEDS IN IFI (Invasive Fungal Infection) EPIDEMIOLOGY IN CANADA

1. Invasive Mold Infection – limited single center surveillance studies, no population based study looking at rates of Invasive *Aspergillosis* in Canada.
2. Lack of microbiological surveillances studies on New or Emerging Mold Infections.

PATH

Prospective Antifungal Therapy Alliance.

A comprehensive fungal registry

Data collection and monitoring trends in pts with IFI- diagnosis, treatments, and outcomes.

As of Dec 31, 2008, 6500 patients , and 6900 proven or probable IFI, from 25 centers across N.America(2 Canadian Centers, Montreal, and Hamilton)

THE PROSPECTIVE ANTIFUNGAL THERAPY ALLIANCE REGISTRY: A TWO CENTER CANADIAN EXPERIENCE.

Haider S, Rotstein C, Horn D, Laverdiere M, Azie N.CJIDMM 2014; 25(1

Patient Categories
Canadian Aggregate Data

Patient Category *	Aggregate N (%) Total N = 369
General Medicine	283 (76.7)
Hematologic Malignancy	60 (16.3)
Hematopoietic Stem Cell Transplant	23 (6.2)
HIV / AIDS	3 (0.8)
Inherited Immunodeficiency Disorder	0
Neonatal Intensive Care Unit	5 (1.4)
Solid Organ Transplant	47 (12.7)
Solid Tumor	56 (15.2)
Surgical (Non-Transplant)	131 (35.5)
Other	1(0.3)

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*Note: Patients may be included in more than 1 category.

Hematologic Malignancy: Characteristics
Canadian Aggregate Data

Hemotologic Malignancy Characteristics	Aggregate N (%) Total N = 60
Type of Hematologic Malignancy *	
Acute Lymphocytic Leukemia (ALL)	5(8.3)
Acute Myelogenous Leukemia (AML)	25(41.7)
Chronic Lymphocytic Leukemia (CLL)	4 (6.7)
Chronic Myelogenous Leukemia (CML)	3 (5.0)
Aplastic Anemia	2 (3.3)
Hodgkin's Lymphoma	2 (3.3)
Non-Hodgkin's Lymphoma	13 (21.7)
Multiple Myeloma	2 (3.3)
Myelodysplastic Syndrome (MDS)	9 (15.0)
Other	4 (6.7)
Current State of Disease *	
New Diagnosis	19(31.7)
In Remission	16 (26.7)
Relapse / Recurence	24 (40.0)
Palliative	2(3.3)
Mucositis	
None	47 (78.3)
Grade I-II	8 (13.3)
Grade III-IV	3 (5.0)
Yes, Grade Unknown	2 (3.3)
Treatment Modalities *	
None	20 (33.3)
Chemotherapy	39 (65.0)
Radiation Therapy	5 (8.3)
Surgery	1(1.7)
Unknown	0

*Note: Patients may be included in more than 1 category

Cases of IFI by Fungal Species
Canadian Aggregate Data

Candida	N (%) Total N = 422
C. *albicans*	175 (41.5)
C. *dubliniensis*	3 (0.7)
C. *glabrata*	80 (19.0)
C. *guillermondii*	2 (0.5)
C. *krusei*	16 (3.8)
C. *parapsilosis*	40 (9.5)
C. *tropicalis*	25 (5.9)
Other *Candida* spp.	2 (0.5)
Unknown *Candida* spp.	4 (0.9)

Aspergillus	N (%) Total N = 422
A. flavus	6 (1.4)
A. fumigatus	32 (7.6)
A. niger	6 (1.4)
A. terreus	1 (0.2)
Other Aspergillus spp.	2 (0.5)
Unknown Aspergillus spp.	5 (1.2)

Zygomycetes	N (%) Total N = 422
Mucor	2 (0.5)
Rhizopus	3 (0.7)
Other *Zygomycetes* spp.	1 (0.2)

Endemic Fungi	N (%) Total N = 422
Histoplasma	3 (0.7)

Other Mould	N (%) Total N = 422
Fusarium	4 (0.9)
Other Mould	1 (0.2)

Other Yeast	N (%) Total N = 422
Cryptococcus	5 (1.2)
Malassezia	1 (0.2)
Rhodotorula	1 (0.2)
Saccharomyces	1 (0.2)

Unidentified Pathogen	N (%) Total N = 5851
Unidentified Yeast	1 (0.2)

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CJIDMM 2014; 25(1)

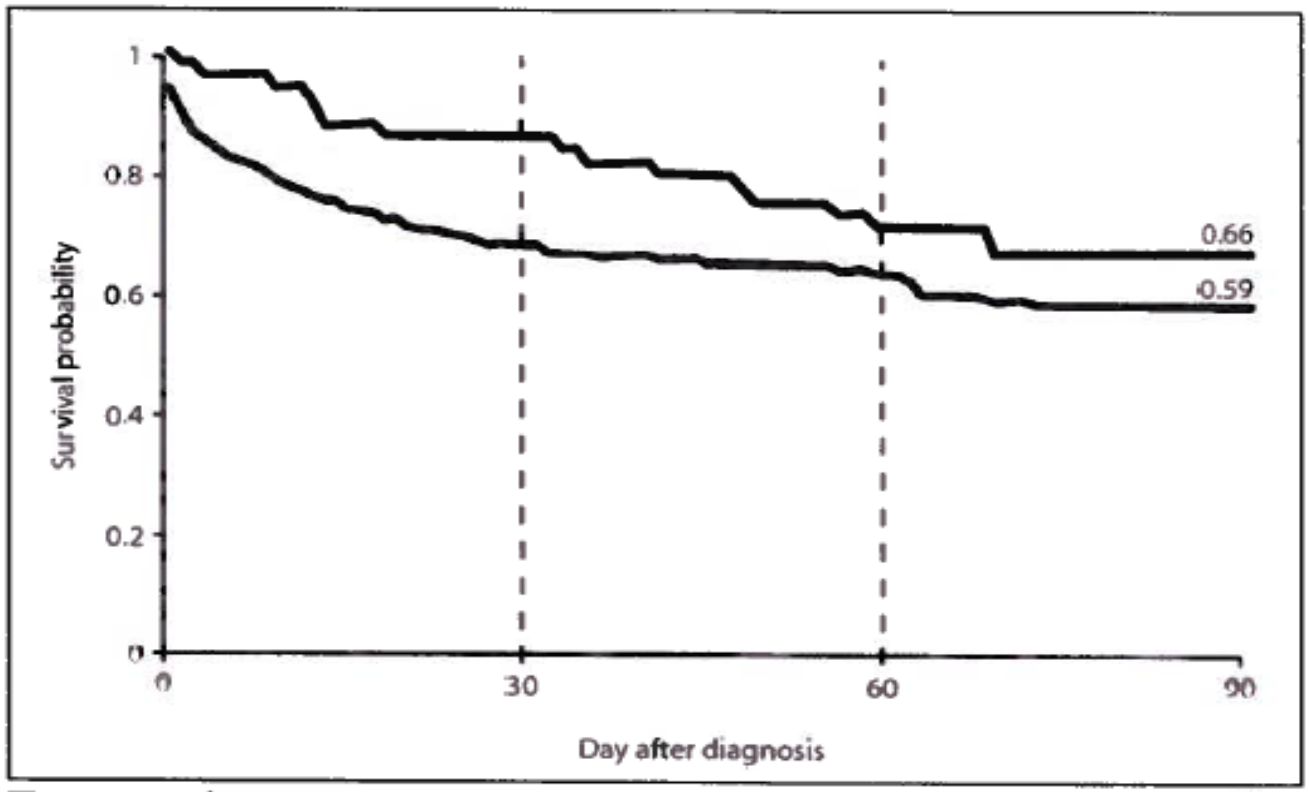
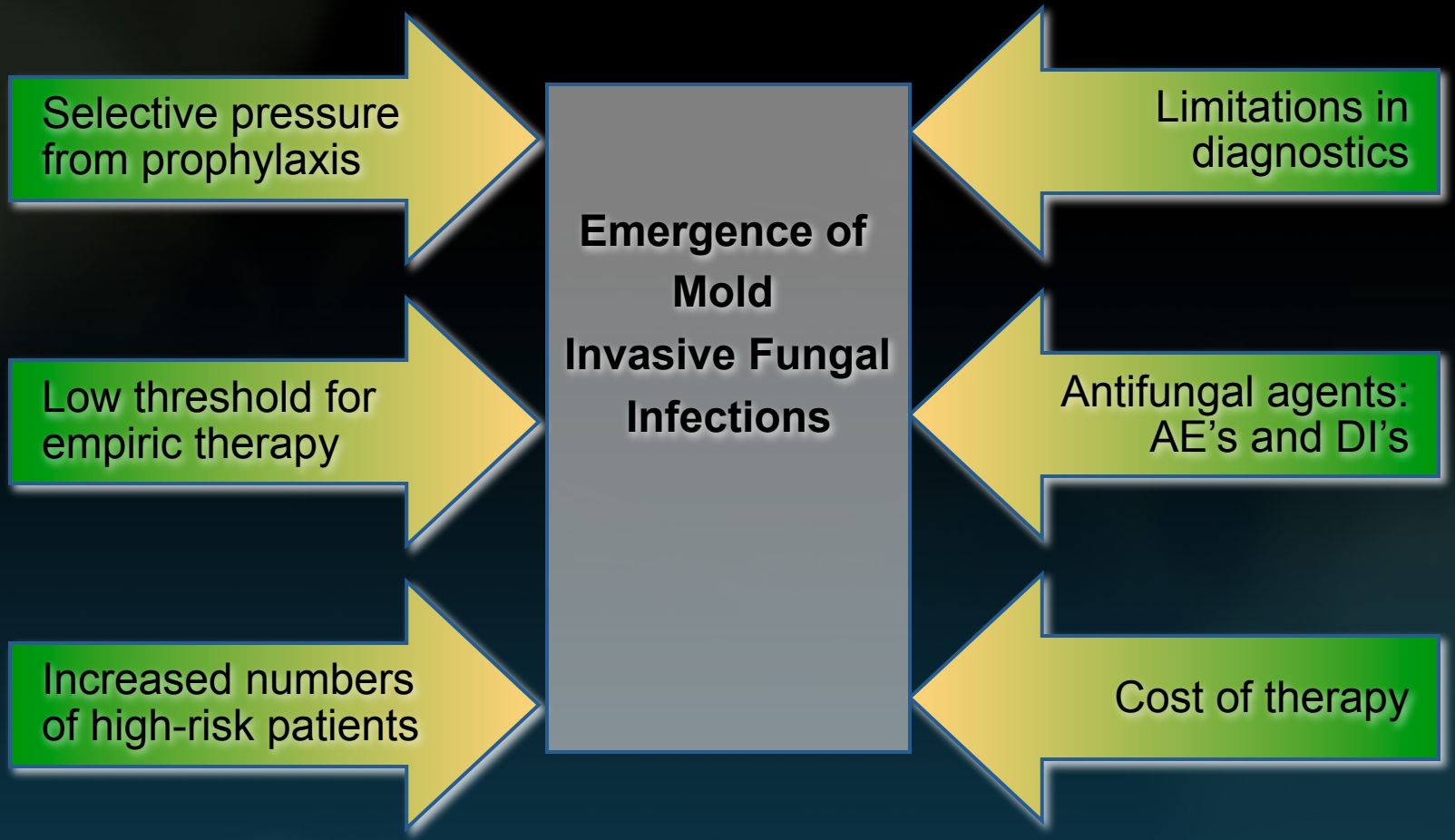


Figure 1) *Kaplan-Meier survival plot of* Candida *and* Aspergillus *patients from two Canadian sites*

Challenges of IFIs in Haematological Patients



De Pauw BE. *Clin Infect Dis.* 2005;41:1251-3.

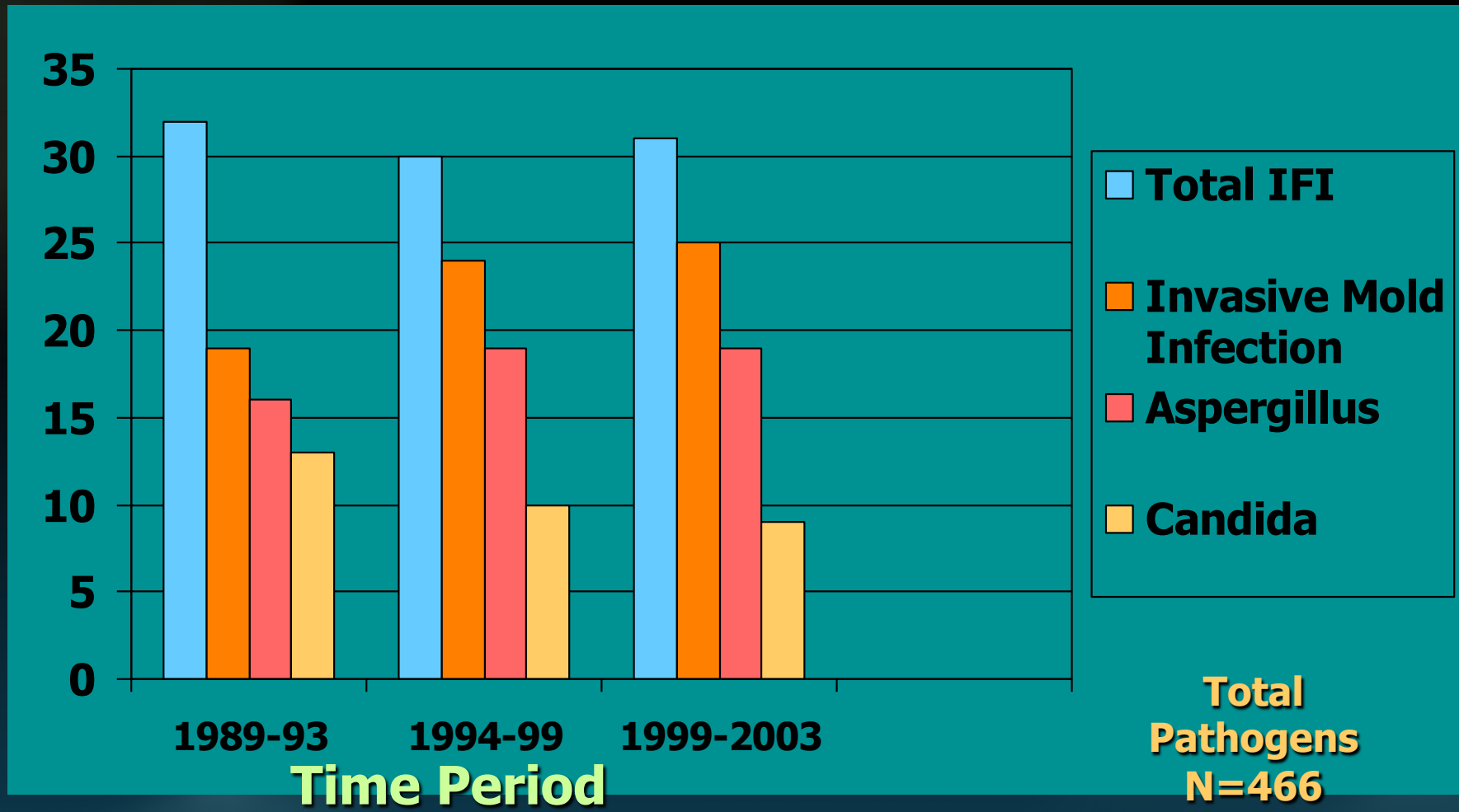
Hematological Malignancies

Clinical Characteristics of Patients with IFIs in MD Anderson Autopsy Sudy

	No. of Patients (%)		
Characteristic	1989-93	1994-98	1999-2003
Median Age (range)	44 (15-87)	49 (2-83)	53 (19-77)
AML	60/147 (41)	41/85 (48)	30/82 (37)
ALL	23/147 (16)	16/85 (19)	17/82 (21)
CML	25/147 (17)	5/85 (6)	5/82 (6)
NHL	15/147 (10)	9/85 (11)	9/82 (11)
CLL	8/147 (5)	3/85 (4)	9/82 (11)
Myelodysplastic Syndrome	8/147 (5)	5/85 (6)	6/82 (7)
Other	8/147 (5)	6/85 (7)	5/82 (6)
Allogeneic HSCT	43/137 (31)	30/88 (34)	26/102 (25)
Severe Neutropenia	29/43 (67)	17/30 (57)	17/26 (65)

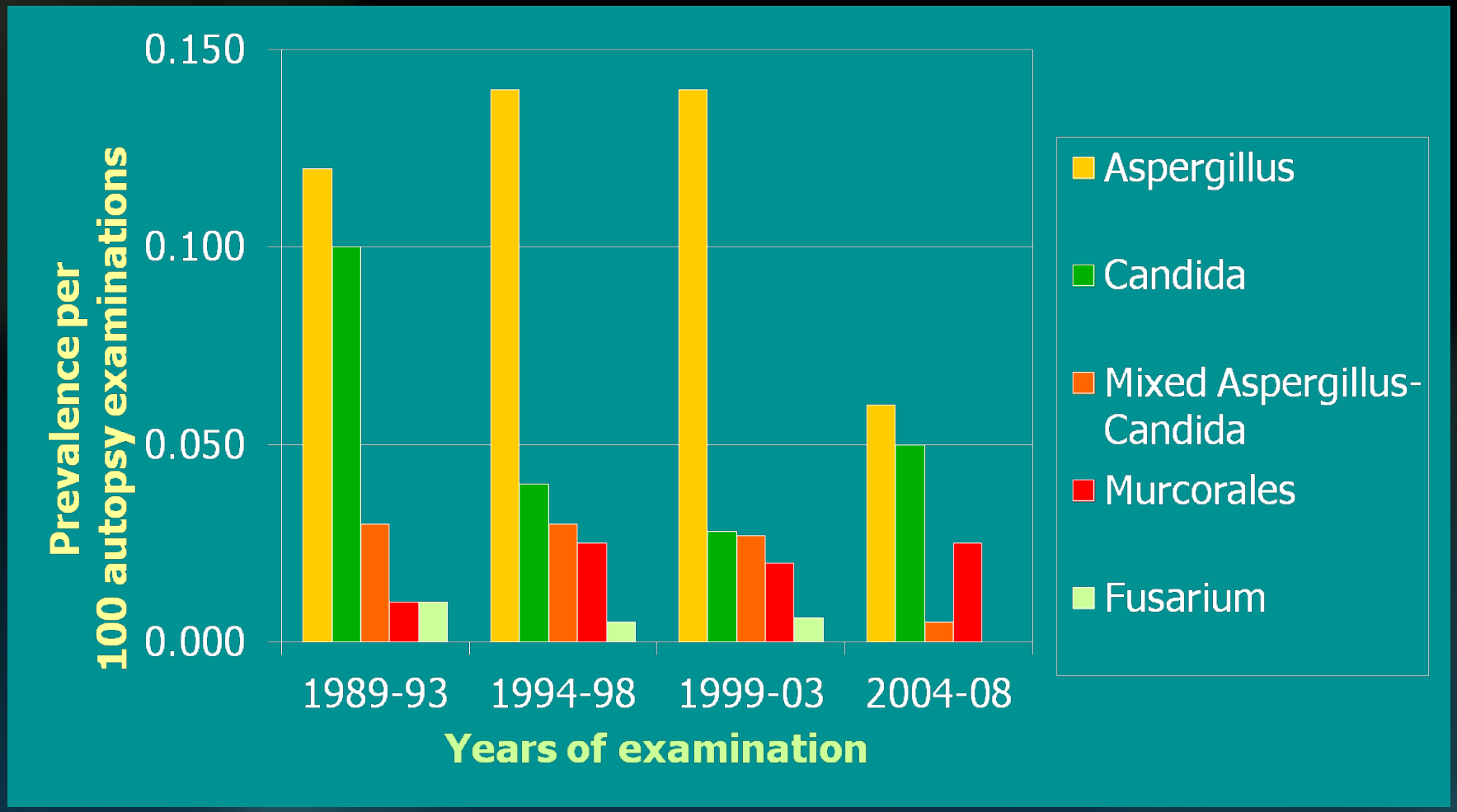
Chamilos G et al. Haematologica 2006;91:986-989

Prevalence of IFIs in Hematological Malignancies: Autopsy Study 1989-93, 1994-98 & 1999-2003 - MD Anderson



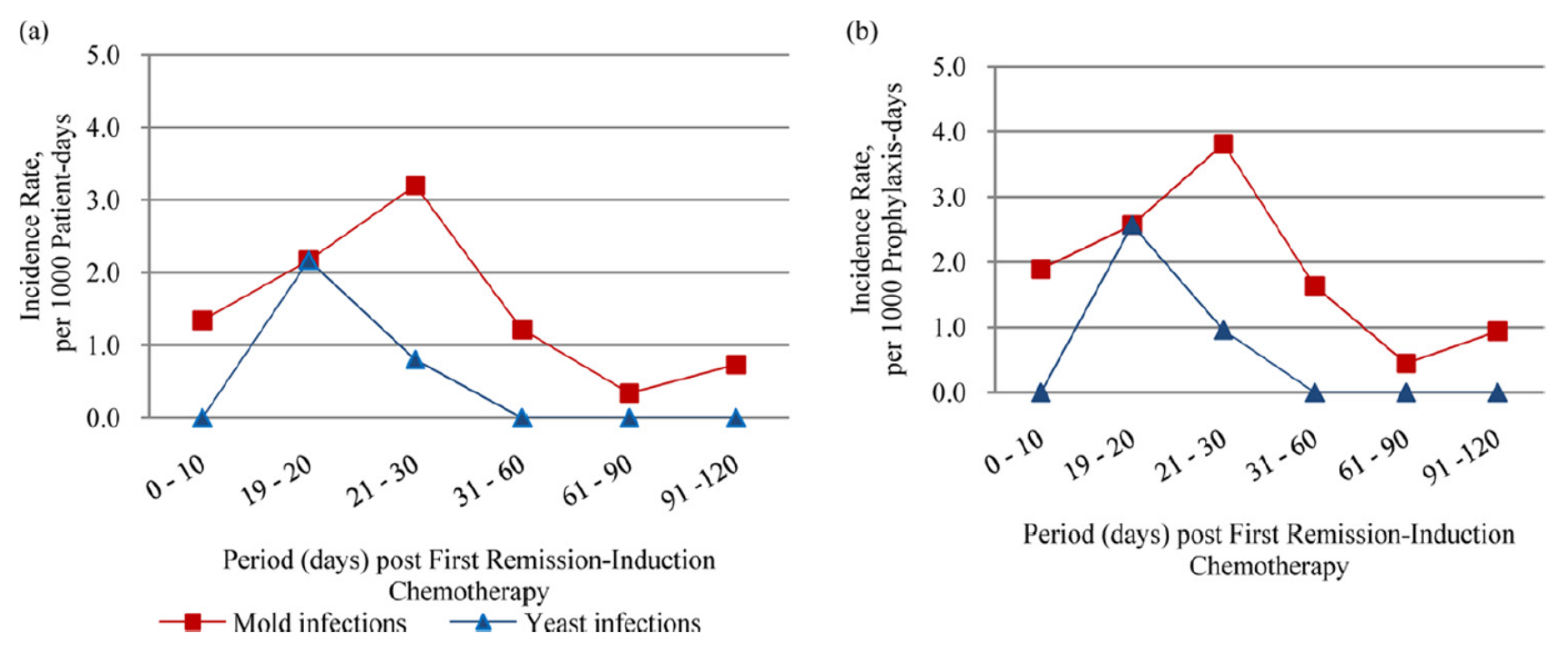
Chamilos G et al. Haematologica 2006;91:986-989

Prevalence of the 5 Most Common IFIs in Patients with Hematological Malignancies – MD Anderson Autopsy Study



Lewis RE et al. Mycoses 2013;56:638-645

IFI with Antifungal Prophylaxis in AML

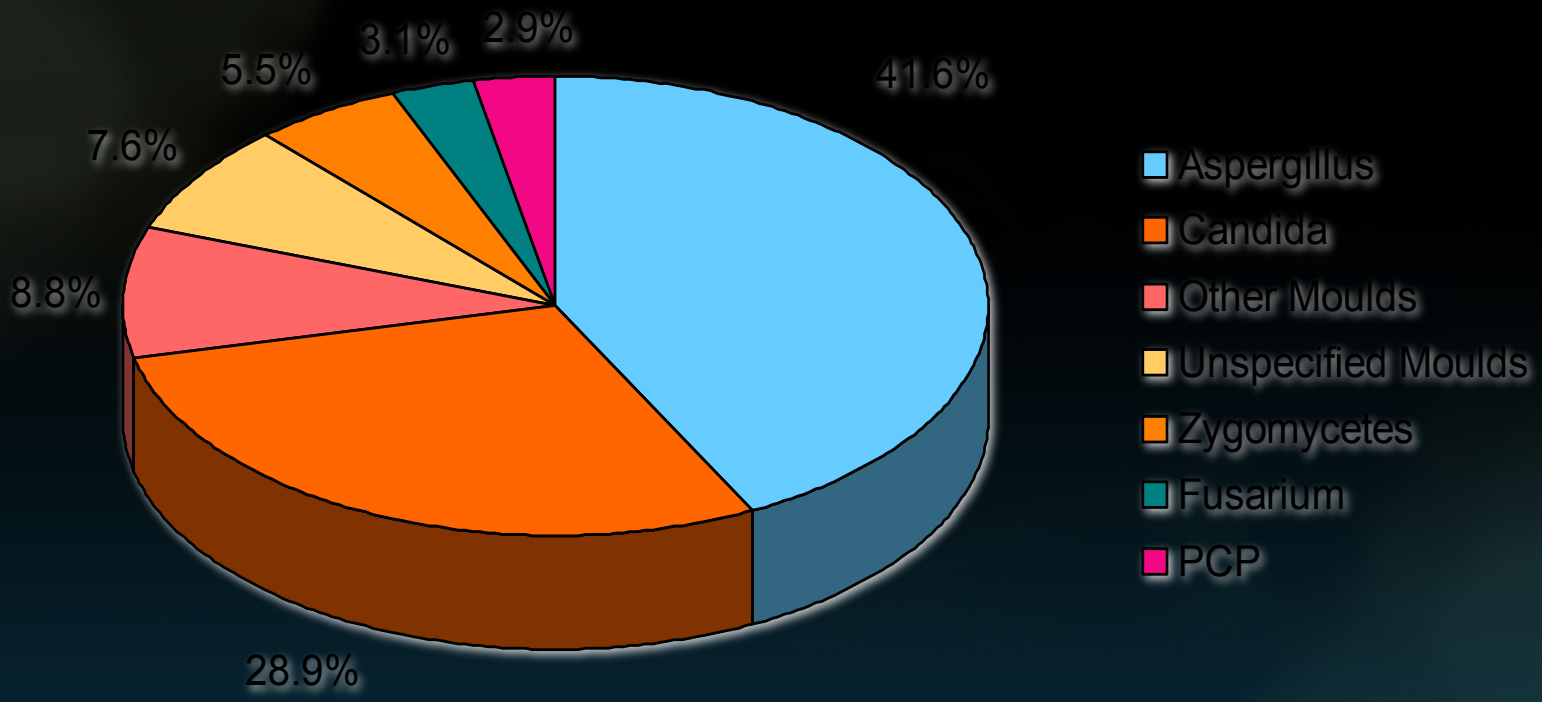


Incidence rates of documented mold and yeast IFIs per 1,000 patient-days (a) and per 1,000 prophylactic-days (b) over the 120-day period after first remission-induction chemotherapy among patients with newly diagnosed AML.

Gomes MZR et al. Antimicrob Agents Chemother 2014;58:865-873

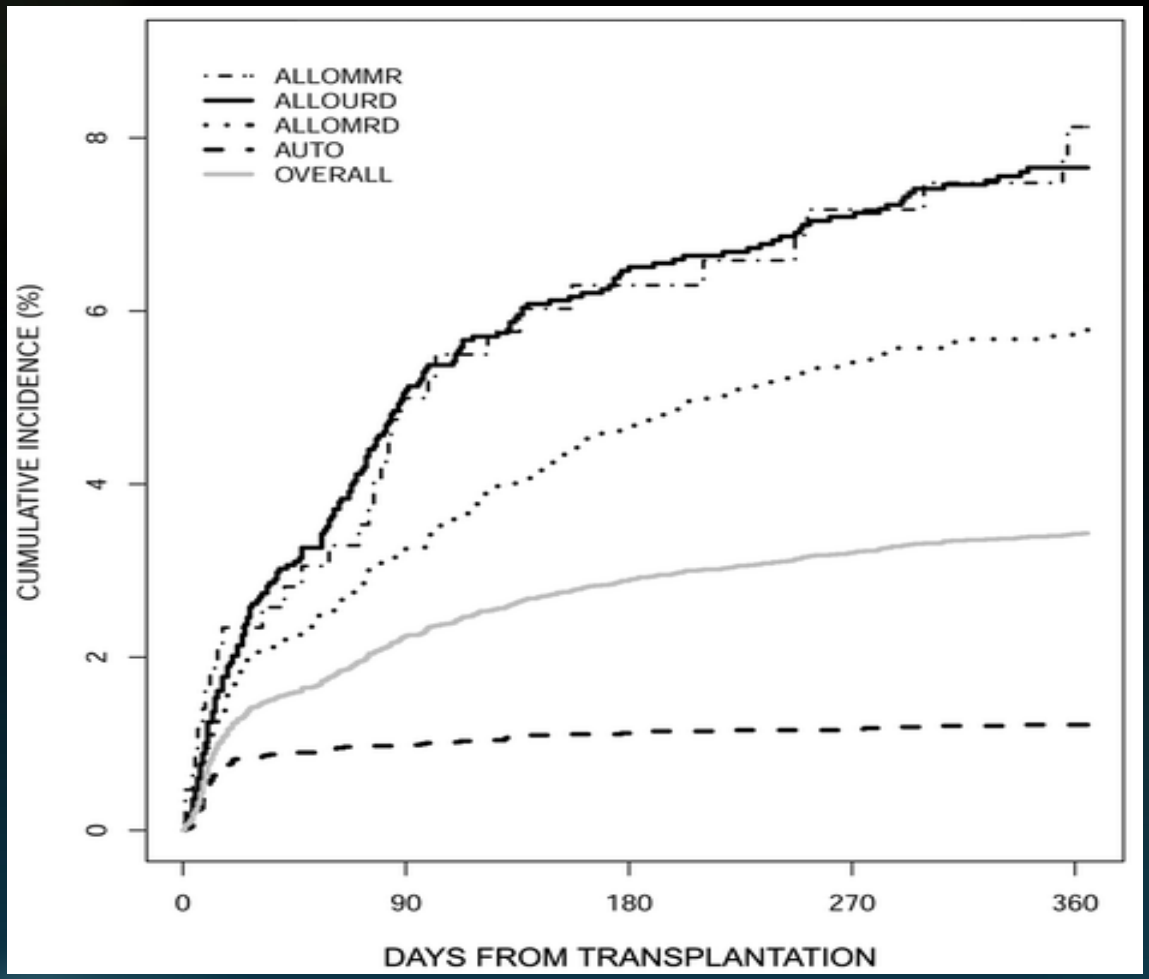
Allo-HSCT

IFIs in HSCTs



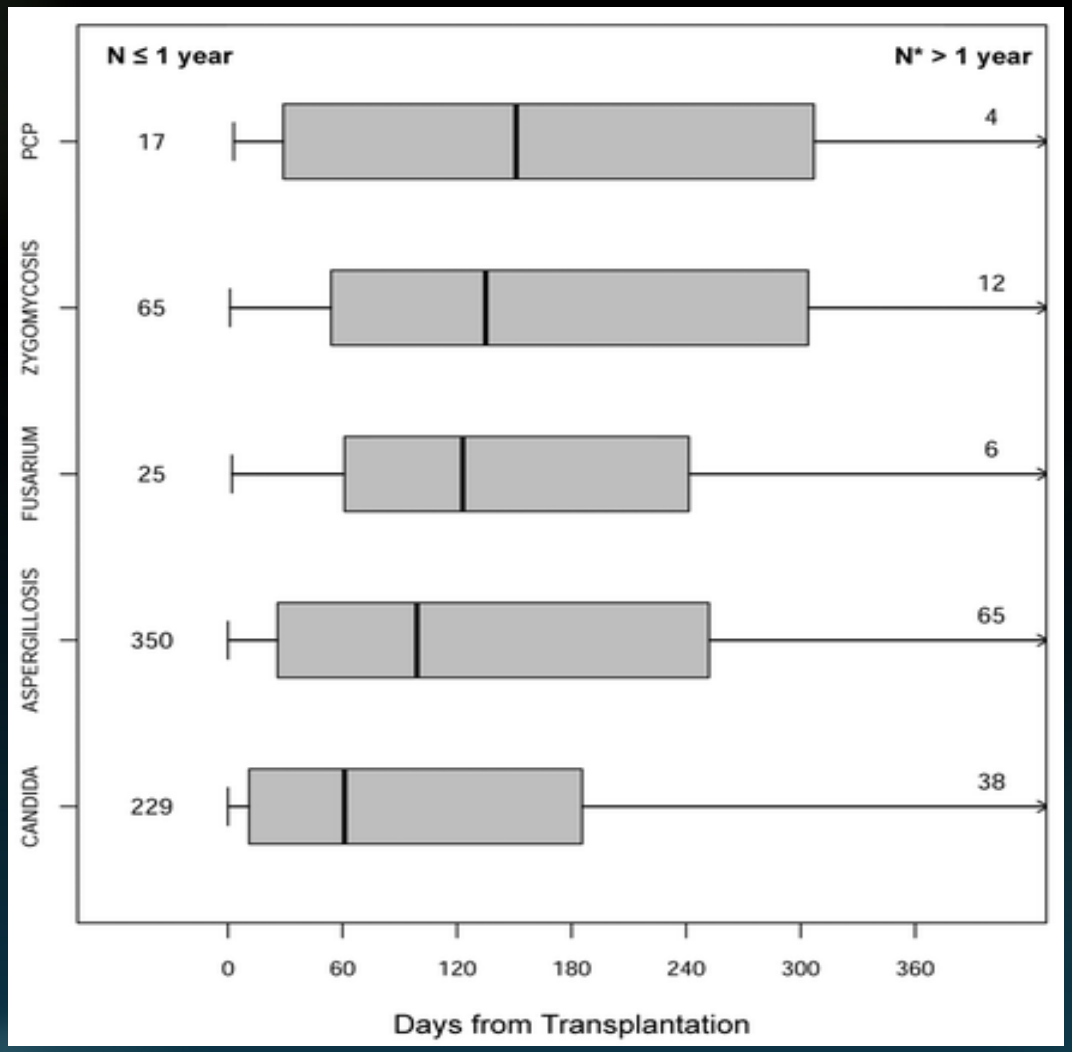
Pappas PG. FOFI 2005.

Cumulative Incidence of IFIs in HSCT



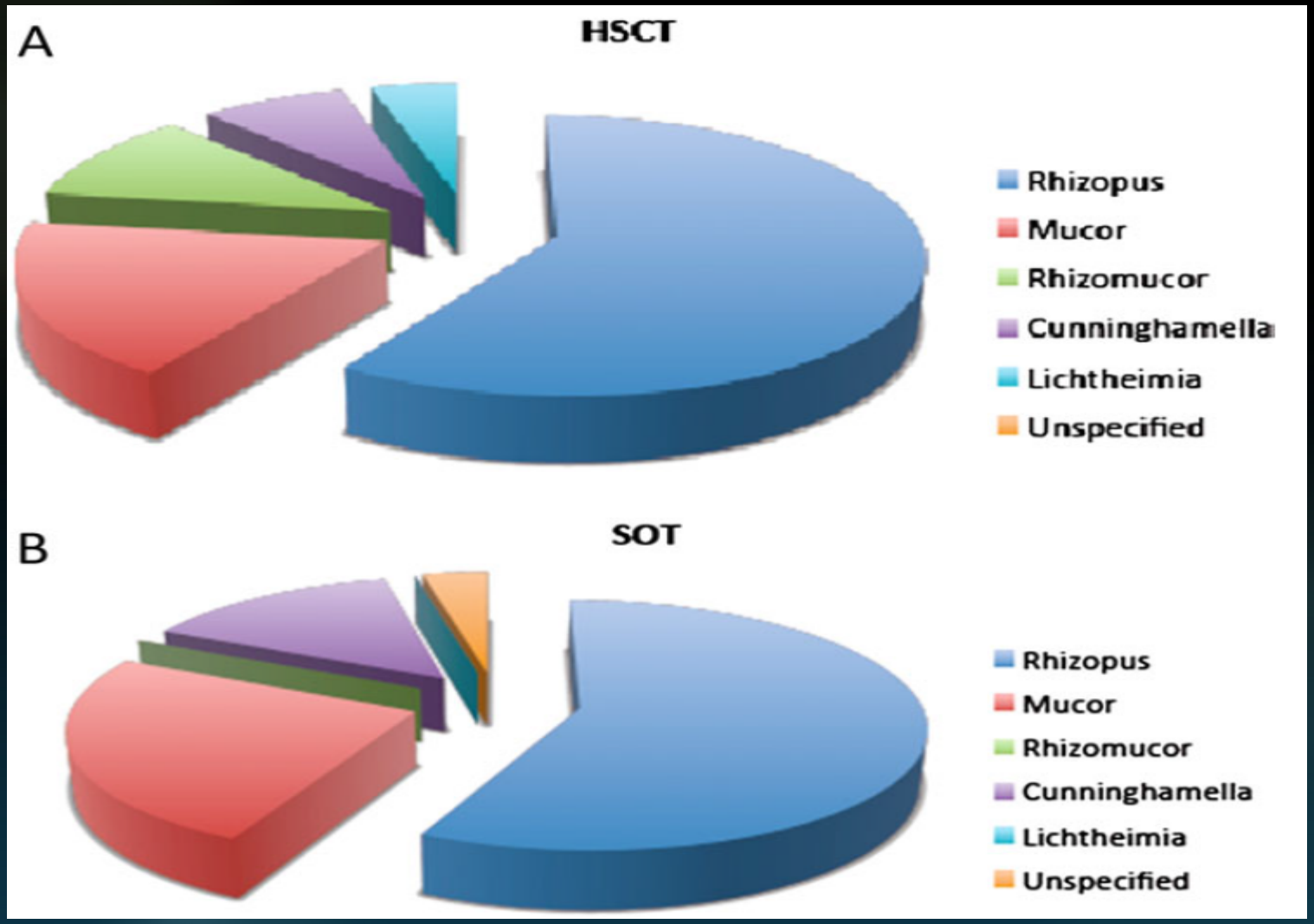
Kontoyiannis DP et al. Clin Infect Dis 2010;50:1091-1100

Time to IFIs in HSCT



Kontoyiannis DP et al. Clin Infect Dis 2010;50:1091-1100

Mucorales Species in HSCT & SOT - Transnet



Lanternier F et al. CID 2012;54:1629-1636

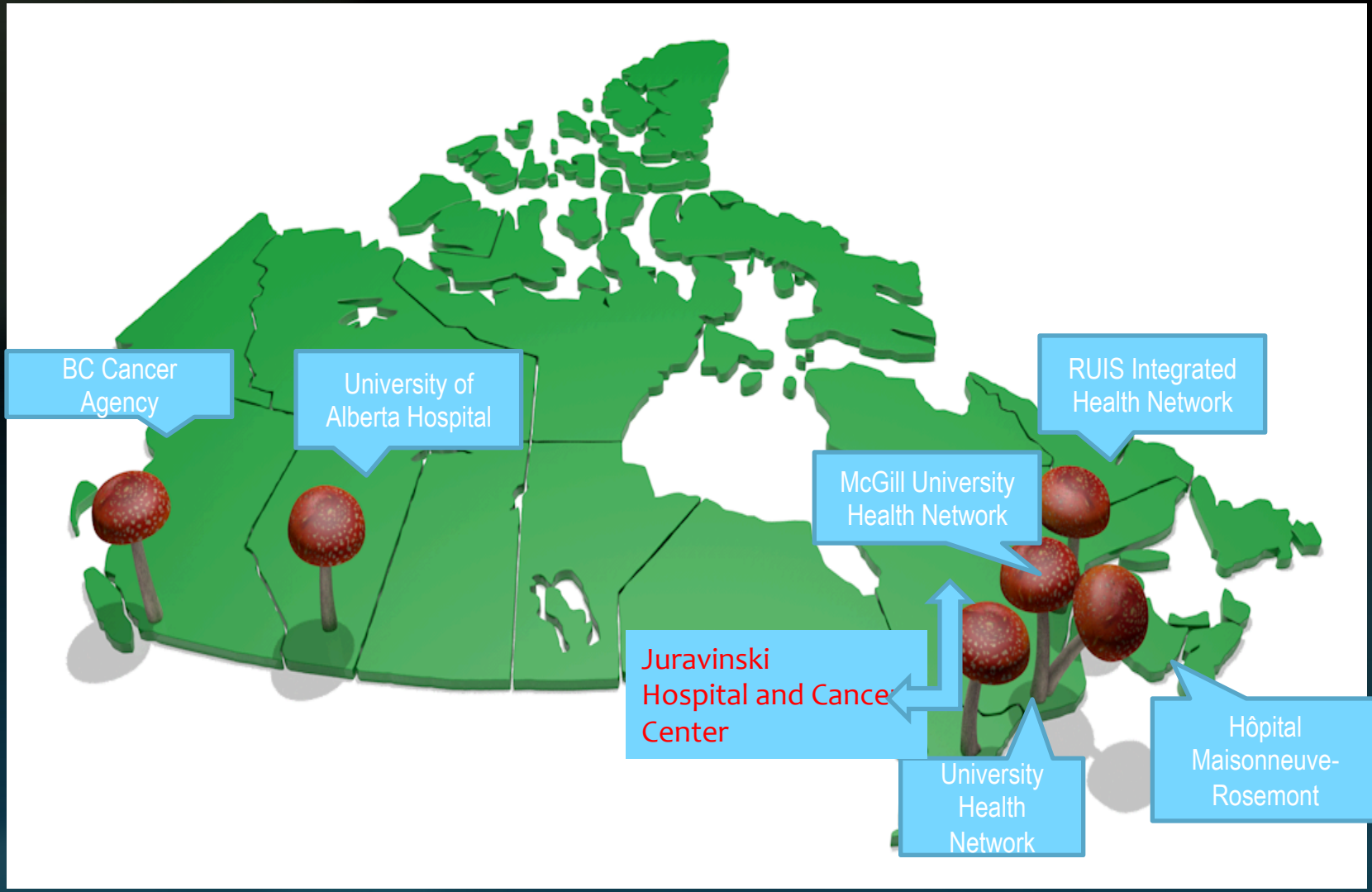
The incidence of IFI in Canada- Pending publication

The purpose of this retrospective review was to determine IFI incidence and mortality rate among patients undergoing HSCT, or chemotherapy for hematologic malignancies at 6 centers in 4 Canadian provinces

The objectives were to determine:

- IFI incidence by site
- Regional differences in IFI incidence
- Impact of different antifungal prophylaxis and treatment strategies on infection rates and mortality

Participating centers in Canada



Incidence of IA/IFI at Canadian Centers

	MUHC		HMR		RUIS	UHN	UAH	BCCA	
	HSCT	AML	HSCT	AL	AL	AL	AL	HSCT	AL
N	37	50	125	101	51	117	215	221	384
Proven/probable IA	8.1%	12.0%	8.8%	8.9%	13.7%	5.1%	2.3%	--	--
Possible IA	10.8%	20.0%	1.6%	0%	19.6%	63.2%	--	--	--
Proven/probable IFI	--	--	--	--	--	--	8.8%	4.5%	5.1%
Possible IFI							–	10.5%	20.7%
Observation period	2006-2010		2000-2006	2008-2010	2008-2011	2009-2011	2009-2010	2006-2012	
Median length of follow up	--	--	229 days	--	180 days	29 days	--	444 days	
Autologous or allogeneic HSCT	Allo	n/a	Allo	n/a	n/a	n/a	n/a	Allo	n/a
Chemotherapy •Induction •Consolidation	n/a	--	n/a	136 0	77 71	117 0	--	n/a	--

IFI screening & prophylaxis

Antifungal prophylaxis was employed at 5/6 centres

Prophylactic agent varied greatly between sites, & included fluconazole, micafungin, caspofungin, voriconazole, nystatin, and amphotericin B

- Incidence did not vary greatly between prophylactic regimens
- BCCA, as an example…

	MUHC		HMR		RUIS	UHN	UAH	BCCA	
	HSCT	AML	HSCT	AL	AL	AL	AL	HSCT	AL
N	37	50	125	101	51	117	215	221	384
Prophylaxis	100%	--	--	100%	19%	89%	--	100%	100%
Agent(s) used in prophylaxis	FLU (100%)	--	--	FLU (80%)	FLU (100%)	FLU (68%) MICA (7%) FLU+MICA (6%) CASPO (2%) FLU+VORI (2%) VORI (2%) FLU+NYA (2%) POSA (1%)	--	AMB MICA-50 MICA-100 FLU	AMB MICA-50 MICA-100 FLU VORI

IFI attributable mortality

	MUHC		HMR		RUIS	UHN	UAH	BCCA	
	HSCT	AML	HSCT	AL	AL	AL	AL	HSCT	AL
N	37	50	125	101	51	117	215	221	384
Overall mortality	--	--	--	--	14%	0%	--	14.8%	31%
Mortality in IFI population	--	--	53.8%	44.4%	23%	0%	52.6%	50%	35%
Mortality attributed to IFI	--	--	--	--	--	0%	22.2% (2/9 in 2009)	26.1%	--

In centers with data on mortality

- ~50% mortality in IFI population
- ~25% of deaths were directly attributable to IFI

Conclusions

In the present survey of Canadian centers

- The incidence of proven/probable IFI ranged from 4.5 to 8.8% in HSCT recipients, and from 5.1 to 13.7% in hospitalized patients with acute leukemias undergoing chemotherapy

There were large regional variations in the selection of antifungal agent for prophylaxis and treatment

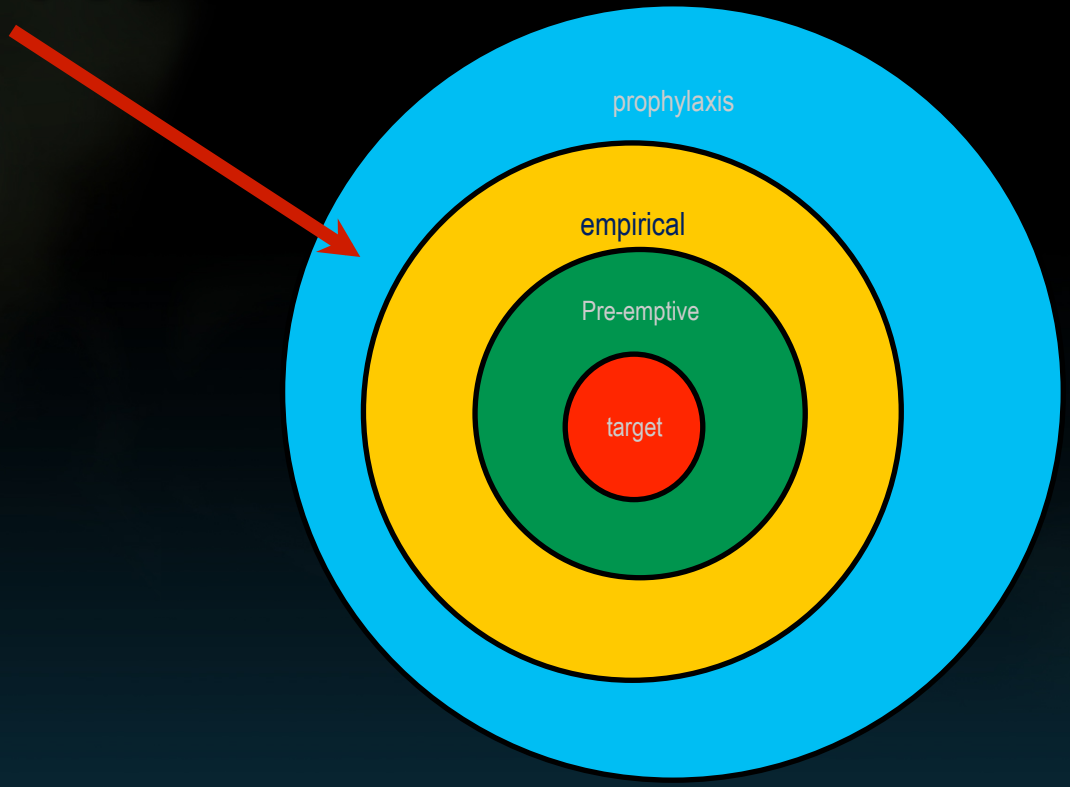
- Prophylaxis does not appear to result in a significantly lower incidence of IFI in at-risk patients

Diagnostic testing (i.e. serum or BAL GM) was inconsistent between centers, and not done in all high-risk patients

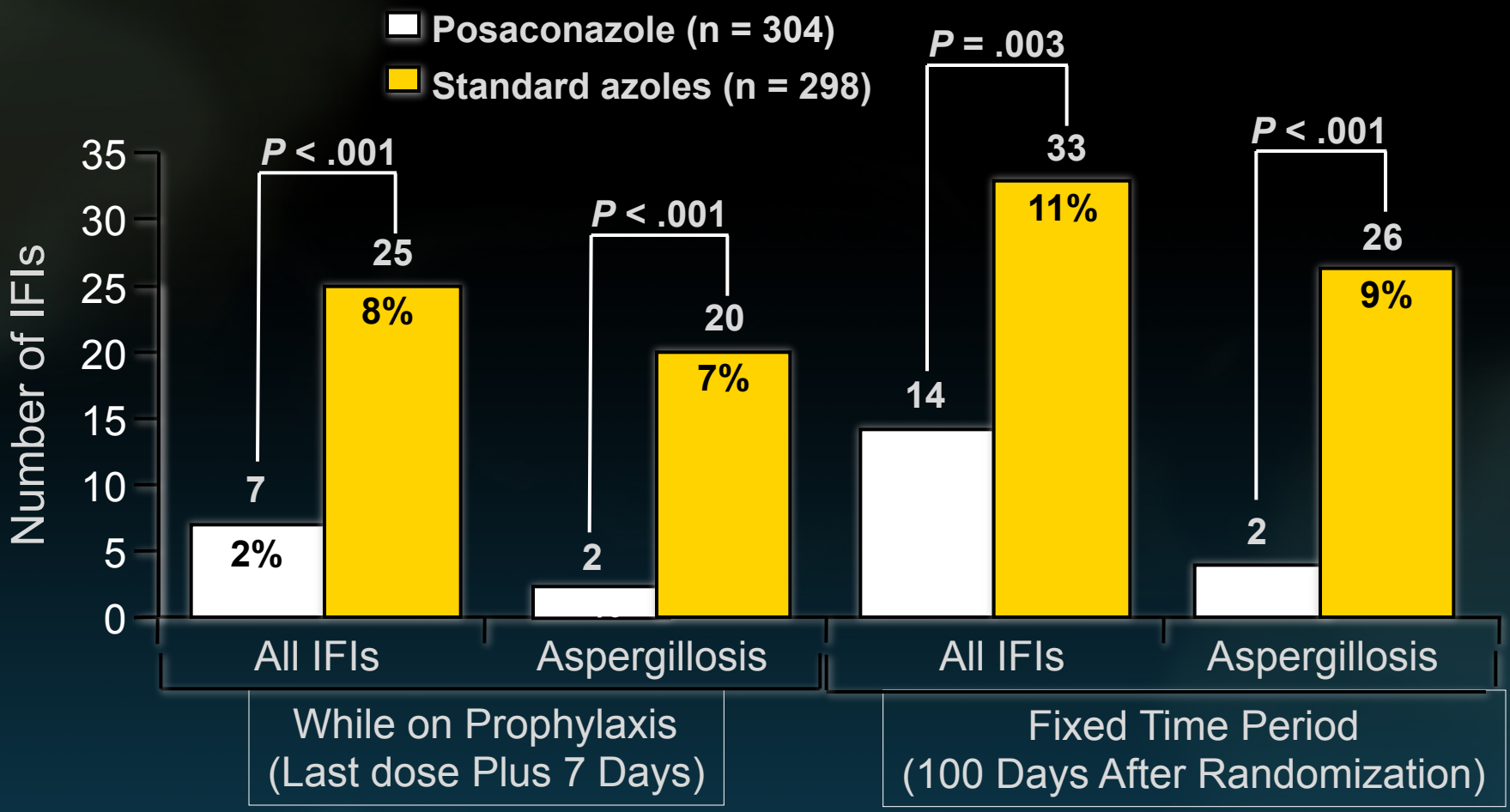
Approximately 25% of patient deaths were attributable to IFI

Hamilton Ontario- 1 year prospective study Aug 2012-Aug 2013- in AML/ALL/MDS patients only proven/probable disease by EORTIC criteria had an 8% rate of Invasive Mold Infection.

BREAKTHROUGH IFI DURING MOLD ACTIVE PROPHYLAXIS



Proven/Probable IFIs



IFI : Invasive Fungal Infection

.Cornely OA, et al. *N Engl J Med.* 2007;356:348-359.

Posaconazole in AML

	Years	Type	N° pts	IFDs	incidence%
RCT					
Cornelly et al, NEJM 2007	2002-05	RCT	304	7	2%
“Real life” series					
Michallet et al, Med Mycol 2011	2007-08	Pros	55	2	3.6%
Candoni et al, EHA 2011	2009-10	Retro	55	2	4%
Lerolle et al, ICAAC 2011	2007-10	Retro	209	8	3.8%
Hahn et al, Mycoses 2011	2007-08	Retro	21	1	5%
Egerer et al, Mycoses 2011	2007-09	Retro	76	1	1.3%
Vehreschild et al, JAC 2010	2006-08	Retro	77	3	3.9%
Busca et al, 5th TIMM 2011	2009-10	Retro	61	0	0
Ananda-Rajah, Haematol 2012	2006-10	Retro	68	0	0
Peterson et al, Mycoses 2013	2006-10	Retro	100	4	4%
ALL STUDIES			722	21	2.9%

Data from the SEIFEM 2010-C registry

1,192 AML recorded in the registry

No intensive therapy
(Support or low dose)
211 patients

981 AML treated with intensive therapies

2010-2012

510 POSACONAZOLE prophylaxis

140 (27%) subsequent i.v. antifungal therapies

Pegano et al. CID 2012; Dec; 55(11)

SEIFEM 2010

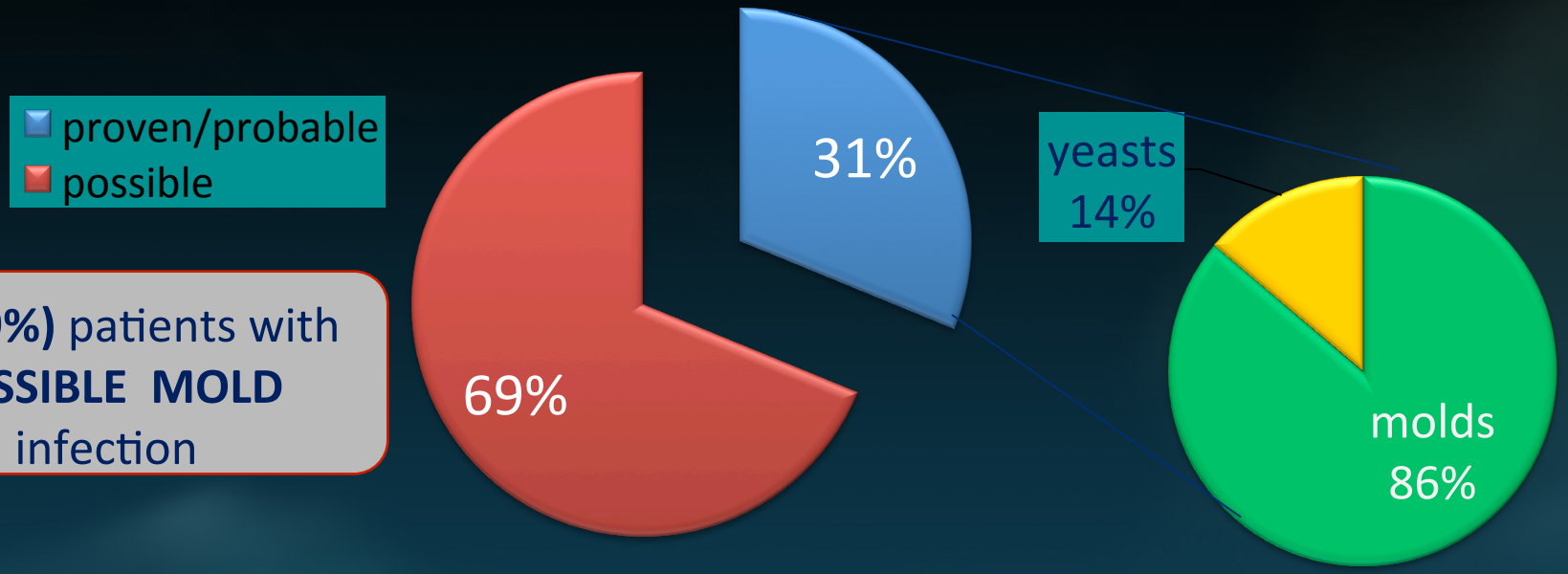
What kind of breakthrough infections do we have to face?

2010-2012

545 POSACONAZOLE prophylaxis

93 patients with IFD (17%)

No rare molds except 1 *Trichosporon*



64 (69%) patients with **POSSIBLE MOLD** infection

SUMMARY

1. Rising burden of IFI in HaematoOncology Patients
2. Need for ongoing epidemiological data on Invasive Mold Infections in Canada
3. Need to monitor microbiologic trends in era of broad azole prophylaxis