

Epidemiology:
“The times, they are a changing..”

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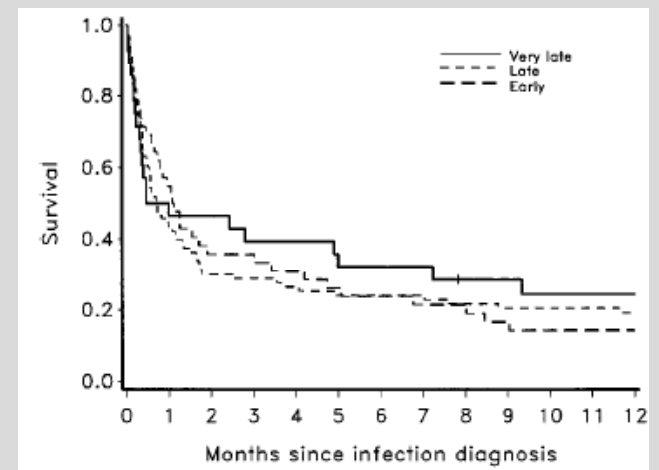
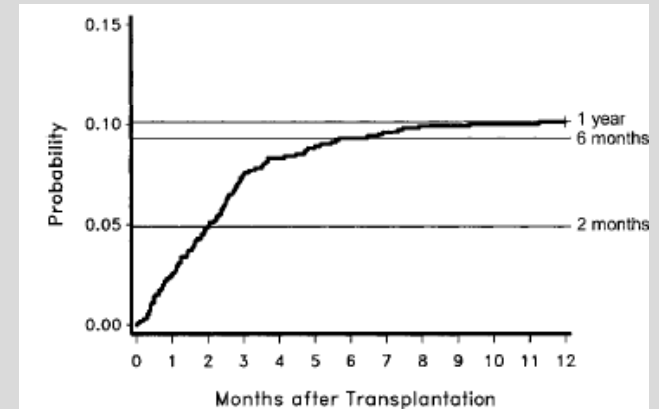
Johns Hopkins University School of Medicine

Historic Observations: 1990 - 2000

- Increase incidence worldwide during 1990s
 - Reported incidence in highest risk populations: 5 – 15%
 - Appreciable amount of late disease
 - ◆ Allo BMT¹
 - ◆ Lung transplant (46% after 9 mo.)²
 - High mortality (60 – 80%)

¹ Marr et al. Blood 2002; 100: 4358-66

² Minari et al. Transplant Infect Dis 2002; 4: 195-200



Changes

- Variable burden of IA, *even within transplant types* reported across centers in multicenter studies
- Better outcomes of IA compared to prior years
- Biology of risks appreciated, expansion of hosts
- Clarification of species, and potential antifungal drug resistance

Multicenter Surveillance Networks

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

Aspergillosis in HCT

■ TRANSNET ¹

- 12-month CI / 100 transplant
- 1.2 (autologous) – 8.1 (MM-URD allo)
- Median 99 days post HCT
 - 22% in 1st month
 - 40% - 60% within 4 months
- Overall survival 1 year 25%

■ PATH Alliance ²

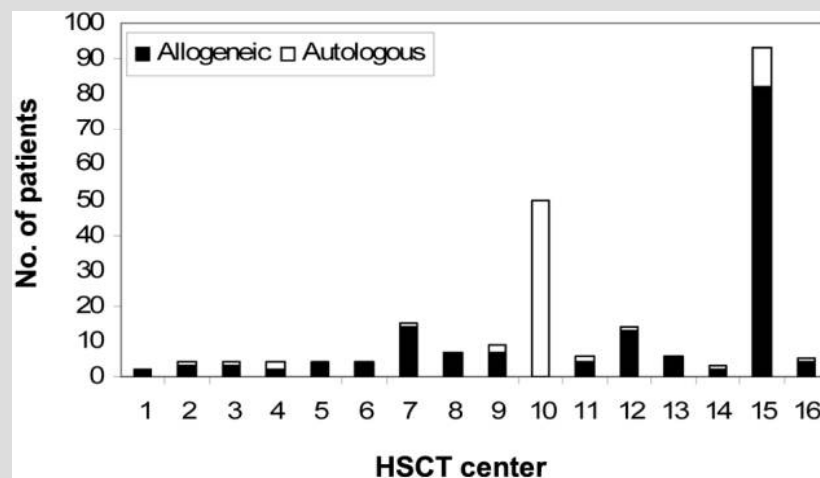
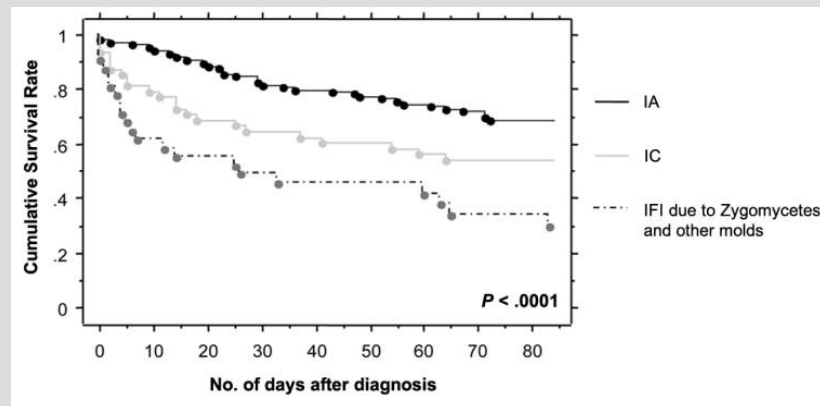
- IA most frequent (59%) of 250 IFIs identified
- Median 82 days after HCT (3-6542)

¹ Kontoyiannis et al.
(submitted)

² Neofytos et al. Clin Infect
Dis 2009; 48: 265-73

Important observations

- Better outcomes
- Variable identification by center
 - 2 centers reported 62.8% of IA



Neofytos et al. Clin Infect Dis 2009; 48: 265-73

Aspergillosis in SOT

■ TRANSNET ¹

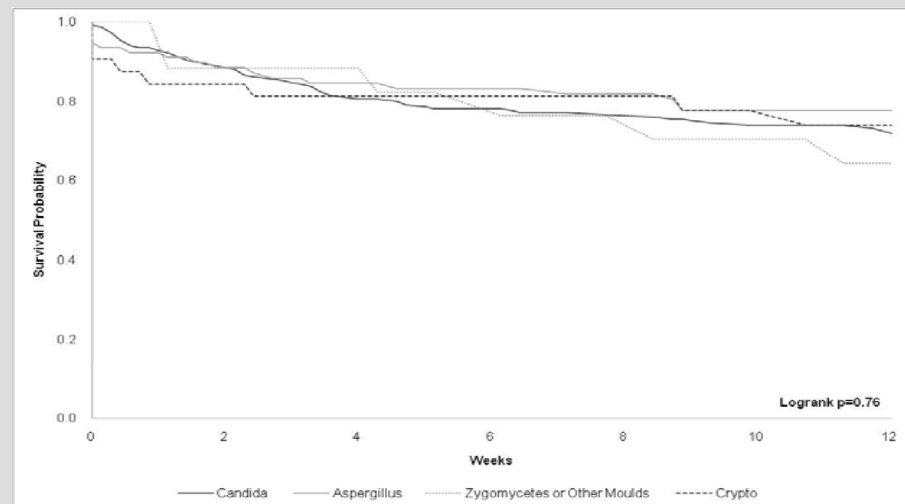
- 1208 IFIs among 1063 SOT
- IA 19%, 1 yr CI 0.65%

■ PATH Alliance ²

- Lung transplant recipients most frequent
- Late disease, outcomes better than previously reported

¹ Pappas et al. (submitted)

² Neofytos et al. (in preparation)



Changes

- Variable burden of IA, *even within transplant types* reported across centers
 - Geographically restricted exposure
 - Variable case identification
 - Surveillance methods
 - Diagnostics
 - Differences in follow up of transplant recipients
 - Long-term follow up of outcomes in referral centers
 - Quality of LTFU clinical data reported from elsewhere
 - Variable case – mix
 - Type of transplants performed
 - Type of patients, regimens within transplant types

IA in autologous transplant recipients

- Few studies show high risks among autologous BMT recipients
 - Nation-wide study of 1188 ASCT in Finland
 - Incidence IA 0.8%
- 1 center reported high number of cases among autologous BMT in PATH Alliance center
 - Aggressive diagnostics
 - Subtle differences in patients
 - High number of MM, relapse 60%
 - 56% treated with multiple transplants, 75% with steroids

¹ Jantunen et al. Eur J Haematol 2004 73(3): 174-8

² Neofytos et al. Clin Infect Dis 2009; 48: 265-73

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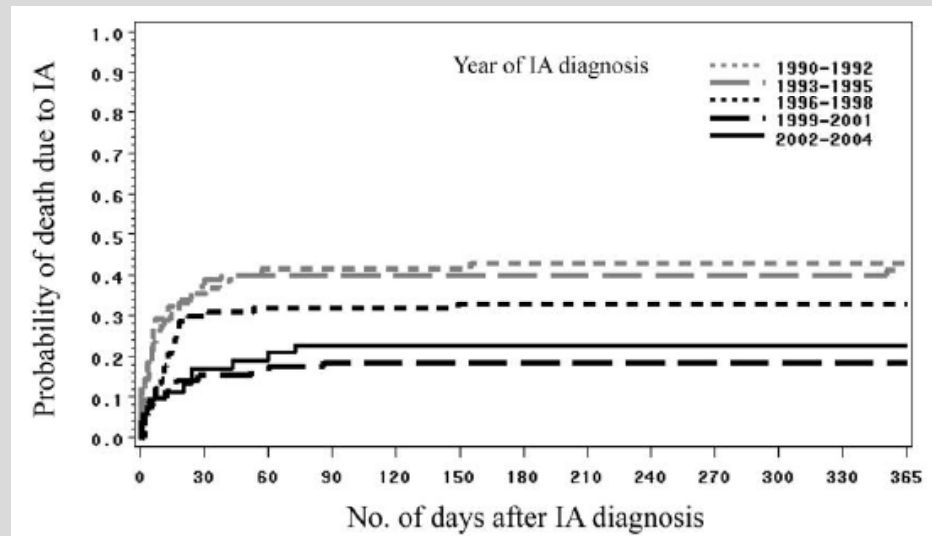
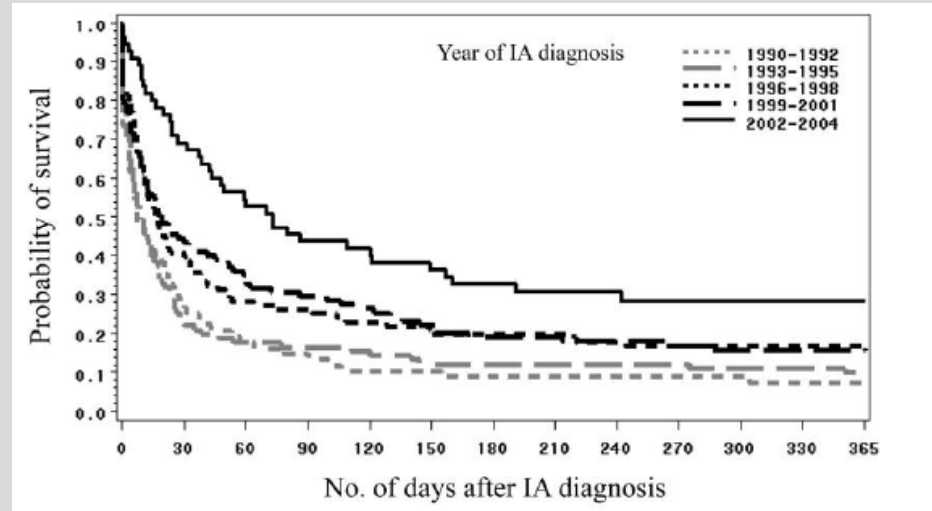
Outcomes

Historical death rates 3-12 mo.
60 – 80%

12 week survival in
randomized trials

Herbrecht: 29%

Ambiload: 34%



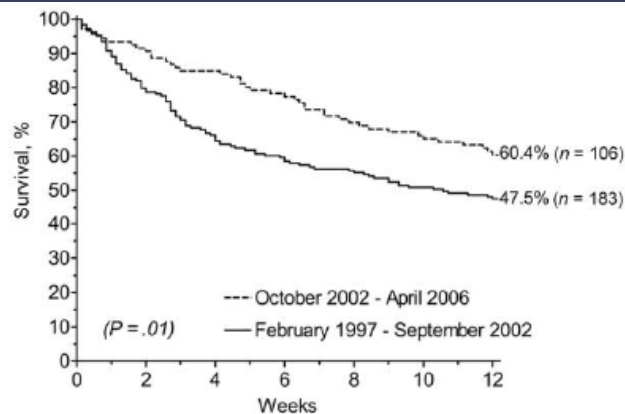
Upton et al. Clin Infect Dis 44(4)531-40 (2007)

Risks for Death

Table 3. Risk factors for death due to all causes in 405 hematopoietic cell transplant (HCT) recipients with proven or probable invasive aspergillosis (IA).

Variable	Unadjusted		Adjusted	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Recipient-related factors				
Year of IA diagnosis (2002–2004 vs. previous)	0.6 (0.5–0.9)	.008
Good-risk underlying disease ^a	0.7 (0.5–0.9)	.001	NS	NS
Severe impairment on PFT ^b	1.6 (1.0–2.8)	.07	2.0 (1.1–3.8)	.03
Transplant-related factors				
HLA mismatch	1.3 (1.0–1.6)	.04	1.4 (1.1–1.8)	.02
Unrelated donor	1.3 (1.1–1.6)	.008	NS	NS
Receipt of PBSCs	0.7 (0.6–0.9)	.009	0.8 (0.6–1.0)	.08
Nonmyeloablative conditioning	0.6 (0.4–0.9)	.006	0.6 (0.4–1.0)	.05
Transplant complications				
Neutropenia ^c	2.3 (1.7–3.1)	<.0001	1.6 (1.1–2.3)	.02
Lymphopenia ^d	1.9 (1.5–2.4)	<.0001
Monocytopenia ^e	1.3 (1.0–1.6)	.05
Acute GVHD ^f	1.8 (1.5–2.2)	<.0001	NS	NS
Hyperbilirubinemia ^g	43.8 (33.5–57.1)	<.0001	2.9 (2.0–4.1)	<.0001
Elevated creatinine level ^h	10.4 (7.5–14.2)	<.0001	2.0 (1.3–3.0)	.001
Cytomegalovirus disease ⁱ	2.1 (1.6–2.8)	<.0001	NS	NS
Corticosteroid dosage of ≥2 mg/kg per day	3.1 (2.2–4.4)	<.0001	1.6 (1.1–2.4)	.008
IA-related factors				
Disseminated IA	4.1 (3.3–5.2)	<.0001	1.9 (1.4–2.6)	<.0001
Late IA	3.7 (2.6–5.3)	<.0001	2.5 (1.7–3.7)	<.0001
Proven IA	2.7 (2.0–3.7)	<.0001	1.3 (1.0–1.6)	.08
Voriconazole monotherapy	0.6 (0.4–1.0)	.06	NS	NS

French outcomes studies



¹Cordonnier et al. Clin Infect Dis 2006 42(7): 955-63

²Nivoix et al. Clin Infect Dis 2008; 47: 1176-84

■ 2002- 64 French HCT centers¹

- Survival at 4 months 40%
- Risks for death: age (young), disseminated IA, pleural effusion, monocytopenia, steroids for GVHD

■ 385 cases over 9 years in Strasbourg, France²

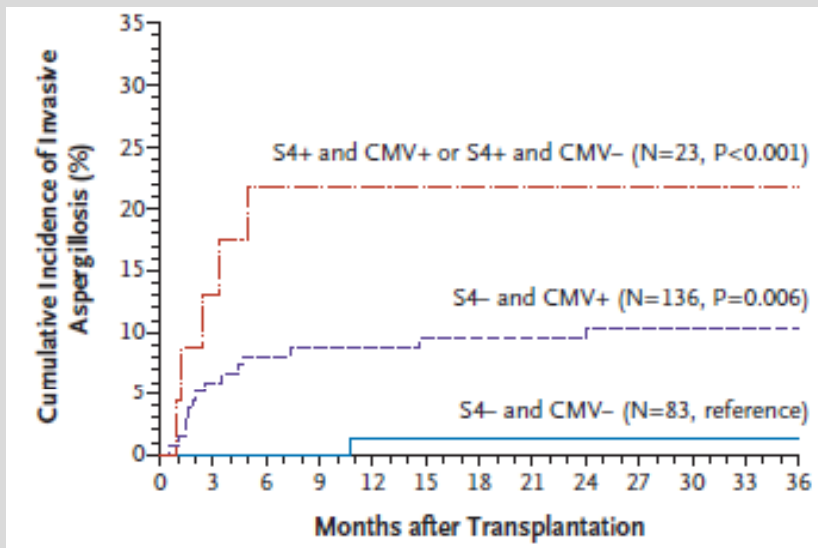
- Overall outcomes improved after 2002
- Risks for death: transplant, underlying disease, prior lung disease, steroids, poor renal function, monocytopenia, dissemination, pleural effusion

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Genetics and IA



■ Moving beyond “neutropenia” or “GVHD”

- Numeric deficiency in all cell types
 - Neutrophils, monocytes, lymphocytes
 - Few functional studies
- Iron overload
- Respiratory virus infections, CMV

■ Genetics

- Plasminogen alleles ¹
 - Computational haplotype-based genetic analysis followed by association study in allo HSCT cohort: polymorphism in plasminogen gene in HCT recipient associated with IA risk
- TLR4 haplotype and CMV seropositivity in HCT *donor* influence risks in recipient ²
- IL1 gene cluster polymorphisms associated with risks for IA, C-reactive protein production³

¹ Zaas et al. PLoS Genetics 2008

² Bochud et al. New Eng J Med 2008; 359: 1766-77

³ Sainz et al. J Clin Immunol 2008; 28: 473-85

Hosts

- Expanded at-risk population for IA
 - COPD ¹
 - ICU ²
 - Rheumatologic conditions ³
 - Other conditions treated with anti-TNF α therapies ⁴

¹ Samarakoon and Soubani Chronic Resp Dis 2008; 5: 19-27

² Meersseman et al. Clin Infect Dis 2007; 45(2): 205-16

³ Cornillet et al. Clin Infect Dis 2006; 43: 577-84

⁴ DeRosa et al. Infect Cont Hosp Epid 2003; 24(7): 477-82

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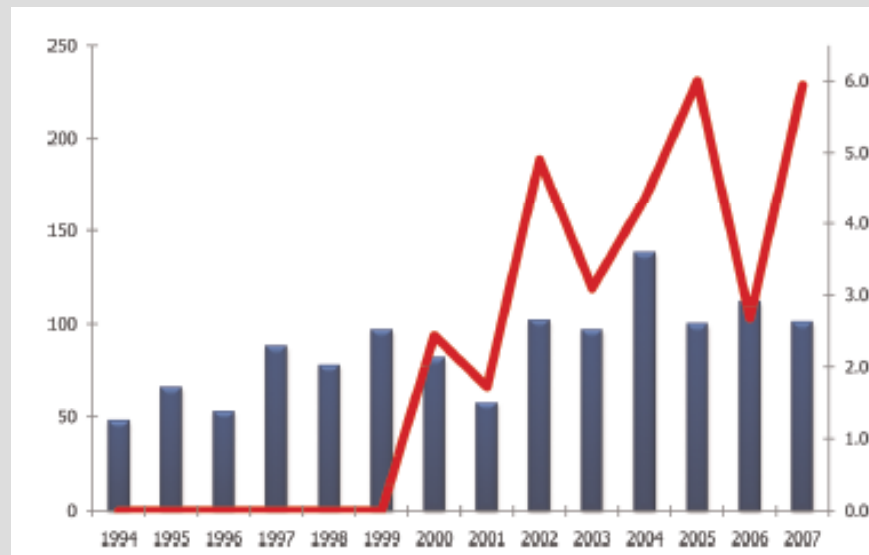


Variable susceptibility

- Voriconazole 'resistance' among some species
 - *Aspergillus ustus*, *A. glaucus*
- Multiple species described among clinical isolates phenotypically identified as *A. fumigatus*
 - *Aspergillus lentulus*
 - *Aspergillus fumisynnematus*
 - *Aspergillus udagawae*
 - *Aspergillus alliaceus*
 - *Aspergillus fumigati*

Azole resistance in *A. fumigatus*

- Resistance among isolates recovered in The Netherlands 1994 – 2007
- Annual prevalence after 1999 6%
- High MICs to voriconazole, ravuconazole and posaconazole
- Genetically similar, changes in *cyp51A* and gene promoter



Snelders et al. 2008 PLoS Med
5(11): e219

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Thank you

“Open your arms to change, but don't let go of your values”
Dalai Lama

“A small group of thoughtful people can change the world. Indeed, it's the only thing that ever has”
Margaret Mead