Primary prophylaxis of invasive fungal infection in patients with haematological diseases

Tunis, May 24 2012

Important questions for antifungal prophylaxis

- Who are the patients at risk?
- Which is the risk: yeasts and/or molds?
- When is the risk?
- According to the answers, what can we do?

Who are the patients?

Classically

Prolonged and deep neutropenia

Acute Myeloid Leukemia: induction and reinduction

Stem cell transplantation, GVH disease, CMV co-infection

Solid organ transplant recipients

Long-term steroids in auto-immune diseases

Diabetes, iron overload, desferoxamine treatment (zygo)

Solid tumors

Role of genetic predisposition to IFI ???

New at-risk populations, new risk factors

ICU, COPD

New, severely immunocompromised populations

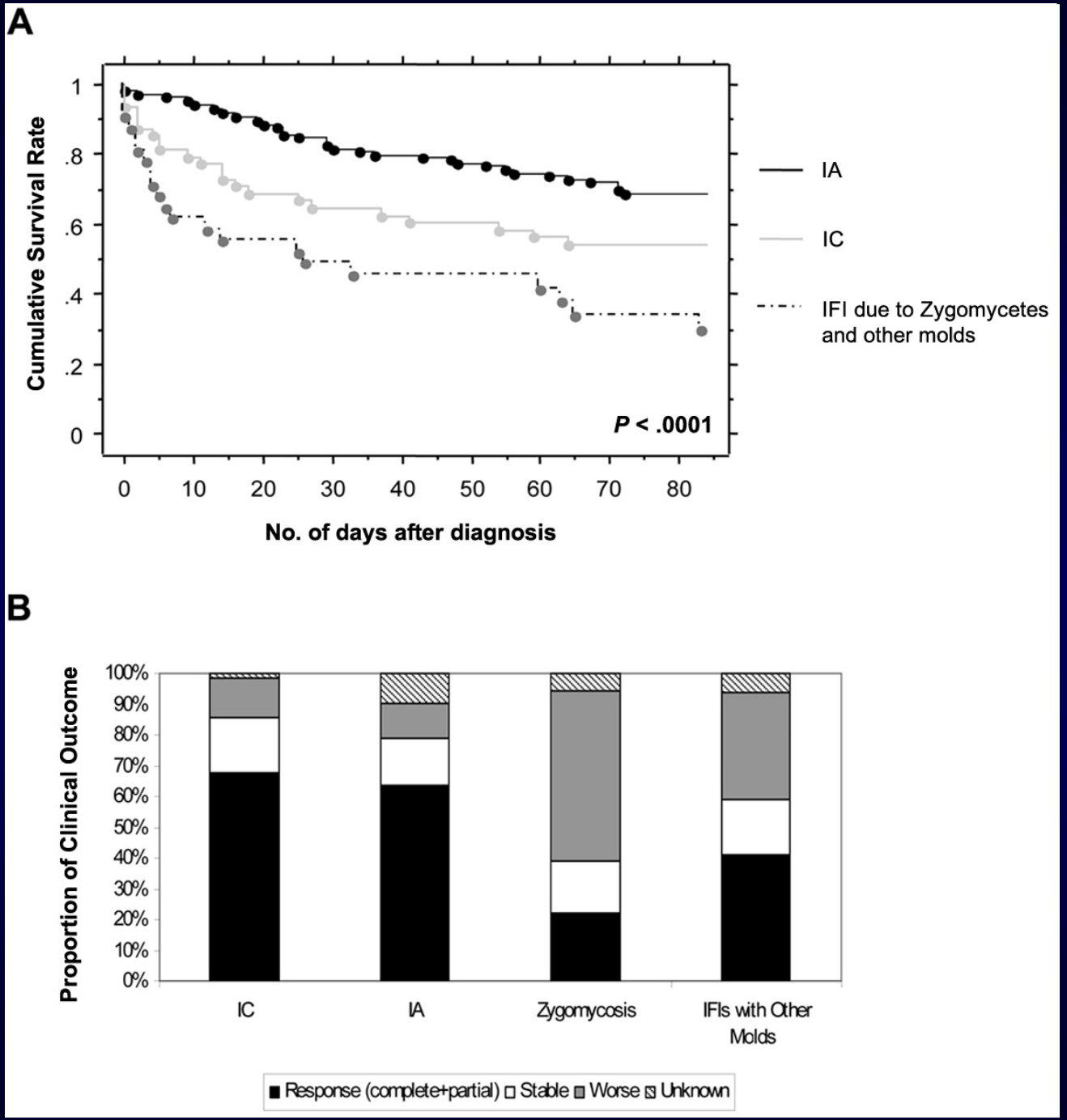
In hematology: more and more fungal diseases

Mainly mold infections: 3/4

- pulmonary aspergillosis +++
- zygomycosis (+/-)
- others

Less and less yeasts infections: ¼

- mainly candida



Muticenter prospective Antifungal Therapy Alliance Registry

Observational Study

2004-2007
16 centres HSCT

IA: 148 (59%)

IC: 62 (25%)

Zygo: 18 (7%)

Other M (17) (7%)

Neofytos, CID 2009;48

The new immunocompromised patients at risk for invasive aspergillosis

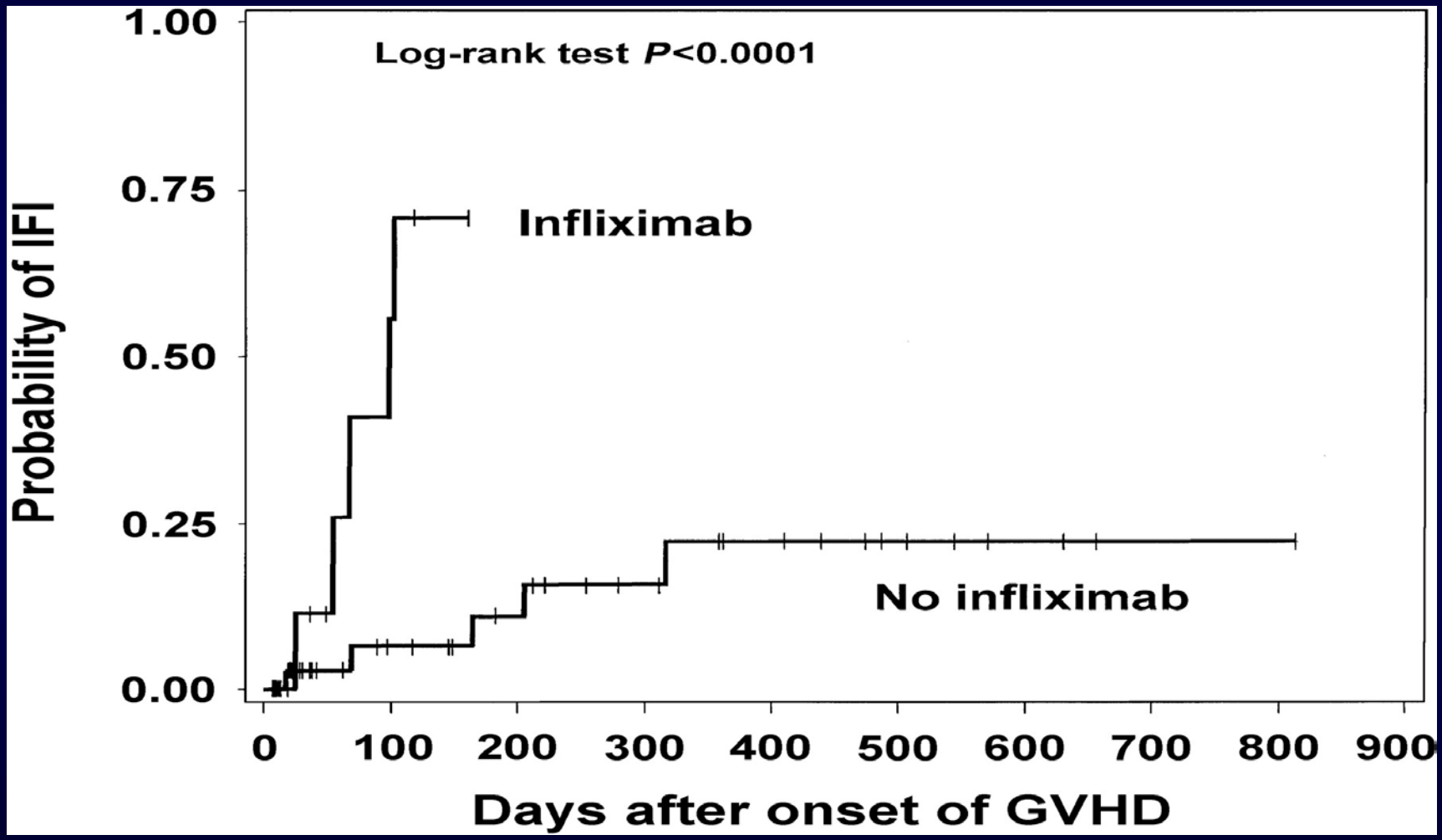
Data from the French prospective surveillance of IA, 2005-2007

N = 393 proven or probable IA

		No.	Total	
Hematology	Acute leukemia	111	28%	**76%**
	MDS, acute T of MPD	24	6%	
	HCT Allo	84	21.5%	
	Lymphoid disorders	81	20.5%	
Solid organ transplant		34	8.5%	**8.5%**
Solid tumor		22		**5.5%**
Systemic diseases		18		**4.5%**
Respiratory diseases		9		**2.3%**
Others		10		**2.5%**

Lortholary O et al. CMI 2011

More immunosuppression has a cost in terms of IFI



Marty F M et al. Blood 2003;102:2768-2776

Prophylaxis should focus on high-risk patients

Pagano L et al. JAC 2010

Pagano et al.

Table 1. Stratification of immunocompromised patients in risk categories for invasive fungal disease according to incidence and mortality rates obtained from current literature[2-7,9-11]

Low risk	Intermediate risk	High risk
autolo…	acute lymphoblastic leukaemia	acute myeloid l… …first induction)
H…	chronic lymphocytic leukaemia	allogenei… …d source)
…	lymphoma	heart, l…
s…	COPD	
myelo…	AIDS	
kidney transplantation	myelodysplastic syndromes	
chronic immunological disease		
systemic lupus erythematosus		

1-2% ?

7-10% ?

CML, chronic myeloid leukaemia; COPD, chronic obstructive pulmonary disease; Ph−, Philadelphia negative.

What is the optimal strategy in a given setting?

If we build our strategy on the risk of invasive aspergillus infection, it is easy to identify the two risk groups who will represent more than 50% of the IA cases:

- AML, MDS with chemo (5-20%)
- Allogeneic HCT recipients (5-25%)

These 2 populations are the first ones to deserve specific strategies to prevent aspergillosis

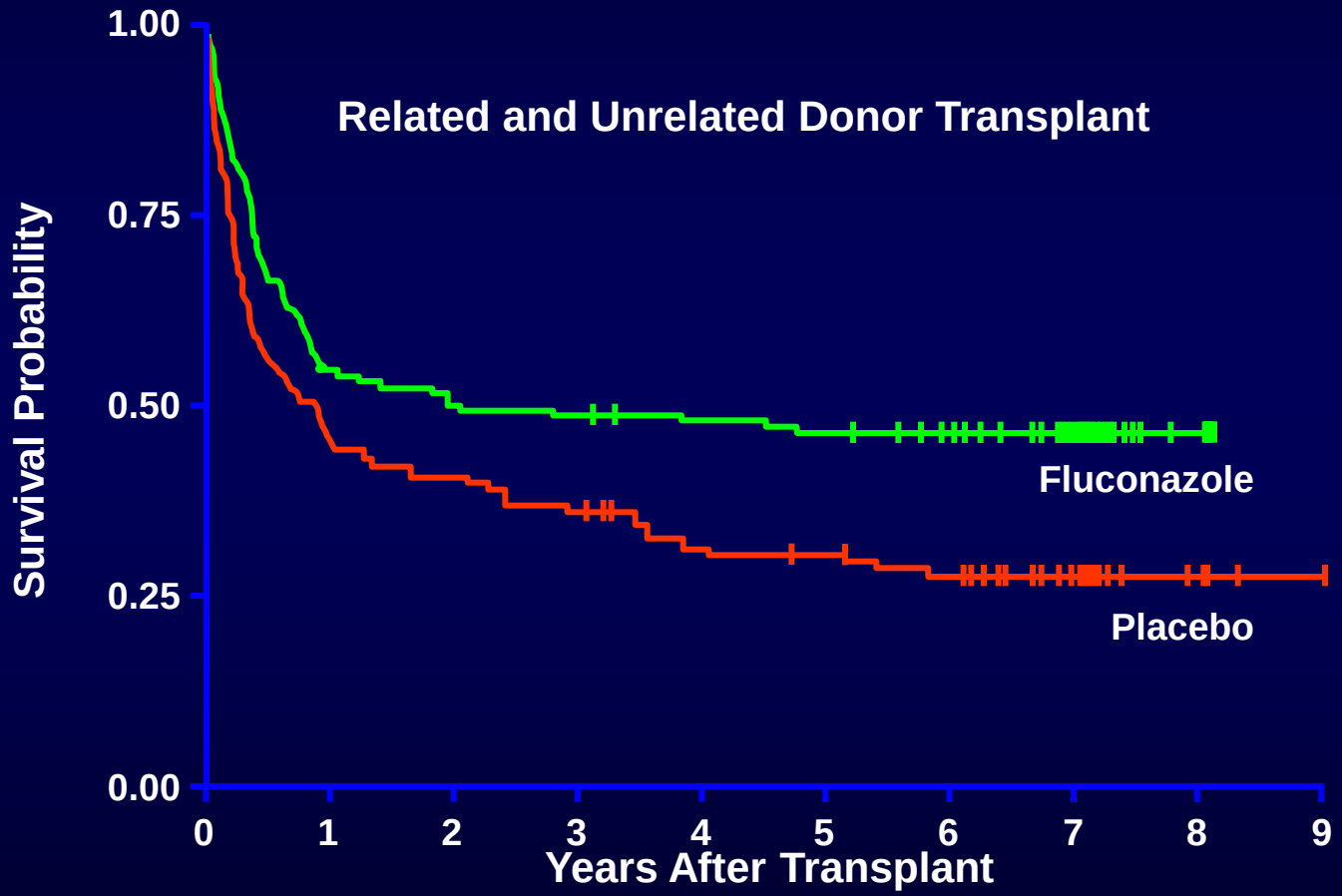
If we favor an environmental prevention of IA (air-filtration, LAF rooms), the risk of many other mould air-borne infections will probably be reduced in parallel with the risk of aspergillosis

Reduction of the risk of IFI by antifungal prophylaxis?

Reference	Drug tested	No. of patients in the study	IFI reduction
Cornely 2007 *AML*	Posaconazole	600	7% → 1%
Ullmann 2007 *Allogeneic SCT with GVHD*	Posaconazole	600	9% → 5.3%
Rjinders 2008 *AML and Allo*	L-ampho B aerosols	271 (407 episodes)	14% → 4%

* For a alpha-risk of 5% and a power of 90%

Fluconazole vs Placebo in auto/allo BMT/SCT
A situation where a long-term benefit of survival has been shown



***P* = .0018**

Slavin M et al. JID 1995. Marr K et al. Blood 2000.

Why primary drug antifungal prophylaxis may be debated ?

- Benefit depending on the risk/disease, local epidemiology and environmental factors
- Exceptionnal benefit in terms of survival (only for Fluco in allogeneic SCT *(Slavin et al, 2000*) and posaconazole in AML *(Cornely et al. 2007)*

Tolerance, drug interferences (with some chemo like Cyclophosphamide or anthracyclins), cost

Selection / induction of resistant strains ?

Specific to azoles: need for drug monitoring ?

……and there are alternatives to drug prophylaxis

There are alternatives to prophylaxis in high-risk populations (i.e., prolonged neutropenia)

- Air-filtration: HEPA filters, LAF rooms

- Empirical antifungal strategy:
  fever-driven, « blinded », but classical

- Pre-emptive antifungal strategy
  « diagnosis-driven », much more appealing:
  - Less antifungals, lower costs
  - May be less toxicity
  - But still not standard, due to a possible increased risk of fungal infections when compared to an empirical strategy

In practice

1) AML: many trials with fluco, itraconazole, posaconazole. Need for prophylaxis at induction and re-induction: air-filtration or Itra, or Posa ++

Fluco in centers with a high prevalence of candidemia.

Oral polyens are acceptable for other centers

2) Autologous SCT: no need for mold prophylaxis. Fluco in centers with candidemia, or no prophylaxis

3) Allogeneic SCT:

- prophylaxis from transplant (neutropenic phase): fluco or vorico ≠
- Prophylaxis from GVHD (Posa ++)

No recommendation / consensus for other populations

Please have a look on the ECIL guidelines on antifungal prophylaxis

« ECIL » for European Conference on Infections in Leukemia

Slide sets available on the websites of:

- ICHS
- EBMT (« ressources »)
- EORTC (Infectious Disease Group)

In summary

Antifungal (and mainly antimold) drug prophylaxis should be proposed only to high-risk patients (sponatenous risk ≥ 10%), for predetermined durations each time possible

Oral prophylaxis are the most convenient, but raise several problems:

- hepatotoxicity of azoles
- need for drug monitoring ? (posa, vorico)

Think also about alternatives:

- air-filtration
- empirical and preemptive strategies