# Antifungal prophylaxis in patients with hematological malignancies

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# Infectious complications in immunocompromised/cancer patients

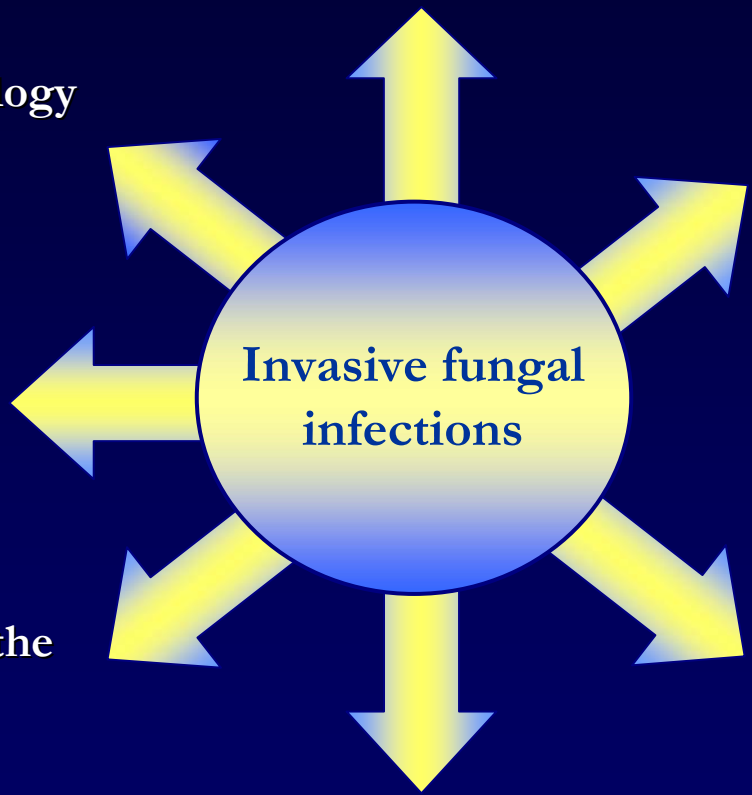
- Absent or minimal symptoms and/or signs of infection
- Rapid progression of infection
- Opportunistic infections
- Delayed therapy – high mortality

- Bacterial infections
- Invasive fungal infections (IFI)
- Viral infections

# Risk factors for infections in cancer patients

- Neutropenia (degree and duration)
- Oral and gut mucositis
- Central venous catheters
- Immunodeficiency
- Colonization
- Concomitant conditions

Increasing rate of invasive fungal infections during past 20 years




Changing epidemiology

20-30% cases of IFI are diagnosed and treated *ante mortem*

Delayed therapy

Response to antifungal therapy - about 50%

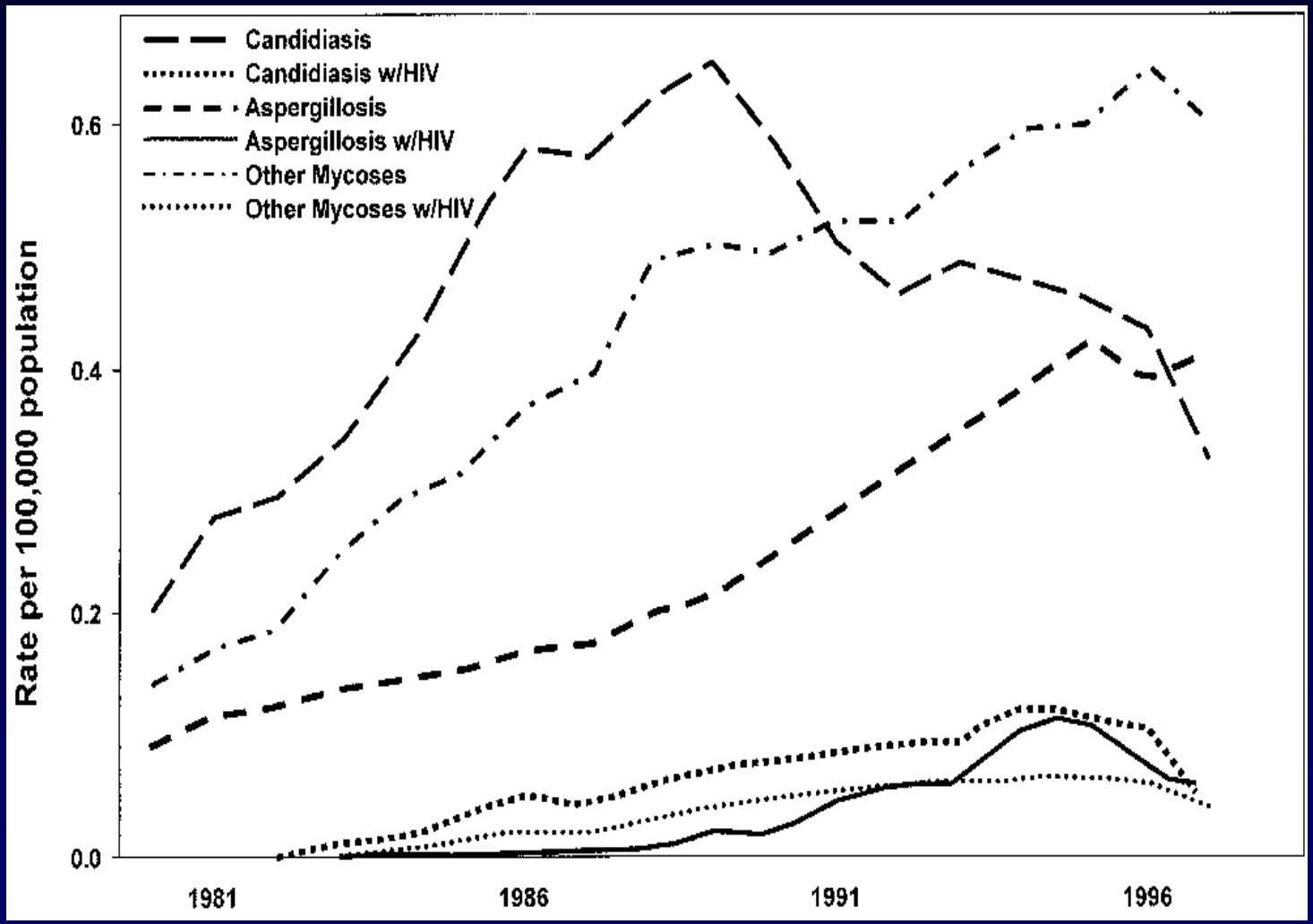
Mortality depending on the start of therapy

< 10 days 41%

> 11 days 90%

Mortality among alloHSCT recipients – 90%

# Invasive fungal infection




Mortality in the United States, 1980-1997, due to candidiasis, aspergillosis, and other mycoses in persons infected and persons not infected with HIV.

McNeil et al. CID 2001;33:641-7

# Invasive fungal infection

| | Incidence | Aspergillus | Candida (azoles) | Candida (without azoles) |
|---|---|---|---|---|
| alloHSCT | 15-25% | 10-20% | < 5% | 15-25% |
| AML | 10-15% | 10% | < 5% | 15-20% |
| ALL | 5-10% | 5% | < 5% | 10% |
| autoHSCT | 2-6% | < 2% | < 5% | 10% |

HSCT – hematopoietic stem cell transplantation; AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia

Mahfous & Anaissie; Thomson Current Drugs; 2003

# Risk groups of invasive fungal infection

- **High risk (15%-30% IFI)**
  - AML
    - HD-AraC
    - >55 yrs
  - alloHSCT
    - GVHD
    - steroids
    - unrelated, mismatched donor
- **Intermediate risk (5%-15% IFI)**
  - alloHSCT
  - fludarabine
  - TBI
  - Colonization
- **Low risk (< 5% IFI)**
  - autoHSCT
  - AML/ALL < 19 yrs
  - Lymphoma

# Antifungal therapy

- **Prophylaxis**
- Empirical antifungal therapy
- Pre-emptive antifungal therapy
- Targeted therapy

# Prophylaxis

| | |
|---|---|
| General prophylaxis | Hand wash<br>Contact izolation<br>Low germ diet<br>HEPA filters/LAF |
| **Pharmacological prophylaxis** | **antibacterial**<br>**antifungal**<br>**antiviral** |
| Other methods | Growth factors<br>Vaccination<br>Immunoglobulins ? |

# Antifungal prophylaxis

| Pro | Contra |
| --- | --- |
| Reduced incidence of IFI | Resistant pathogens |
| Reduced mortality | Toxicity |
| Reduced antifungals use | Drug interactions |
| | Costs |

# Antifungal prophylaxis

- What is the patient population likely to benefit from primary antifungal prophylaxis ?
- An impact of antifungal prophylaxis on
  - the incidence of invasive fungal infection (yeast vs moulds)
  - overall mortality
  - fungal infection – related mortality
  - use of empirical antifungal therapy
  - toxicity
- Is antifungal prophylaxis associated with increased resistance or selection of specific pathogens
- How long should antifungal prophylaxis be continued
- Should serum levels of specific antifungal compounds be measured and what is the target level?

# ECIL RECOMMENTATION
# (European Conference on Infection in Leukemia)

- **EBMT** (European Blood and Bone Marrow Transplantation Group)
- **EORTC** (European Organisation for Research and Treatment of Cancer)
- **LeukemiaNet**
- **ICHS** (International Immunocompromised Host Society)

**www.ichs.org/ecilslides.htm**

# ECIL recommendation - methods

- Questionnaire
- Review of the literature
  - PubMed
  - Medline
  - Cochrane
  - ICAAC, EBMT, ASH, ASCO, ECCMID 2002-2007
- CDC grading system

# CDC grading system

| Quality of evidence | Strength of recommendations |
| --- | --- |
| I. Evidence from at least one well-executed randomized trial<br><br>II. Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments<br><br>III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees | A. Strongly recommended<br><br>B. Generally recommended<br><br>C. Optional<br><br>D. Generally not recommended<br><br>E. Never recommended |

# Antifungal prophylaxis

- Primary prophylaxis
  - Standard practice of care in neutropenic cancer patients and HSCT recipients *(IDSA, CDC, ASBMT)*
  - Indications
    - high and intermediate risk (alloHSCT, AML)
  - Antifungal drugs
    - azoles
    - amphotericin
    - nystatin
    - echinocandin
- Antifungal prophylaxis in Europe (38 centers)
  - alloHSCT 85%
  - autoHSCT/AML 63%
- 80 randomized trials; >9000 patients

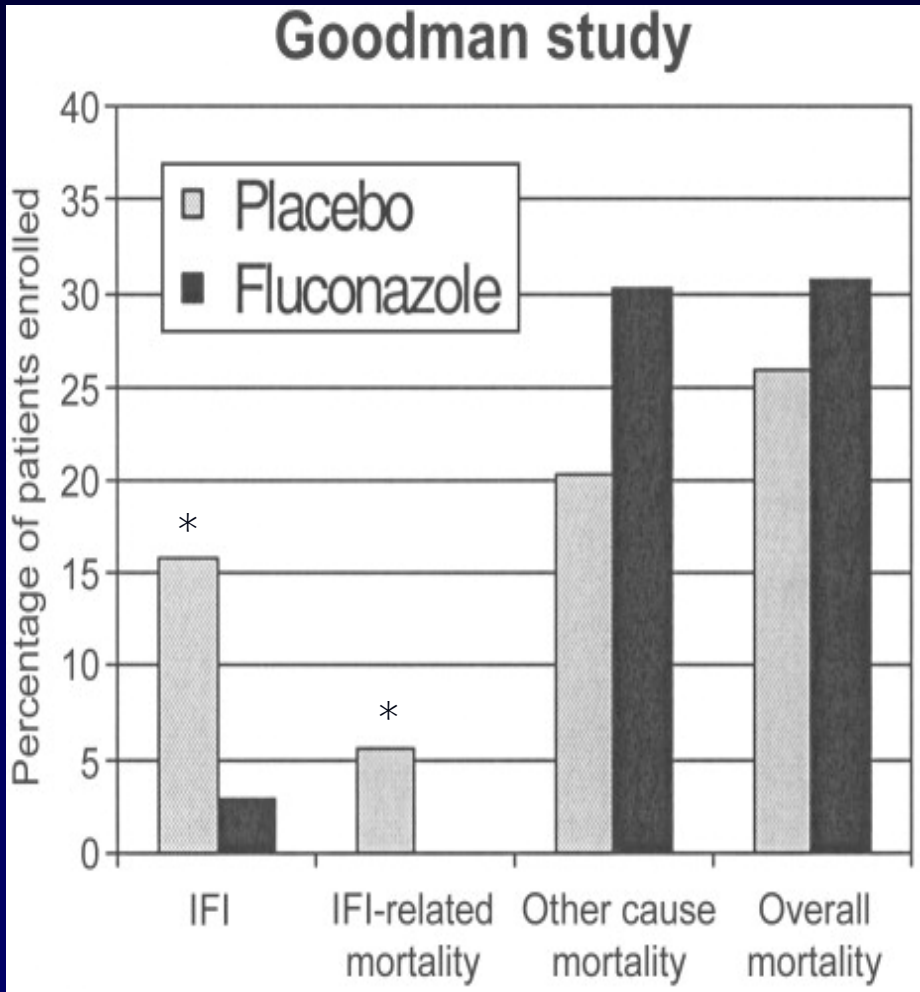
# Fluconazole prophylaxis

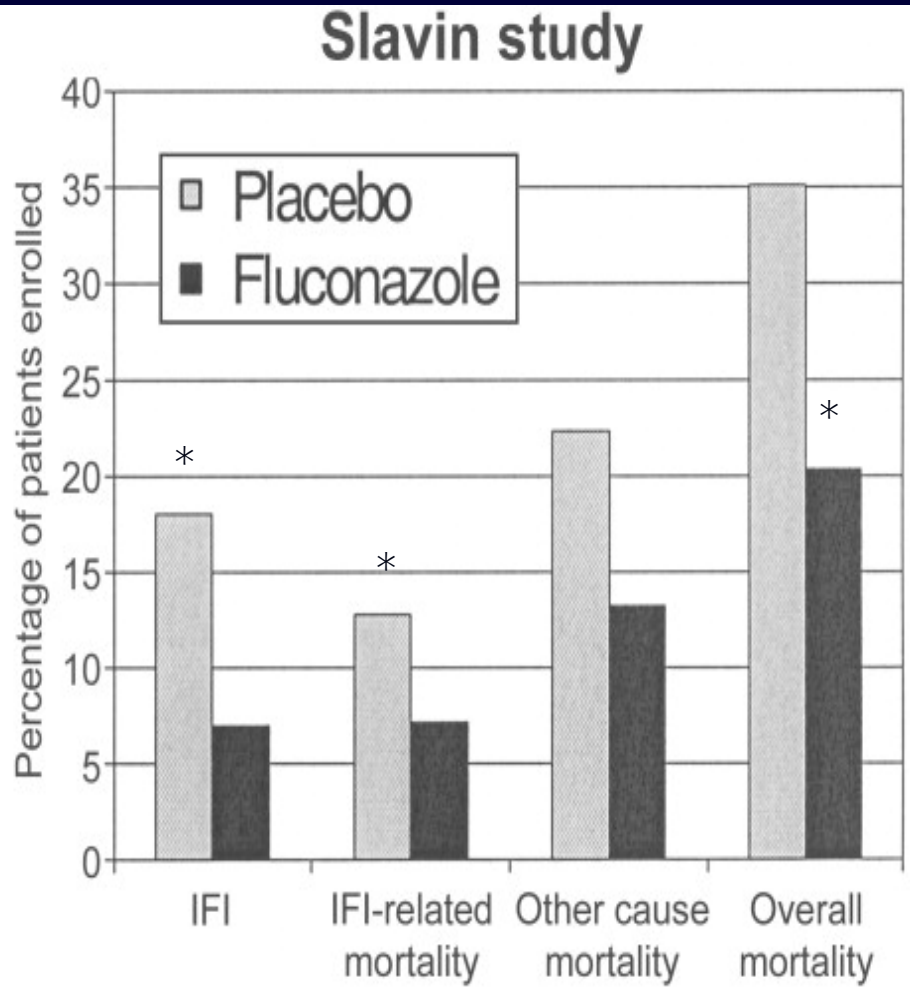
- 400 mg qd in allogeneic HSCT: **AI**
  - Reduces the incidence of IFI
  - Reduces attributable mortality
  - Reduces overall mortality
    - Slavin 1995 and Marr 2000
- 50-400 mg qd in autoHSCT/acute leukemias: **CI**
  - Less convincing reductions
    - Goodman 1992; Schaffner 1995; Rotstein 1999
- When to stop?
  - At engraftment or day +75 or day +100 or at immune recovery?

# Fluconazole prophylaxis

Auto (48%) + Allo (52%)

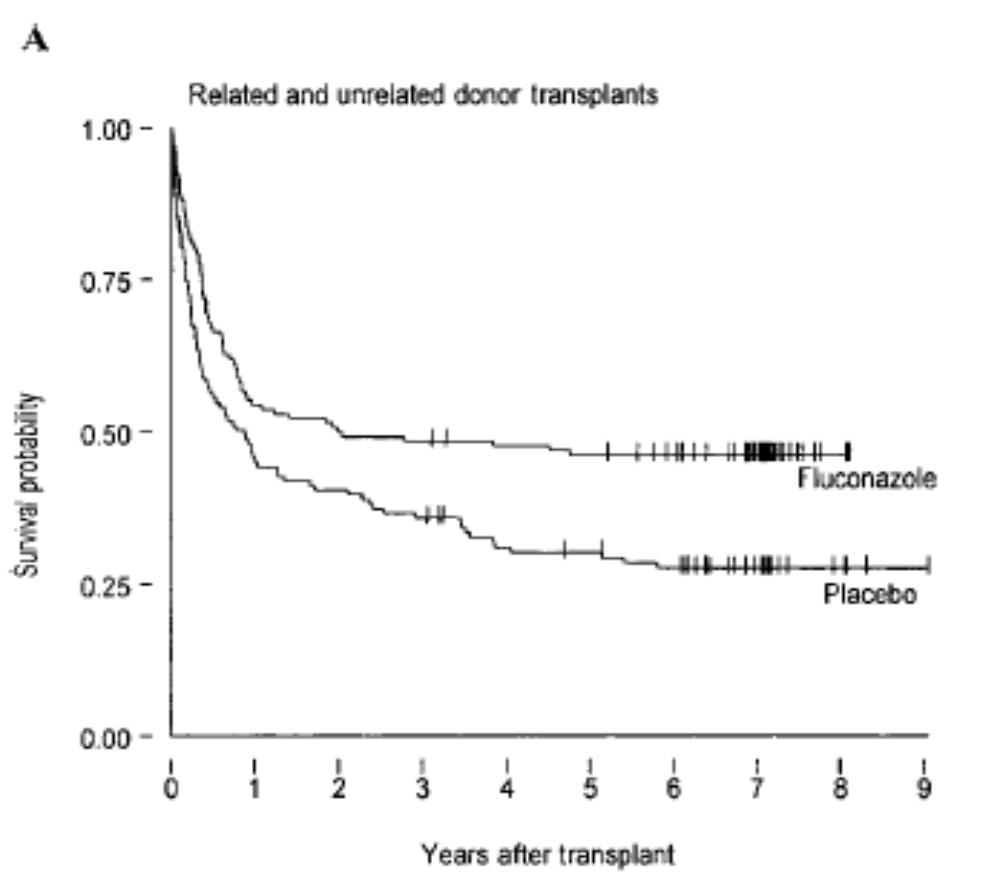
Auto (12%) + Allo (88%)




Goodman et al. N Engl J Med. 1992
Slavin et al. J Infect Dis. 1995

# Fluconazole prophylaxis




$p < 0.001$

**Fluconazole vs placebo; alloHSCT**

**Marr et al. Blood 2000**

# Itraconazole prophylaxis

Itraconazole works to prevent IFI

- Itraconazole capsules: not recommended
  - Glasmacher 2003
- Itraconazole iv/solution in allogeneic HSCT: BI
  - If not limited by drug interactions and/or patient tolerability
    - Winston 2003 & Marr 2004
- Itraconazole solution 2.5 mg/kg bid in auto/AL: CI
  - Menichetti 1999; Morgenstern 1999; Harrouseau 2000; Boogaerts 2001; Glasmacher 2006
- Itraconazole level monitoring BII

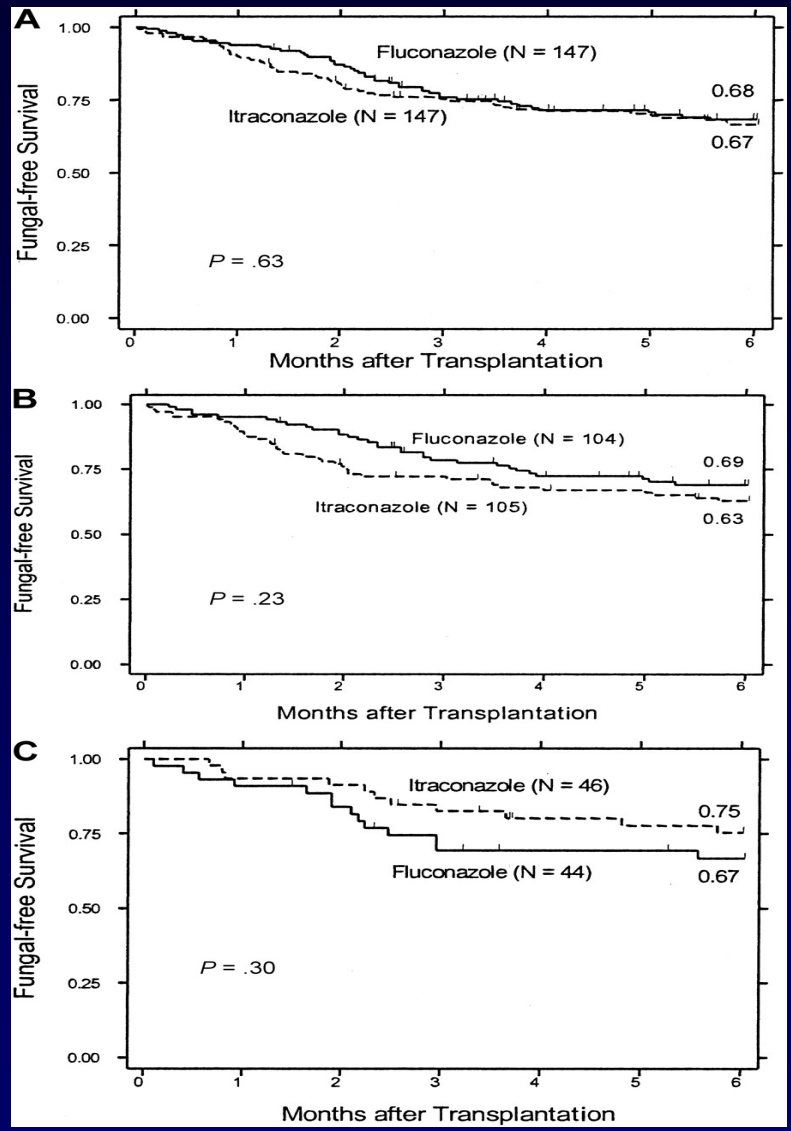
# Itraconazole prophylaxis

- Single center open-label study in 304 myeloablative allogeneic HSCT

- Fluconazole 400 mg (iv/oral) vs Itraconazole oral (2.5 mg/kg tid) or iv (200 mg)
  - From start of conditioning until day +120 (off steroids) or max +180
  - Itra dose adjustments to serum levels (target > 500 µg/mL)

- Primary end point: incidence of proven and probable IFI

- Secondary end point:
  - "on treatment" infections
  - overall and fungal-free survival
  - withdrawal of study drug




Marr et al. Blood 2004

# Voriconazole prophylaxis

- Multi-center, randomized double-blind trial comparing fluconazole with voriconazole
  - alloHSCT
  - 600 patients; 43 years (3-66)
  - Study drugs to be given for 100 days (or 180 days if on steroid therapy)
  - Galactomannan screening twice weekly for 60 days (then once weekly until day 100 in no GVHD or twice weekly if GVHD)
  - Antifungal targeted therapy in case of probable or proven IFI
  - Standardized empirical atifungal therapy permitted for suspected IFI limited to <14 days:
- Primary end point: fungal-free survival
- Results:
  - FLU 75% vs VORI 78% (p=ns) at 6 months
  - FLU 65% vs VORI 63% (p=ns) at 12 months

Wingard et al. ASH 2007

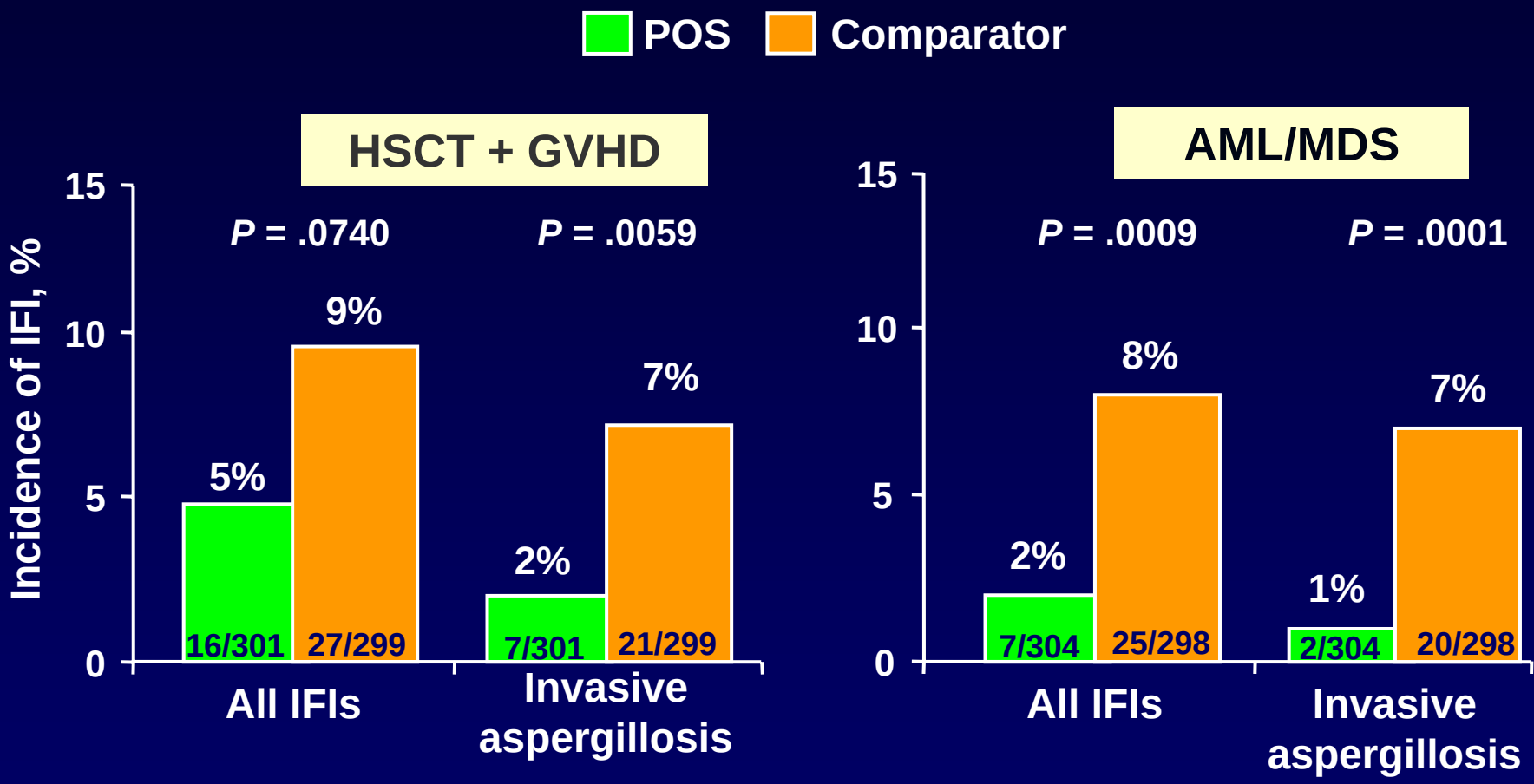
# Posaconazole prophylaxis

| | Study 1 | Study 2 |
|---|---|---|
| **Design** | Double blind, double dummy | Prospective, randomized, evaluator blinded |
| **Populations** | HSCT recipients with acute or chronic GVHD treated with intensive immunosuppressive therapy | Newly diagnosed or 1st relapse AML or MDS patients receiving intensive chemotherapy who are neutropenic (ANC ≤500 cells/$mm^3$) for ≥7 days |
| **Treatment regimen** | POS 200 mg oral suspension 3x/day or FLU 400 mg capsule 1x/day | POS 200 mg oral suspension 3x/day or standard azole (FLU 400 mg oral suspension 1x/day or ITZ 200 mg oral solution 2x/day) |
| **Duration of treatment** | Up to 112 days | Initiated with each cycle of chemotherapy for up to 84 days |
| **Follow up** | 2 months after end of treatment | 100 days postrandomisation |

Ullmann et al. N Engl J Med 2007; 356: 335-347

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

# Incidence of proven and probable IFI





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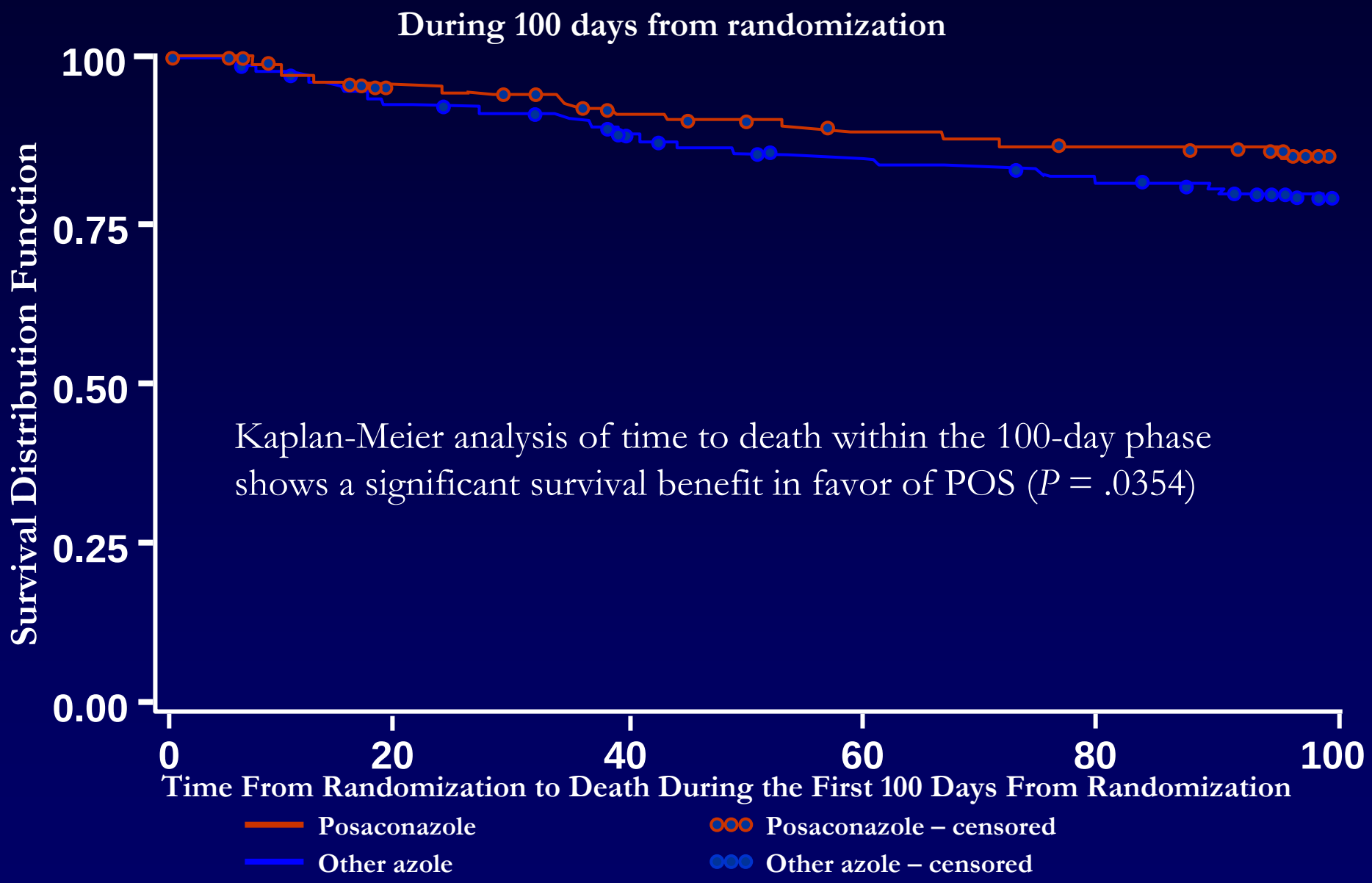
Cornely et al. N Engl J Med 2007; 356: 348-359

# AML/MDS time to death (overall mortality)



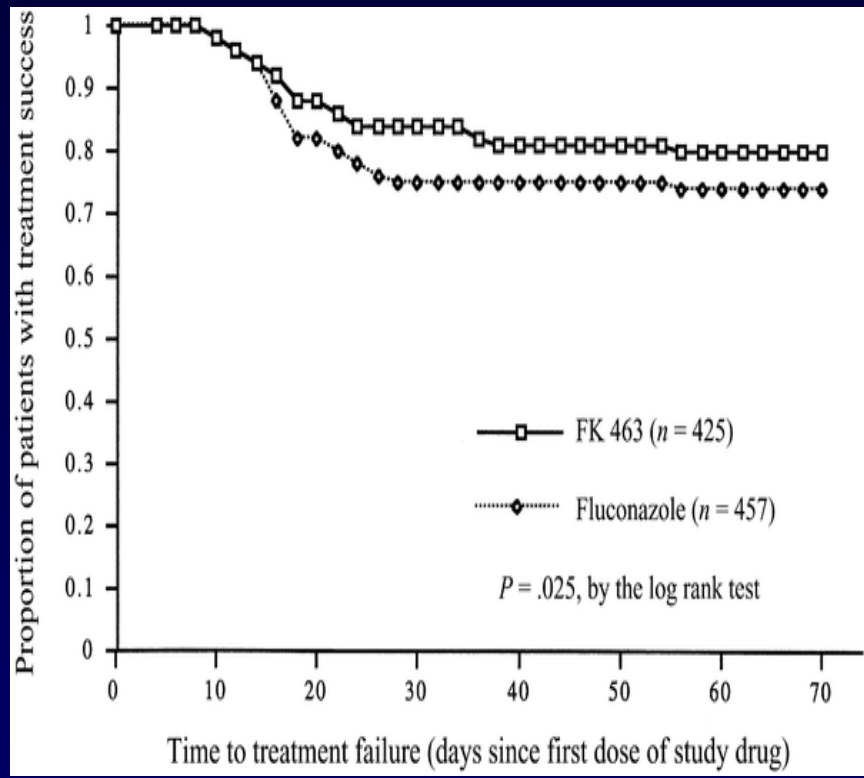

Kaplan-Meier analysis of time to death within the 100-day phase shows a significant survival benefit in favor of POS ($P = .0354$)

# Poliens prophylaxis

- **Oral suspension (1.5-3 g/d):** **not recommended**
- **Aerosolized AmB:** **not recommended**
  - Prospective randomized trial by Schwartz et al. Blood 1999: no difference in IA and increased toxicity
- **IV conventional AmB:** **not recommended**
  - 0.1-0.2 mg/kg/d or 0.5 mg/kg, 3 times week
  - Nephrotoxic
  - **Studies not powered to detect significant differences**
    - Perfect 1992; Rousey 1991
- **Lipid-bases formulations:** **not recommended**
  - Toxicity (ABCD vs. fluconazole)
  - Liposomal AmB (2 double-blind placebo controlled studies, meta-analysis) should be avoided in BMT recipients due to the lack of supporting evidence, its high cost, and common side effects. In case od prolonged neutropenia recommendation (Penack et al. An Oncol 2006) **CI**
  - Studies not powered to detect significant differences
    - Tollemar 1993; Kelsey 1999; Timmers 2000

# Echinocandin prophylaxis

- **Micafungin 50 mg/day - HSCT: CI**
  - neutropenic phase of HSCT : micafungin vs fluconazole. Van Burik et al. CID 2004
- **Micafungin in acute leukemia: no data**
- **Anidulafungin: no data**
- **Caspofungin:**
  - hematological malignancies: caspofungin vs itraconazole. Similar efficacy. Mattuzzi et al. AAC 2006
  - Insufficient data to propose recommendation




**Micafungin (FK463) vs Fluconazole**

# Primary antifungal prophylaxis

- **alloHSCT** **AI**
  - neutropenia
  - up to +100 day
  - GVHD
  - **Acute leukemias** **AI**
    - Induction chemotherapy
  - **autoHSCT** **CIII**
    - Consider in patients
      - prolonged neutropenia
      - TBI or HD-AraC
      - graft purging
      - purine analogues or monoclonal antibodies
      - prolonged steroid therapy

# Antifungal prophylaxis

## Acute leukemia – induction chemotherapy

| Drug | Dose | Recommendation | |
|---|---|---|---|
| Fluconazole | 50-400mg qd iv/po | CI | |
| Itraconazole | 5mg/kg bid po (sol) | CI | level monitoring<br>drug interaction<br>poor tolerability |
| Posaconazole | 3x200mg tid po | AI | level monitoring |
| Echinocandin | No data | | |
| Polyene | 0.5-1mg/kg | CI | low dose iv,<br>aerosolized DI |

# Antifungal prophylaxis

## HSCT

| Drug | Dose | Recommendation | |
|---|---|---|---|
| Fluconazole | 400mg iv/po | AI | |
| Itraconazole | 200mg iv<br>2x 200mg po | BI | level monitoring<br>drug interaction<br>poor tolerability |
| Posaconazole | 3x200mg tid po | AI | level monitoring |
| Micafungin | 50mg qd iv | CI | |
| Polyene | 0.5-1mg/kg | CI | low dose iv,<br>aerosolized DI |

# Secondary antifungal prophylaxis

- **Risk of reactivation/progression of invasive fungal infection in patients undergoing intensive chemo-radiotherapy**
  - 35% (Cordonnier et al. BMT 1995)
  - 29% (Fukuda et al. BBMT 2004)
  - 22% (Martino et al. Blood 2006)
- **Secondary antifungal prophylaxis has not been studied in a well-designed prospective, randomized clinical trial**
- **RIC-HSCT**
- **Antifungal drugs**
  - Voriconazole
  - Amphotericine
  - Caspofungin
  - Posaconazole

# Secondary antifungal prophylaxis - risk factors for breakthrough IFI

- duration of neutropenia, per each day
- high-dose cytarabine
- number of antibiotics, per each antibiotic
- partial response as outcome of prior IFI
- newly diagnosed AML
- high efficiency particulate air filter during prior IFI

# Antifungal prophylaxis

- Fluconazole prophylaxis has an established role in high risk patients undergoing HSCT and patients receiving intensive antileukemic therapies
- Anti-mould prophylaxis studies are promising in patients at risk for invasive mould infections
- Heterogeneity of risk suggests prophylaxis in some patients may be appropriate but not clear in other groups