Le infezioni fungine nel trapianto di cellule staminali emopoietiche

Claudio Viscoli
Professor of Infectious Disease
University of Genova, Italy

Potential conflicts of interest

- Received grants as speaker/moderator in national or international meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, BMS, Novartis
- Received grants for participation in national or international advisory boards by Gilead, Astellas, MSD, Pfizer, Novartis
- Obtained research grants for my institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis
- Expert for the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency
- Member of several local boards (Genoa, Liguria, Italy and my hospital) (Hospital Infection Control and Antibiotic Stewardship, HIV, vaccination, Hospital Formulary)

Allogeneic HSCT

- A real challenge for transplant physicians and ID consultants
- In the same patient multiple immune defects occur in sequence and sometimes overlapping
- The first month is usually dominated by severe neutropenia
- Then, if engraftment is successfull, the grafted immune system starts reacting more or less strongly against the recipient (Graft versus Host Disease-GvHD)
- This reaction should not be suppressed but rather «modulated», because of its an anti-leukemia effect
- Modulation of GvHD needs additional immunosuppressive therapy, but T-cell related defects now predominate

What I am going to deal with you in the next 20 minutes

- Incidence, etiology and timetable of IFI in HSCT
- Variables associated with Invasive Aspergillosis (IA)
- IA: impact on overall survival

Biol Blood Marrow Transplant xxx (2014) 1–9

Girmenia C, et al

Incidence and Outcome of Invasive Fungal Diseases after Allogene
of the Gr

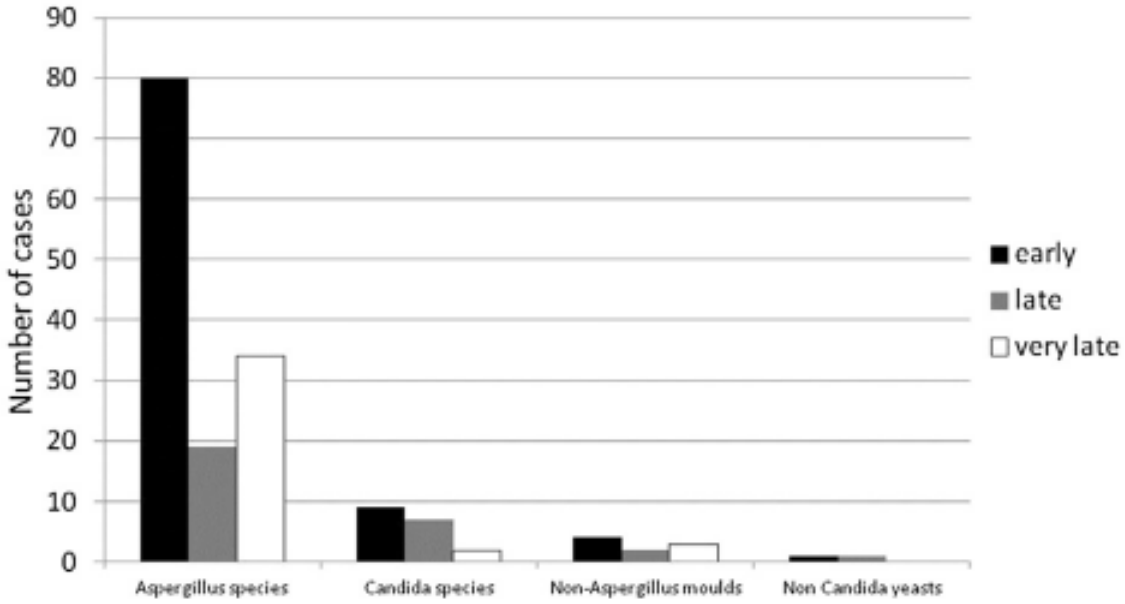


Figure 3. Timing of IFD. Early IFD refers to infection diagnosed on days 0-40 after allo-HSCT; late IFD, to infection diagnosed on days 41-100; and very late IFD, to infection diagnosed after day 100.

60	5.81	5.81	5.82
100	6.73	6.72	6.73
365	8.83	8.82	8.84

Epidemiology and outcomes of invasive fungal infections in allogeneic haematopoietic stem cell transplant recipients in the era of antifungal prophylaxis: a single-centre study with focus on emerging pathogens

GmbH
336

Do
Au

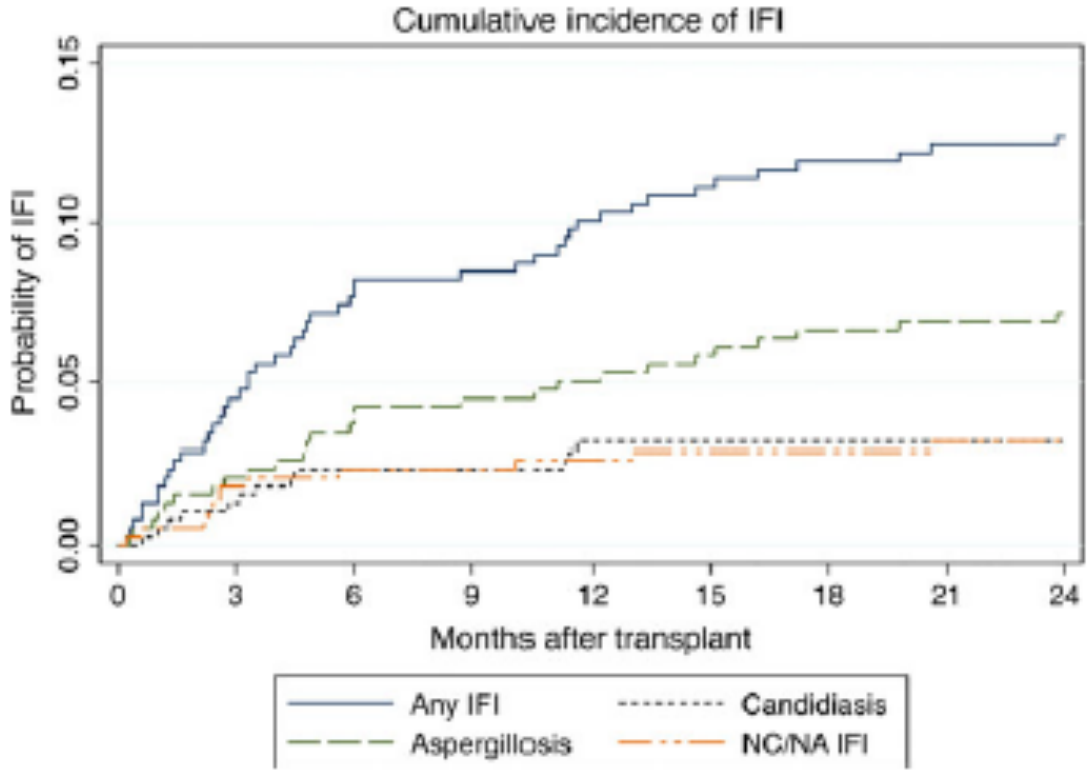


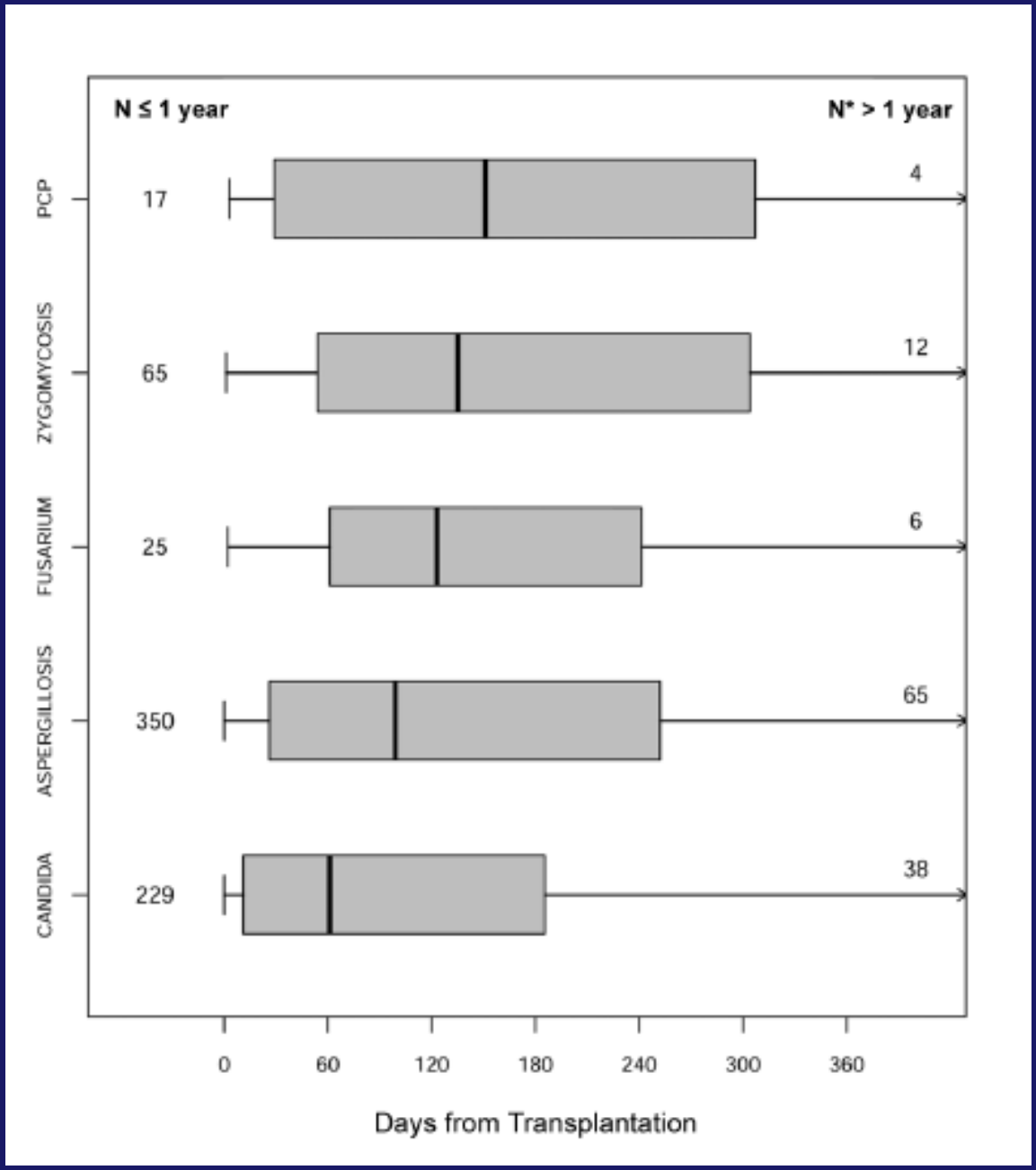
Figure 2 Incidence of invasive fungal infection after transplantation, stratified by infection type.

transplant prior to diagnosis of IFI. There were no sta-

Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database

Dimitrios P. Kontoyiannis, Kieren A. Marr, Benjamin J. Park, Barbara D. Alexander, Elias J. Anaissie, Thomas J. Walsh, James Ito, David R. Andes, John W. Baddley, Janice M. Brown, Lisa M. Brumble, Alison G. Freifeld, Susan Hadley, Loreen A. Herwaldt, Carol A. Kauffman, Katherine Knapp, G. Marshall Lyon, Vicki A. Morrison, Genovefa Papanicolaou, Thomas F. Patterson, Trish M. Perl, Mindy G. Schuster, Randall Walker, Kathleen A. Wannemuehler, John R. Wingard, Tom M. Chiller, and Peter G. Pappas[a]

Clinical Infectious Diseases 2010;50:1091–1100


N ≤ 1 year
N* > 1 year
PCP
ZYGOMYCOSIS
FUSARIUM
ASPERGILLOSIS
CANDIDA
17
65
25
350
229
4
12
6
65
38
0
60
120
180
240
300
360
Days from Transplantation

Invasive aspergillosis in allogeneic stem cell transplant recipients from alternative donor: incidence, risk factors and outcome.

M. Mikulska, et al, BMT , 2009

- Incidence 15%
- 50% early
- 50% late

Bow *et al. BMC Infectious Diseases* (2015) 15:128
DOI 10.1186/s12879-015-0855-6

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients

Eric J Bow[1*], David J Vanness[2], Monica Slavin[3], Catherine Cordonnier[4], Oliver A Cornely[5], David I Marks[6], Antonio Pagliuca[7], Carlos Solano[8], Lael Cragin[9], Alissa J Shaul[9], Sonja Sorensen[9], Richard Chambers[10], Michal Kantecki[11], David Weinstein[11] and Haran Schlamm[12]

Table 1 Outcomes extracted from the randomized clinical trials and included into the mixed treatment comparison

Study	All-cause mortality	Incidence of proven/ probable IFI overall	Incidence of proven/ probable IA	Incidence of proven IC	Incidence of OLAT use
Winston 2003 [29]					
Fluconazole	28/67 (42%)	17/67 (25%)	8/67 (12%)	8/67 (12%)	Not reported
Itraconazole	32/71 (45%)	6/71 (8%)	3/71 (4%)	2/71 (3%)	Not reported
Marr 2004 [26]					
Fluconazole	44/148 (30%)	25/148 (17%)	20/148 (14%)	5/148 (3%)	25/148 (17%)
Itraconazole	55/151 (36%)	19/151 (13%)[a]	16/151 (11%)	4/151 (3%)	19/151 (13%)
Ullmann 2007 [27]					
Fluconazole	59/299 (20%)	27/299 (9%)	21/299 (7%)	4/299 (1%)	29/288 (10%)
Posaconazole	58/301 (19%)	16/301 (5%)	7/301 (2%)	4/301 (1%)	31/291 (11%)
Wingard 2010 [28]					
Fluconazole	59/295 (20%)	24/295 (8%)	17/295 (6%)	5/295 (2%)	89/295 (30%)
Voriconazole	57/305 (19%)	14/305 (5%)	9/305 (3%)	3/305 (1%)	73/305 (24%)
Marks 2011 [10]					
Itraconazole	44/241 (18%)	5/241 (2%)	5/241(2%)	0/241 (0%)	101/241 (42%)
Voriconazole	40/224 (18%)	3/224 (1%)	1/224 (0.4%)	2/224 (1%)	67/224 (30%)

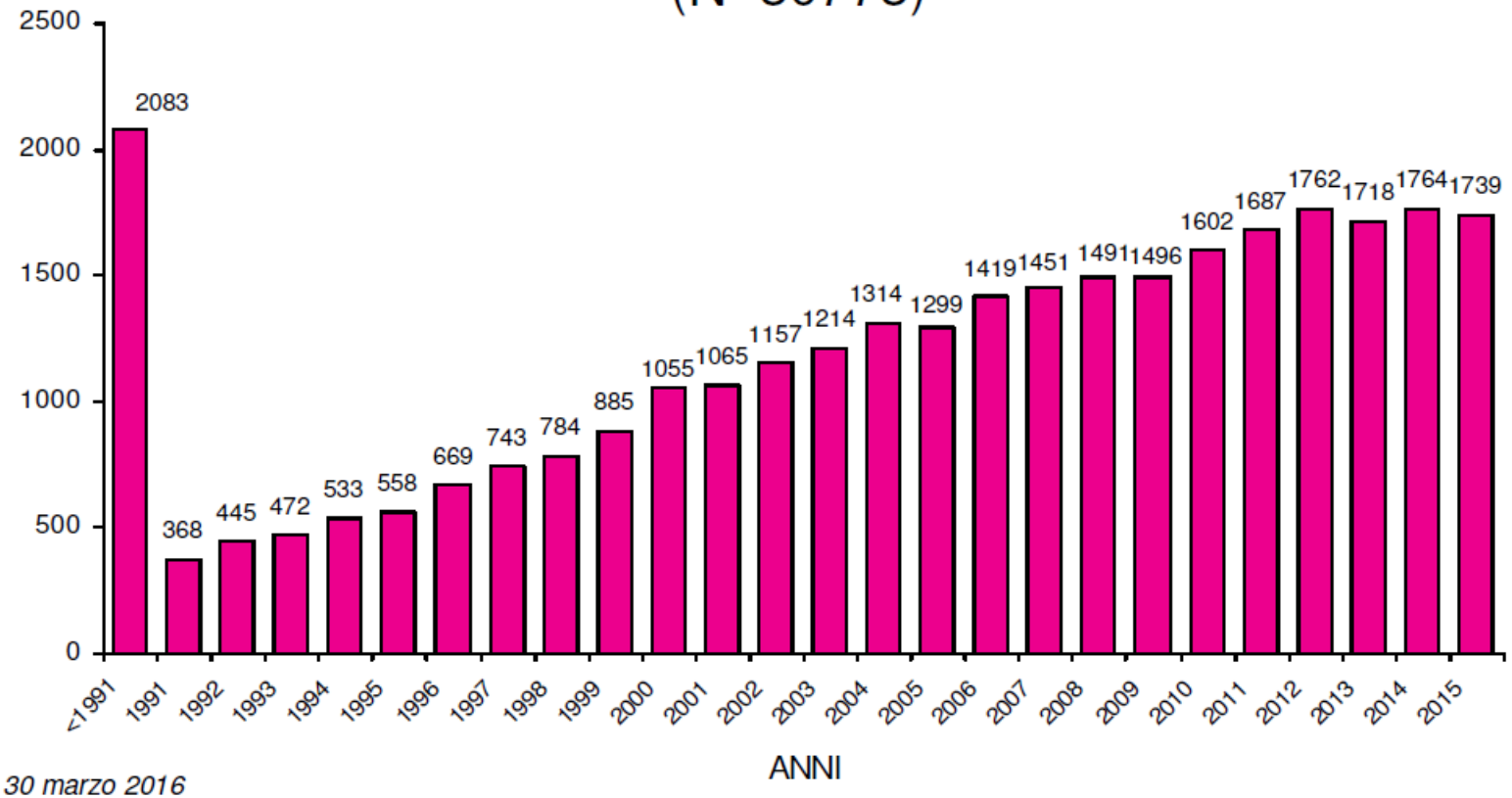
Bow *et al. BMC Infectious Diseases* (2015) 15:128

What I am going to deal with you in the next 20 minutes

- Incidence, etiology and timetable of IFI in HSCT
- Variables associated with Invasive Aspergillosis (IA)
- IA: impact on overall survival

GITMO Trapianto Allogenico

Allotrapianti registrati
(N=30773)

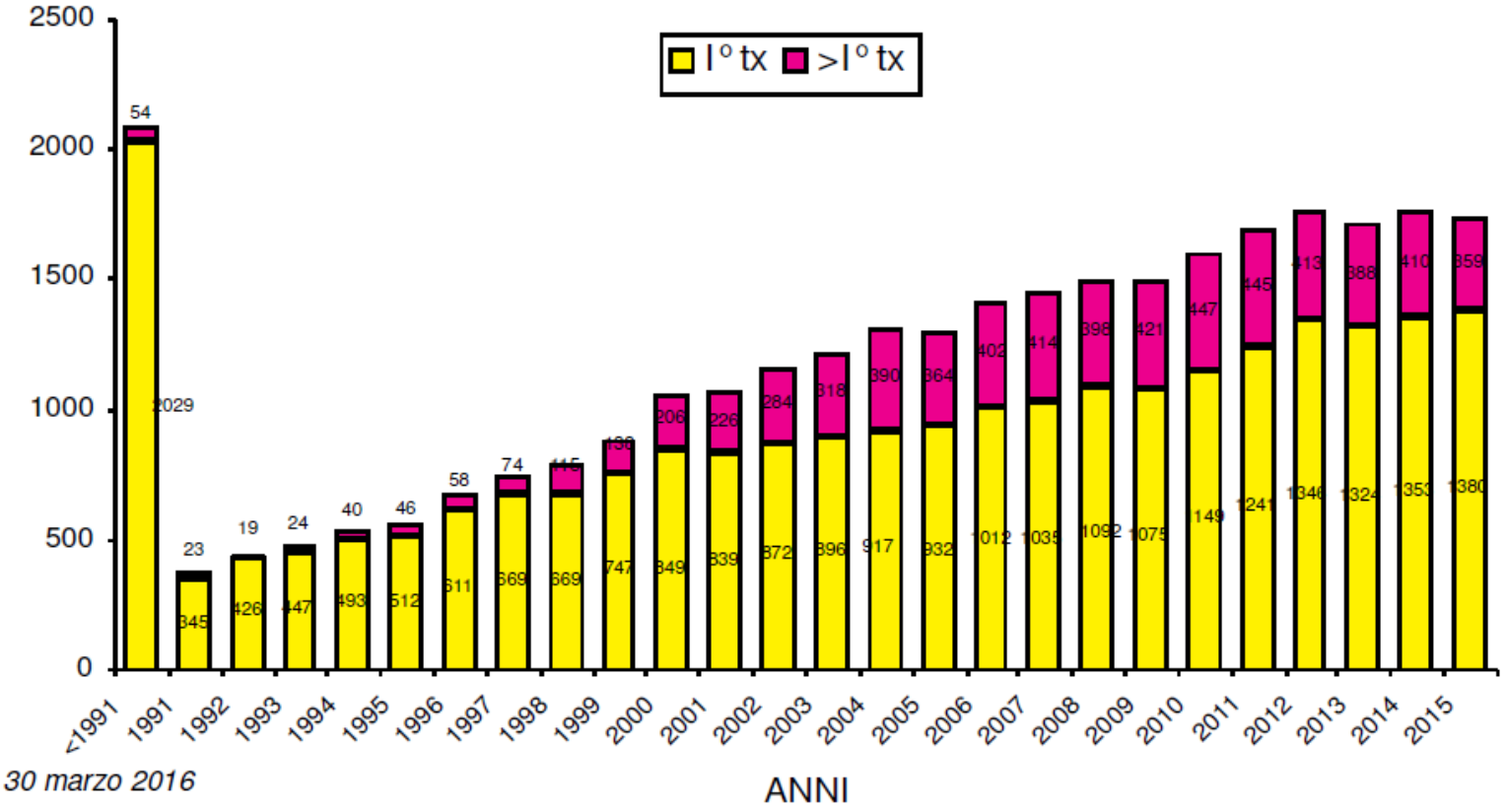


al 30 marzo 2016

GITMO

GITMO Trapianto Allogenico

Allotrapianti registrati
(N=30773)

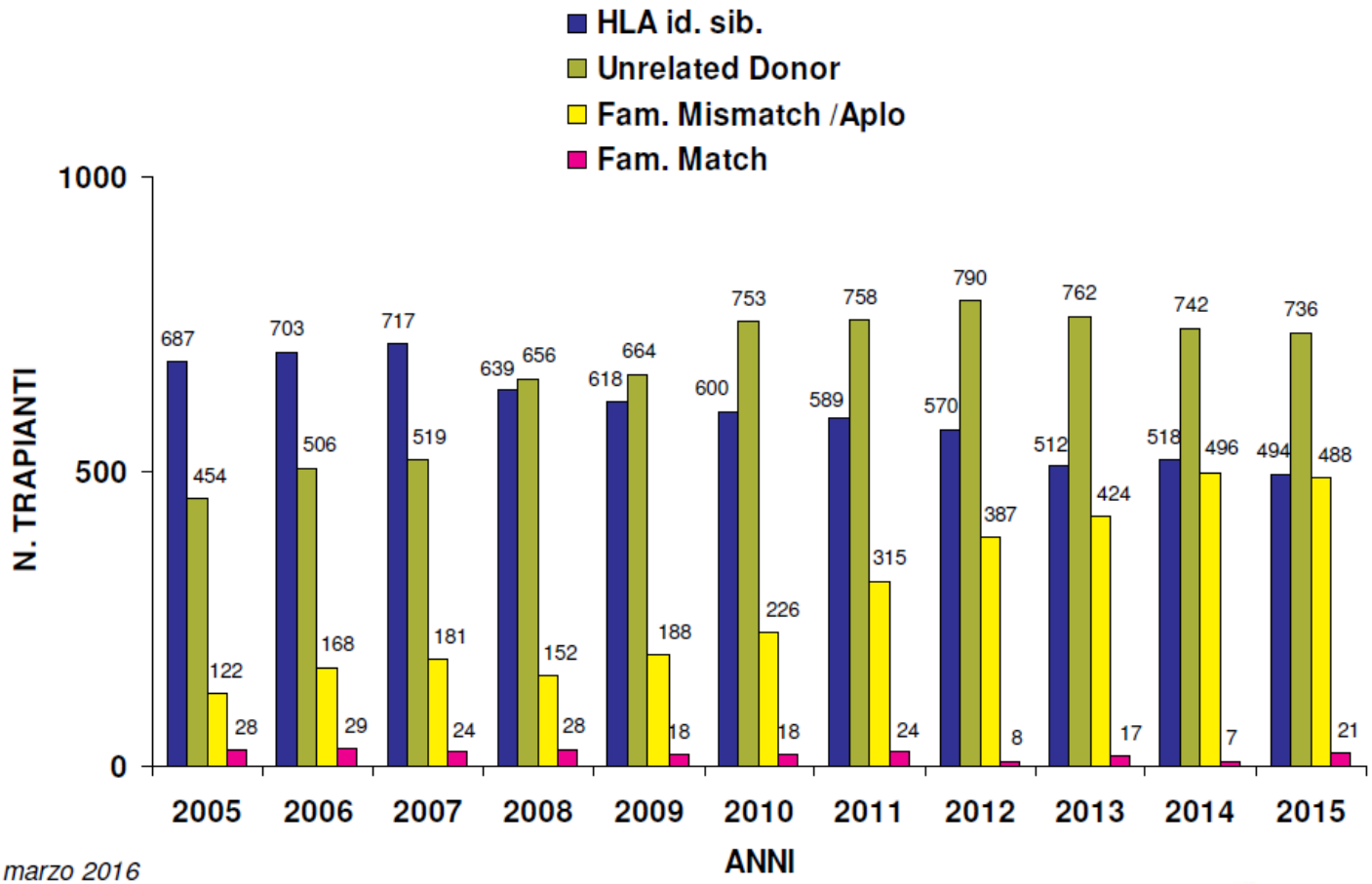


al 30 marzo 2016

GITMO

GITMO Trapianto Allogenico

Tipo di trapianto



al 30 marzo 2016

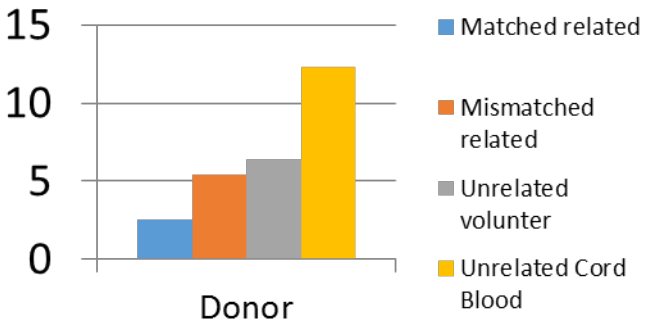
GITMO

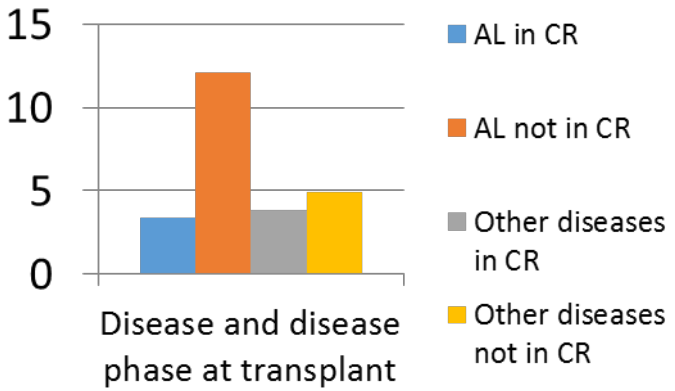
Incidence and Outcome of Invasive Fungal Diseases after Allogeneic Stem Cell Transplantation: A Prospective Study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO)

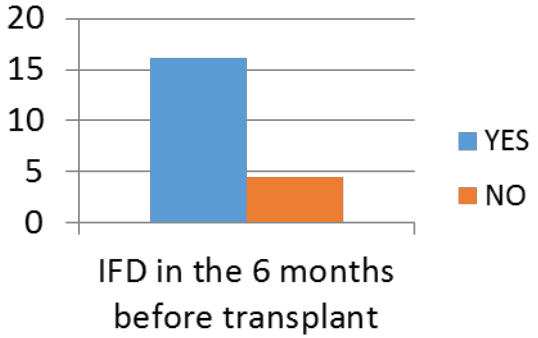
Post-transplant IFD:

10% if pre-transpl IFD in CR
27% if pre-transpl IFD not in CR

Parameter		ard io	95% Hazard Ratio Confidence Limits	
Donor type				
Mismatched related vs matched re		0	0.75	4.81
Unrelated volunteer vs matched re		6	1.68	4.84
Unrelated cord blood vs matched		0	2.43	8.69
Phase of the underlying disease at				
AL - CR vs AL - no CR	<0.0001	0.29	0.17	0.49
Other – CR vs AL - no CR	0.03	0.39	0.17	0.91
Other – no CR vs AL - no CR	.003	0.45	0.27	0.77
IFD in 180 days before transplant, NO vs YES	<.0001	0.27	0.15	0.48







Risk factors for early and late IA in multivariable analysis

M. Mikulska, et al, BMT , 2009

Early

- Status of underlying disease at transplant (p=0.002)
  - 2nd remission OR 1.9
  - Relapse OR 7.2
- Days to engraftment (p=0.001)
  - Each day OR 1.016
- CMV reactivation (p= 0.05)
  - Yes OR 2.8

Late

- Chronic GVHD (p=0.05)
  - Yes extensive OR 3.6
- Steroids (p=0.04)
  - Yes (<2 mg/Kg) OR 7.26
  - Yes (>2 mg/Kg) OR 16.4
- Relapse (p=0.004)
  - Yes OR 5.55
- Secondary neutropenia (P=0.001)
  - Yes OR 5.01

IA 2008-2012

- **45/434 (10%) after first transplant**
- **15/60 (25%) after second transplant**

HSCT Center, Genova, Italy

- **Cumulative incidence**
  - **8.8% (6.3% – 11.7%) at 3 months,**
  - **9.7% (7.1% - 12.7%) at 6 months**
  - **10.4% (7.8 – 13.5%) at 1 year.**

According to the type of donor:

At 3 months

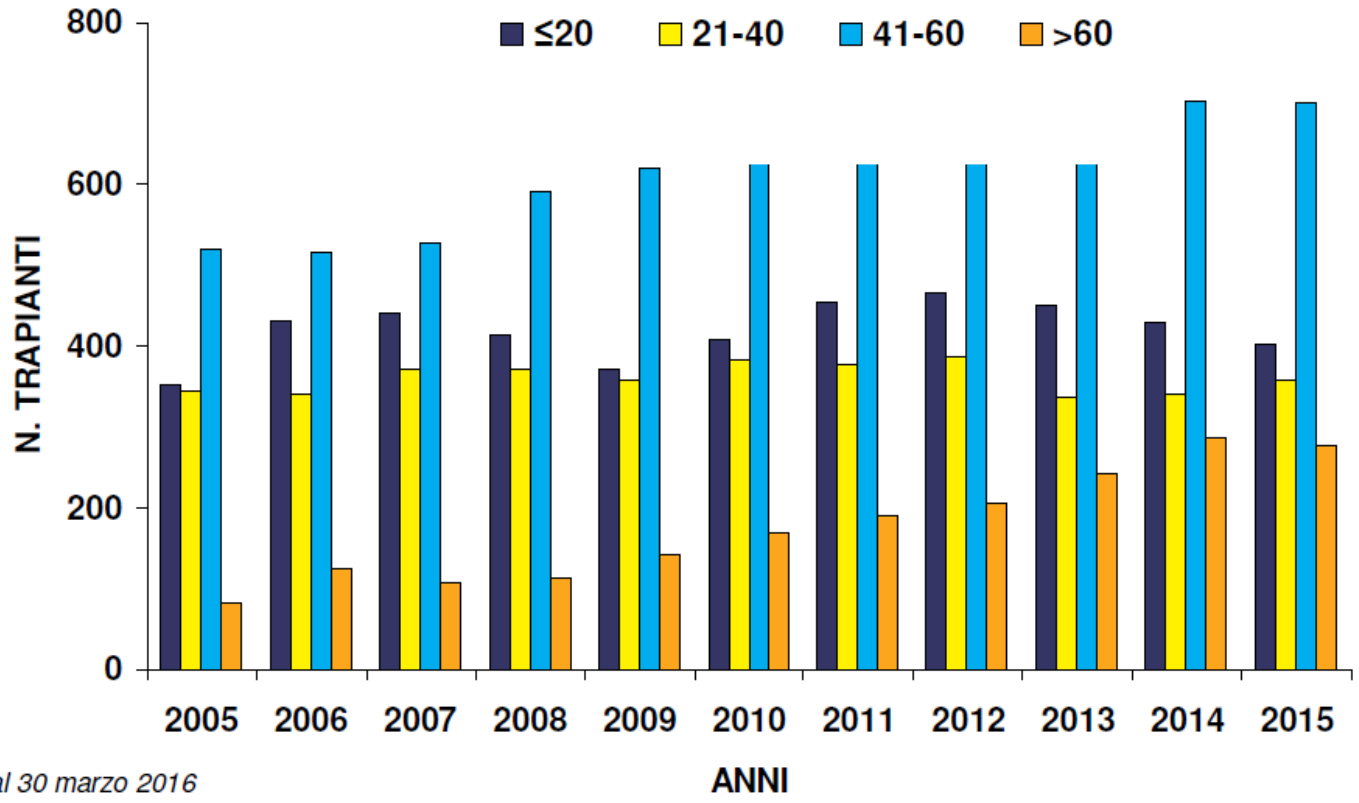
- **matched related → 3.8% (1.6 – 7.7)**
- **matched unrel. mismatch rel → 7.1% (3.1 – 13.2)**
- **CBT → 11.6% (6 – 19.4)**
- **Haplo → 10.5% (5.1 – 18)**

Other factors affecting susceptibility to fungal infections in allo HSCT

- Age
- Air filtration while in hospital (HEPA)
- Pre or post engraftment exposure to dust, wood, etc (type of work, hobbies)
- Use of cocaine
- Seasonal factors
- Catheters
- Immunological predisposing factors

GITMO Trapianto Allogenico

Età al trapianto



al 30 marzo 2016

GITMO

Other factors affecting susceptibility to fungal infections in allo HSCT

- Age
- Air filtration while in hospital (HEPA)
- Pre or post engraftment exposure to dust, wood, etc (type of work, hobbies)
- Use of cocaine
- Seasonal factors
- Catheters
- Immunological predisposing factors

Pre-chemotherapy risk factors for invasive fungal diseases: prospective analysis of 1,192 patients with newly diagnosed acute myeloid leukemia (SEIFEM 2010-a multicenter study)

haematologica | 2015; 100(2)

Morena Caira,[1] Anna Candoni,[2] Luisa Verga,[3] Alessandro Busca,[4] Mario Delia,[5] Annamaria Nosari,[6] Cecilia Caramatti,[7] Carlo Castagnola,[8] Chiara Cattaneo,[9] Rosa Fanci,[10] Anna Chierichini,[11] Lorella Melillo,[12] Maria Enza Mitra,[13] Marco Picardi,[14] Leonardo Potenza,[15] Prassede Salutari,[16] Nicola Vianelli,[17] Luca Facchini,[18] Monica Cesarini,[1] Maria Rosaria De Paolis,[19] Roberta Di Blasi,[1] Francesca Farina,[3] Adriano Venditti,[20] Antonella Ferrari,[21] Mariagrazia Garzia,[22] Cristina Gasbarrino,[23] Rosangela Invernizzi,[24] Federica Lessi,[25] Annunziata Manna,[26] Bruno Martino,[27] Gianpaolo Nadali,[28] Massimo Offidani,[29] Laura Paris,[6] Vincenzo Pavone,[30] Giuseppe Rossi,[9] Antonio Spadea,[31] Giorgina Specchia,[5] Enrico Maria Trecarichi,[32] Adriana Vacca,[33] Simone Cesaro,[34] Vincenzo Perriello,[35] Franco Aversa,[7] Mario Tumbarello,[32] and Livio Pagano[1] on behalf of the SEIFEM Group (*Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne*)

Table 3. Multivariate analysis of the PRE- and POST-chemotherapy risk factors for proven/probable invasive mold infections and proven yeast infections.

VARIABLES	Proven/probable mold infection OR	*P* value	95% CI	Proven yeast infection OR	*P* value	95% CI
Pre-chemotherapy						
Performance status ≥2*	3.10	<0.001	1.69-5.67	---	---	---
House renovation	4.01	<0.001	1.89-8.52			
Higher body weight	0.34	0.012	0.15-0.79	---	---	---
High exposure job	3.43	0.003	1.52-7.70	---	---	---
COPD	3.96	0.012	1.35-11.55	---	---	---
Post-chemotherapy						
Days of neutropenia	1.03	0.042	1-1.06	---	---	---
Esophagitis grade >2**	3.52	0.005	1.45-8.57	4.24	0.013	1.35-13.3
Central venous catheter	---	---	---	7.25	0.058	0.93-56
Posaconazole prophylaxis	0.37	0.002	0.20-0.69	0.22	0.006	0.08-0.65

*COPD: chronic obstructive pulmonary disease. * According to the ECOG scale. ** According to the WHO scale*

Other factors affecting susceptibility to fungal infections in allo HSCT

- Age
- Air filtration while in hospital (HEPA)
- Pre or post engraftment exposure to dust, wood, etc (type of work, hobbies)
- Use of cocaine
- Seasonal factors
- Catheters
- Immunological predisposing factors

Geoclimatic Influences on Invasive Aspergillosis after Hematopoietic Stem Cell Transplantation

Anil A. Panackal,[1] Hong Li,[2,3] Dimitrios P. Kontoyiannis,[4] Motomi Mori,[2,3] Cheryl A. Perego,[4] Michael Boeckh,[5] and Kieren A. Marr[5,6,7]

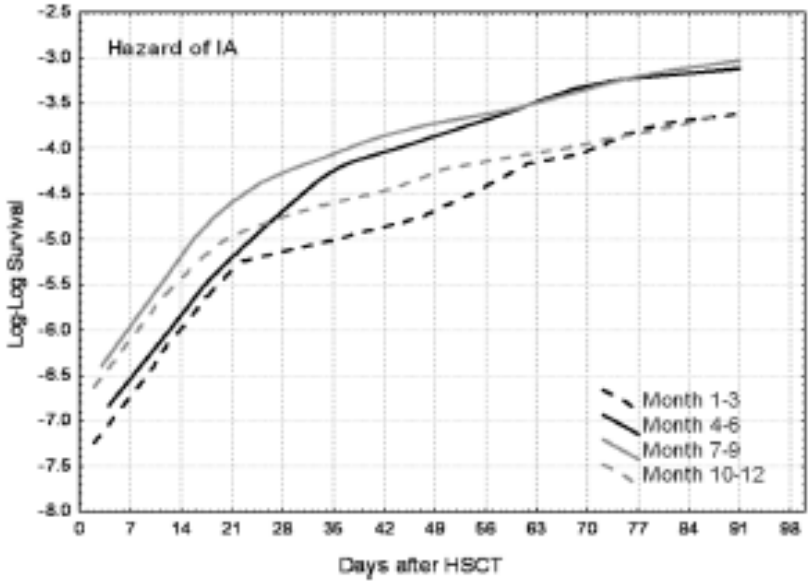


Figure 2. Hazard of invasive aspergillosis (IA) in the first 3 months after hematopoietic stem cell transplantation (HSCT) at the Fred Hutchinson Cancer Research Center (1992–2003) according to month of transplantation (1 indicates January and 12 indicates December).

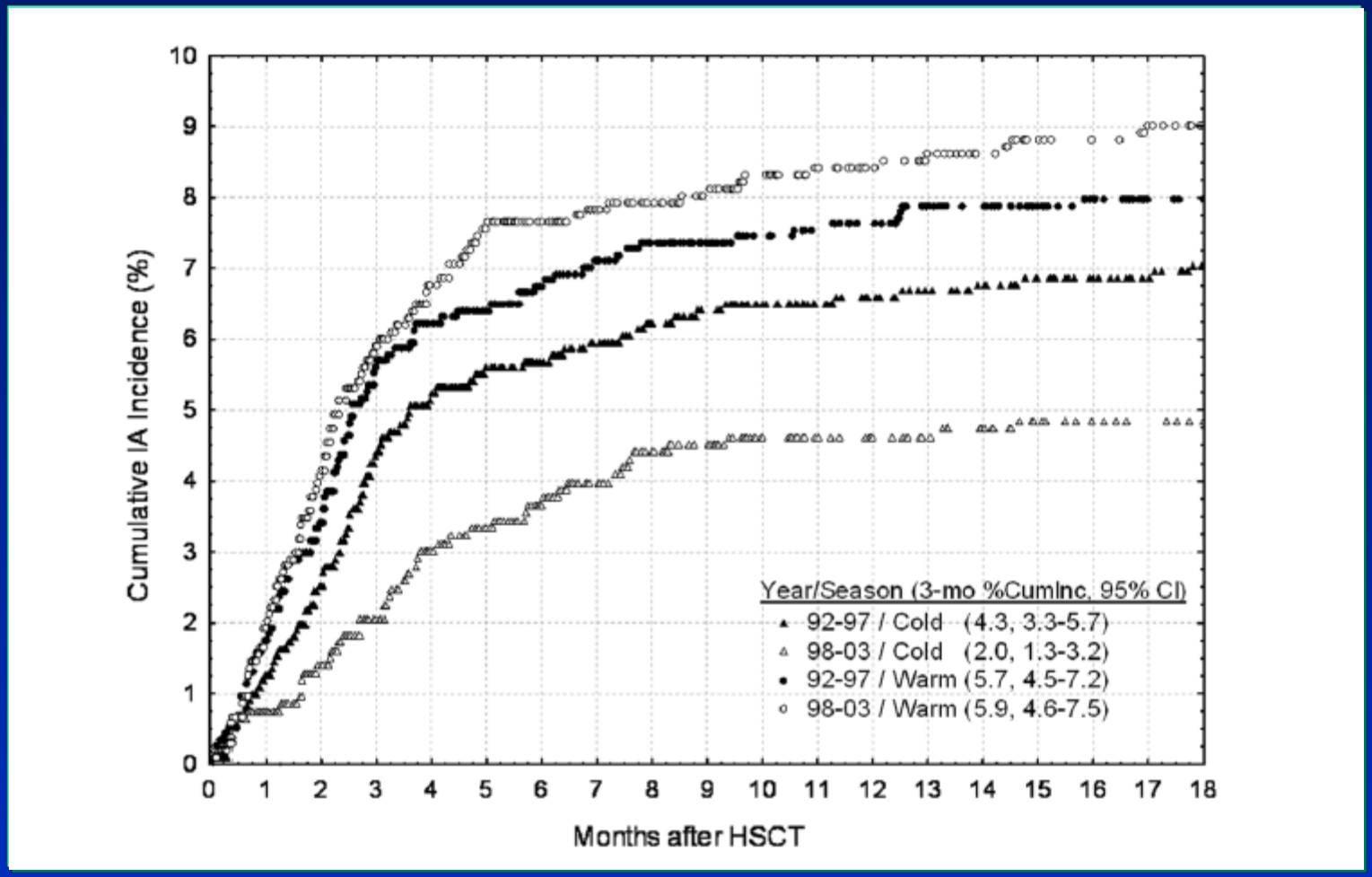


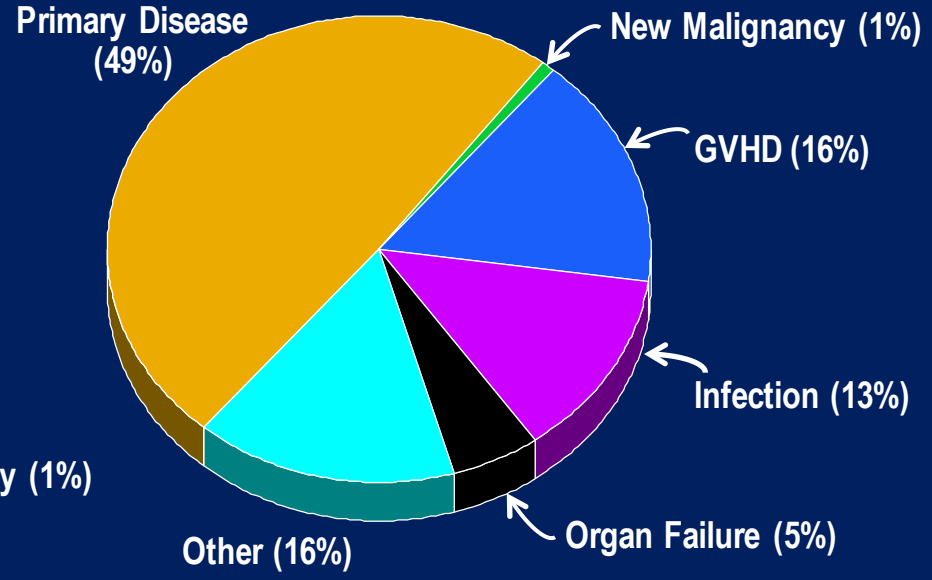
Figure 3. Estimated cumulative incidence (CumInc) of invasive aspergillosis (IA) by season and year of hematopoietic stem cell transplantation (HSCT) in allogeneic HSCT recipients at the Fred Hutchinson Cancer Research Center. CI, confidence interval.

What I am going to deal with you in the next 20 minutes

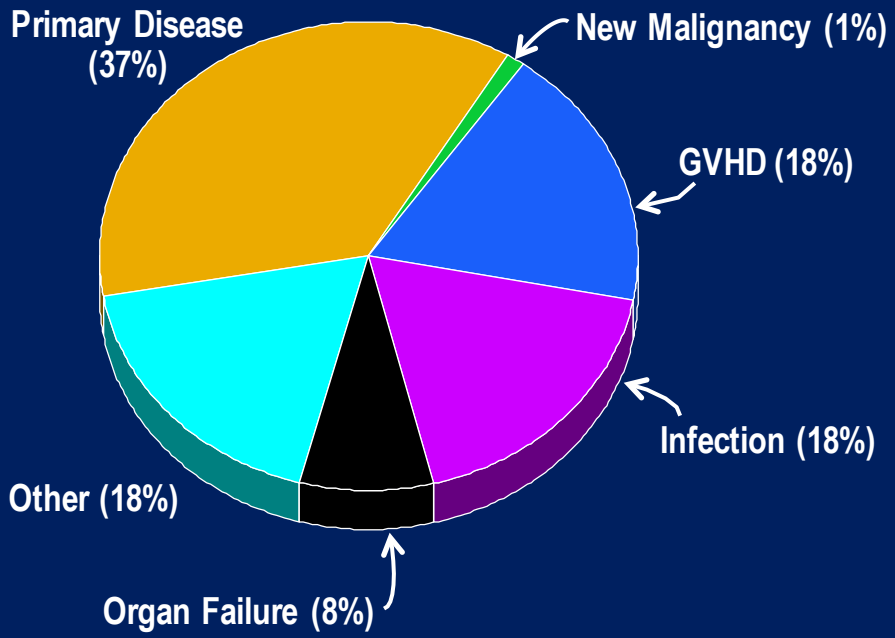
- Incidence, etiology and timetable of IFI in HSCT
- Variables associated with Invasive Aspergillosis (IA)
- IA: impact on overall survival

Causes of Death after Transplants Done in 2009-2010

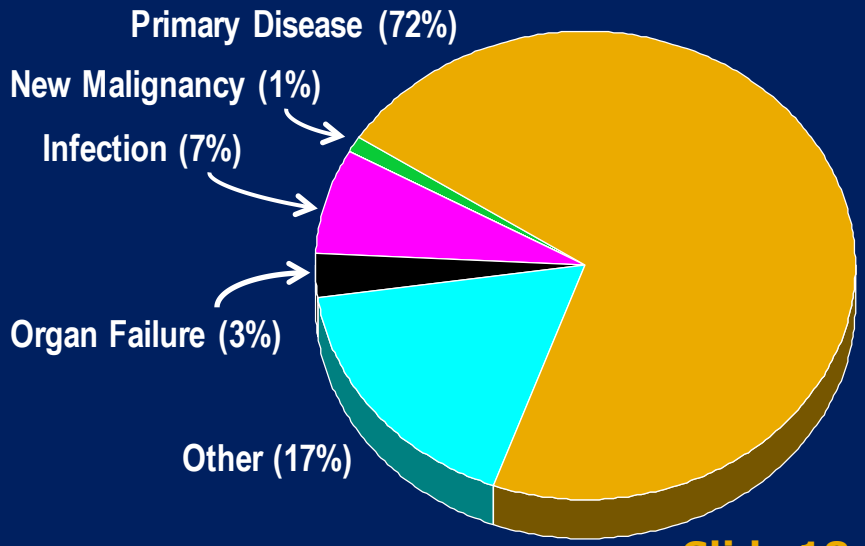
HLA-identical Sibling



Unrelated Donor



Autologous

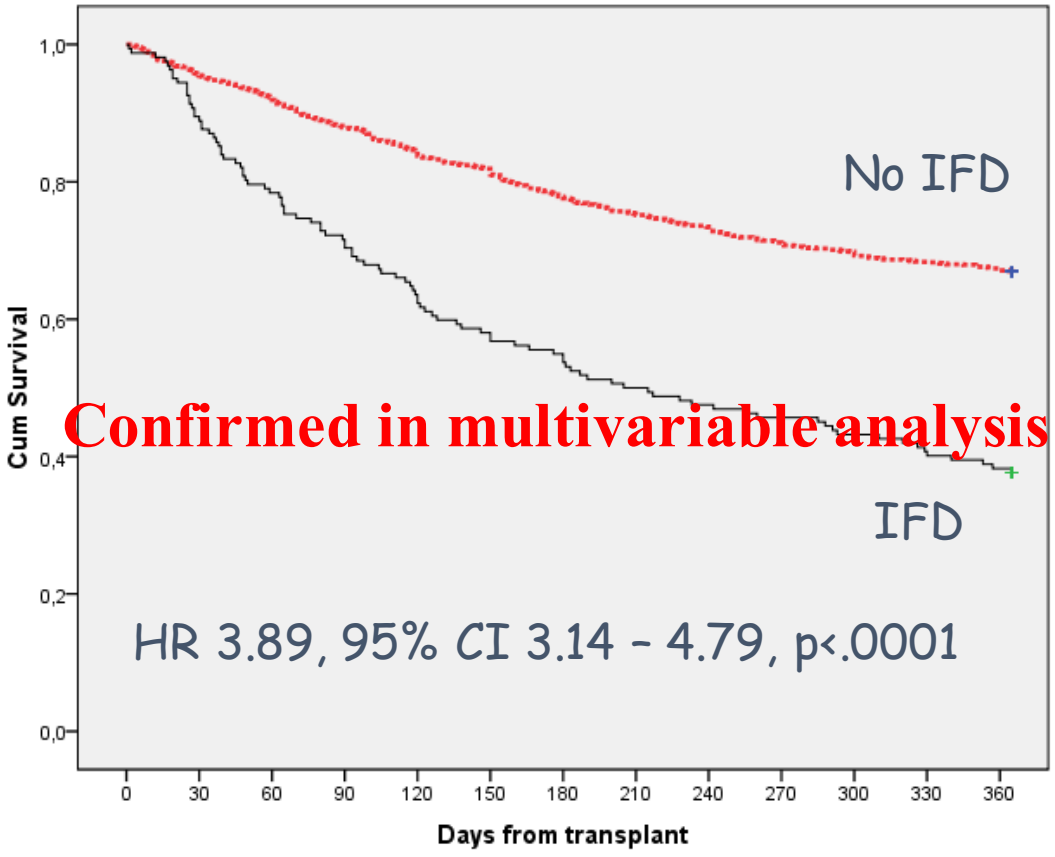


CIBMTR

Girmenia et al. Biol Blood Marrow Transplant 20 (2014) 872–880

Incidence and Outcome of Invasive Fungal Diseases after Allogeneic Stem Cell Transplantation: A Prospective Study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO)

Survival of allo SCT patients according to IFD development



Confirmed in multivariable analysis

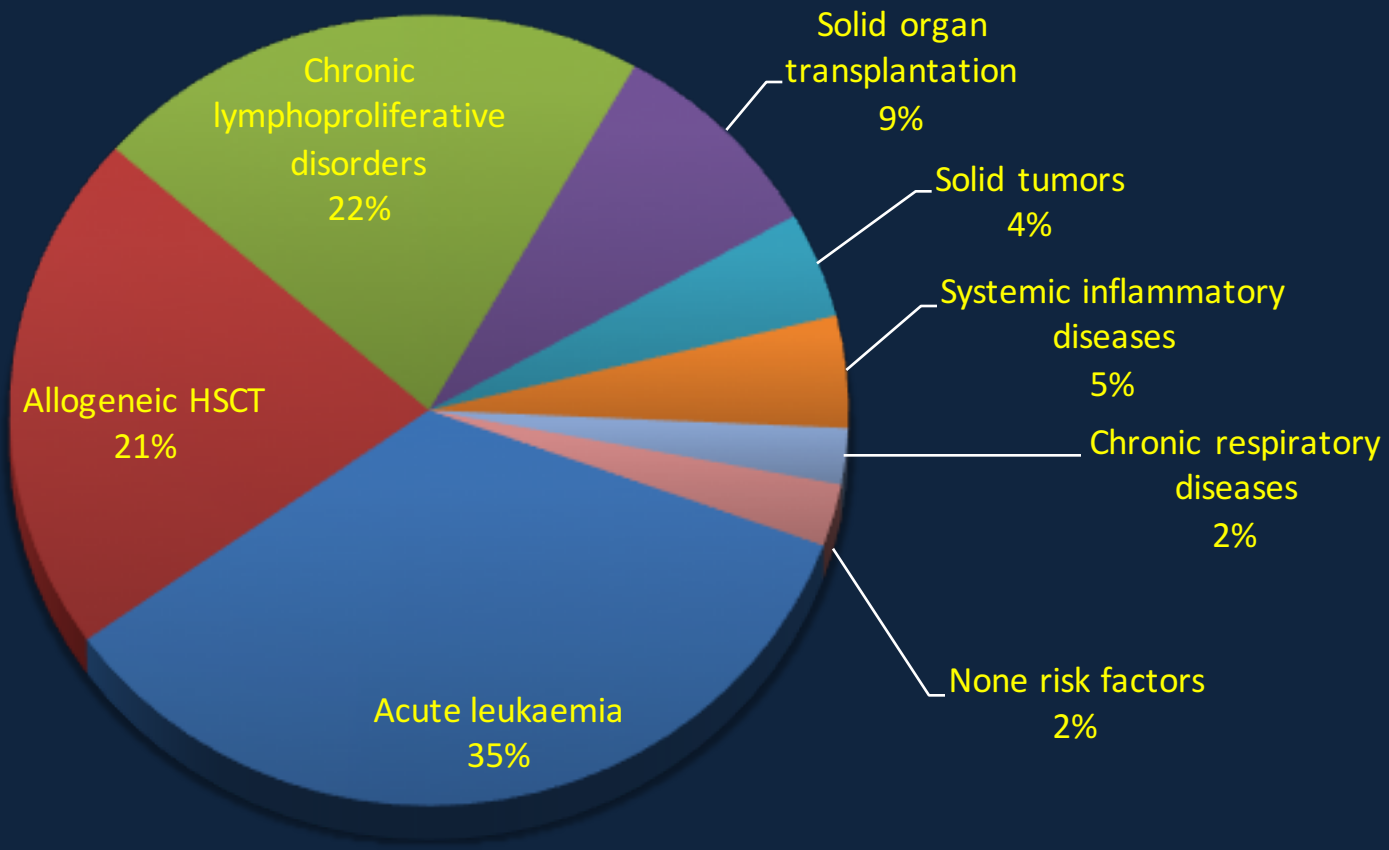
HR 3.89, 95% CI 3.14 – 4.79, p<.0001

Death attributed to IFD : 31/164 cases, 19%

In conclusion

- IFI incidence is 10-15% in alloHSCT, apparently decreasing with mold-active prophylaxis
- Emerging resistant pathogens might be a problem in the near future
- Main risk factors correlated with type of transplant (source of donor cells), previous IFI, status of leukemia and probably other non-transplant and non-disease-related risk factors
- Many Authors report an impact of IFI on overall mortality

Risk factors for invasive aspergillosis and underlying diseases of the 393 adult patients of the study



O. Lortholary et Al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007), Clin Microbiol Infect., 17(12), 2011