



# **Antifungal agents for prophylaxis, preemption, or for proven aspergillosis: The argument for prophylaxis**

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## Disclosures

1. Pfizer: Speaker honoraria, Advisory board
2. Schering-Plough: Speaker honoraria, Advisory board
3. Astellas: Advisory Board

## **Proposition –**

**Mould-active prophylaxis should be used  
in patients at high risk for invasive  
aspergillosis**

1. Agree
2. Disagree
3. Don't know

**Before the debate**



**End Interactive Slide**

## **Premises for antifungal prophylaxis and early treatment strategies**

- The more dangerous the infection, the more likely we are to use prophylaxis
- The higher the incidence of infection within a given population, the more likely we are to use prophylaxis.
- The safer the agent, the more likely we are to use it in a large number of patients (e.g., as prophylaxis) in which only a minority would be expected to benefit but very few would incur toxicity.
  - toxicity may not be obvious (e.g., drug-drug interaction)
- The better the methods for early detection of early infection, the more willing we are to withhold prophylaxis or to not modify the antibiotic regimen with negative screening results
- Cost-effectiveness of prophylaxis vs. other strategies

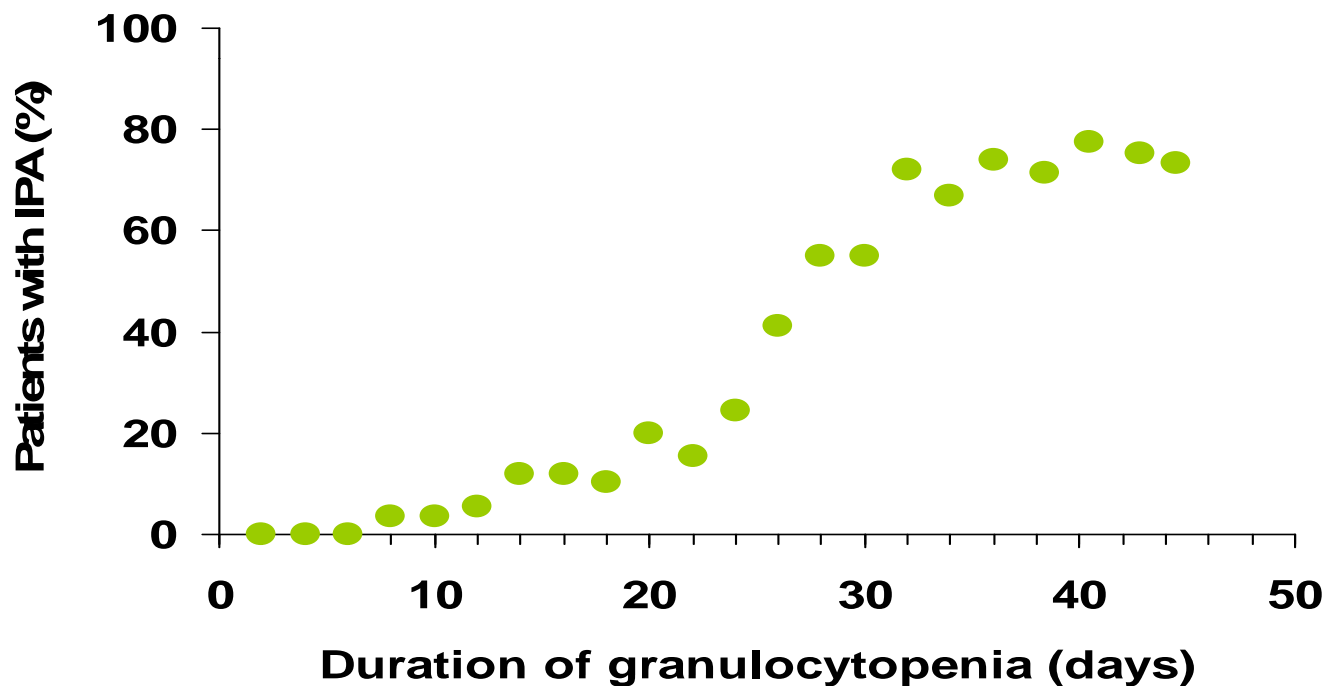


**The Doctor's  
Dilemma**

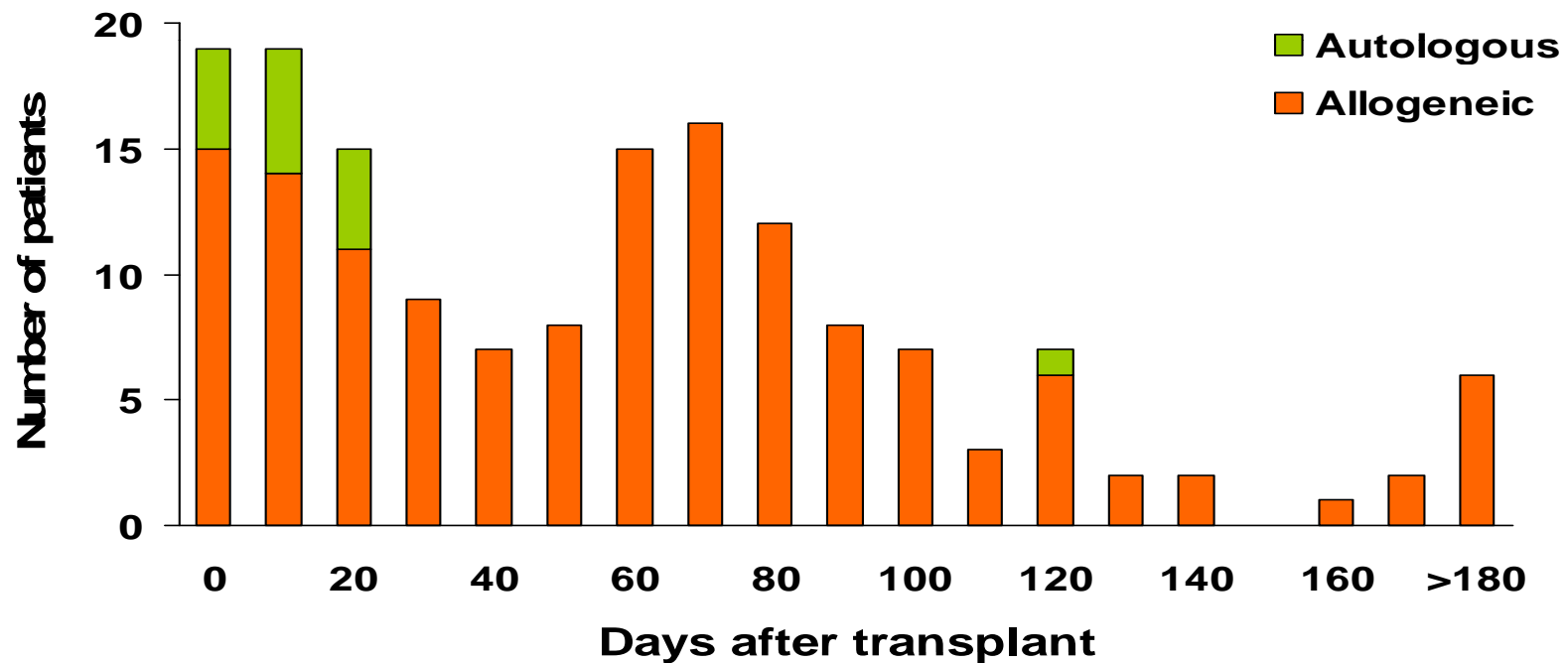
**George Bernard  
Shaw**



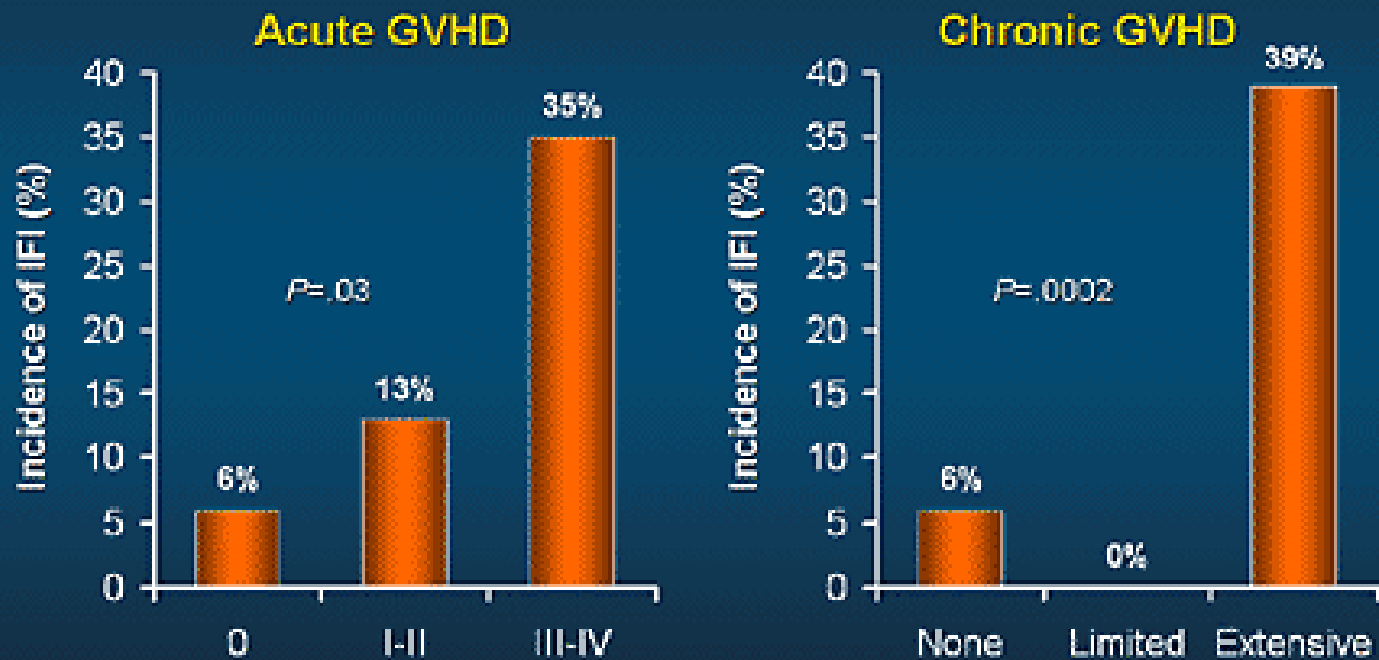
## Prolonged Granulocytopenia and Invasive Pulmonary Aspergillosis



# Invasive Aspergillosis in HSCT Recipients



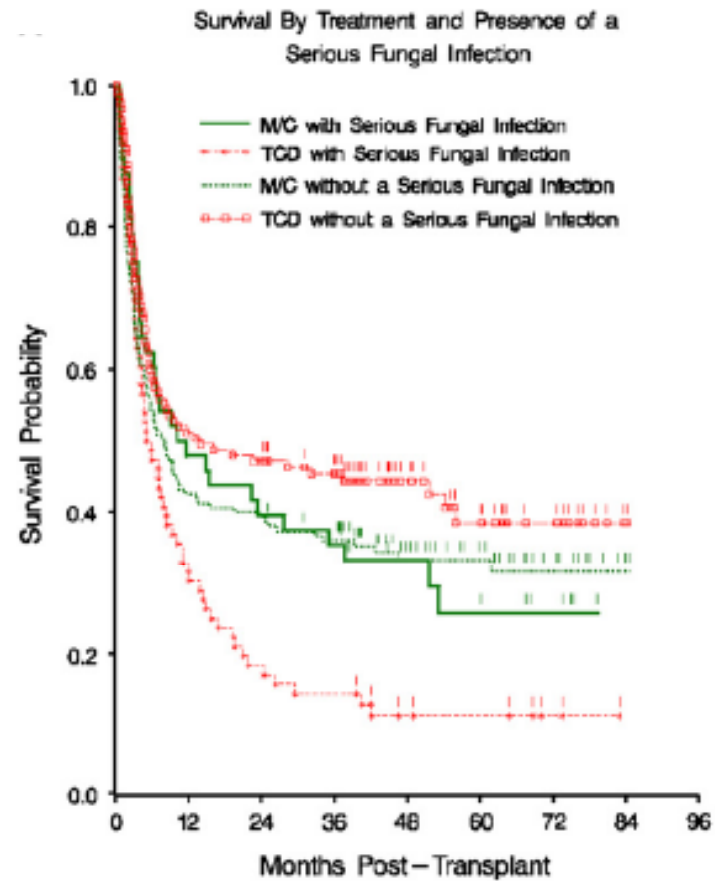
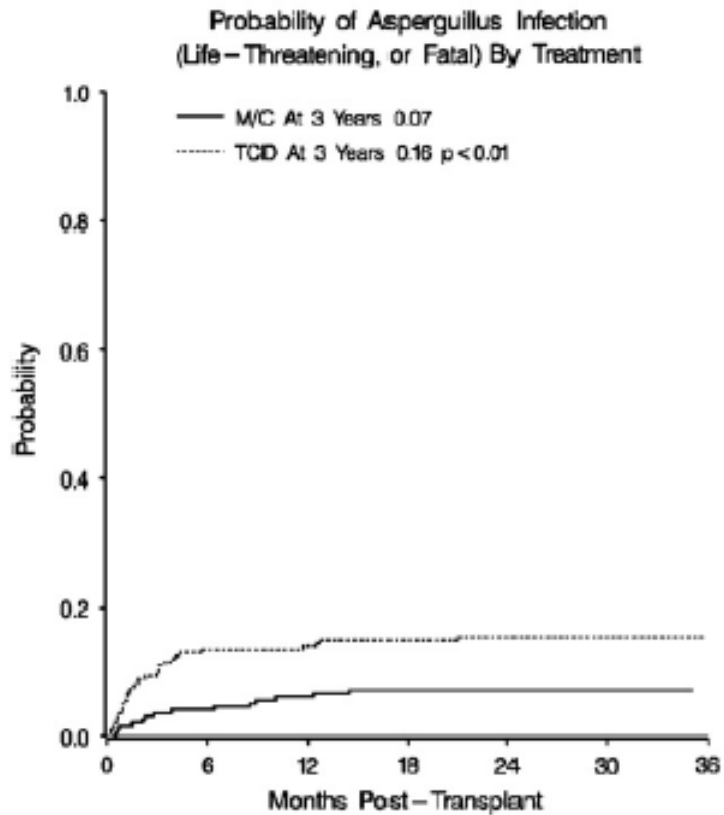
## Percentage of Patients With GVHD Developing Invasive Fungal Infections



IFI=invasive fungal infection.

Jantunen et al. *Bone Marrow Transplant*. 1997;19:801-808.

## Increased invasive fungal disease after T-cell depletion versus immunosuppressive tx to prevent GVHD



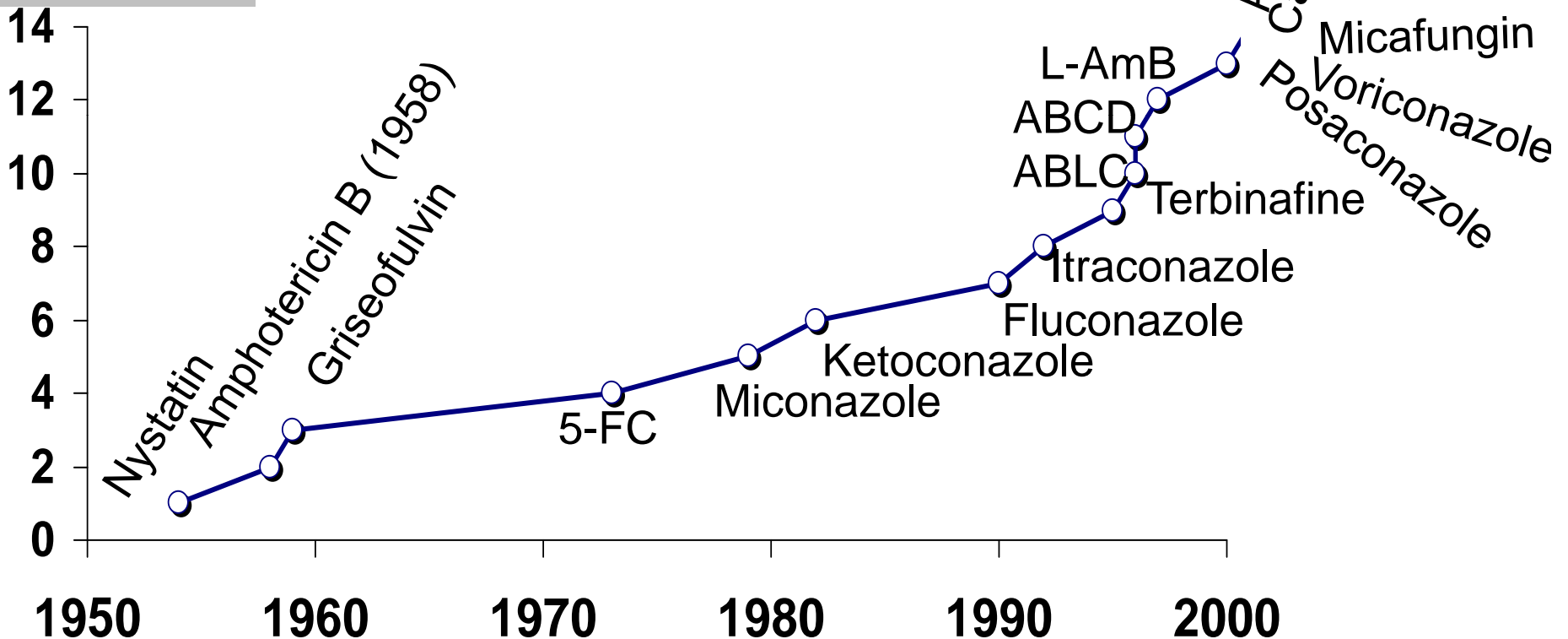
## **Rarer moulds**

1. Zygomycetes
2. Fusarium sp.
3. Scedosporium sp.
4. Dark-walled moulds



## Medical Mycology: The Last 50 Years

# of drugs

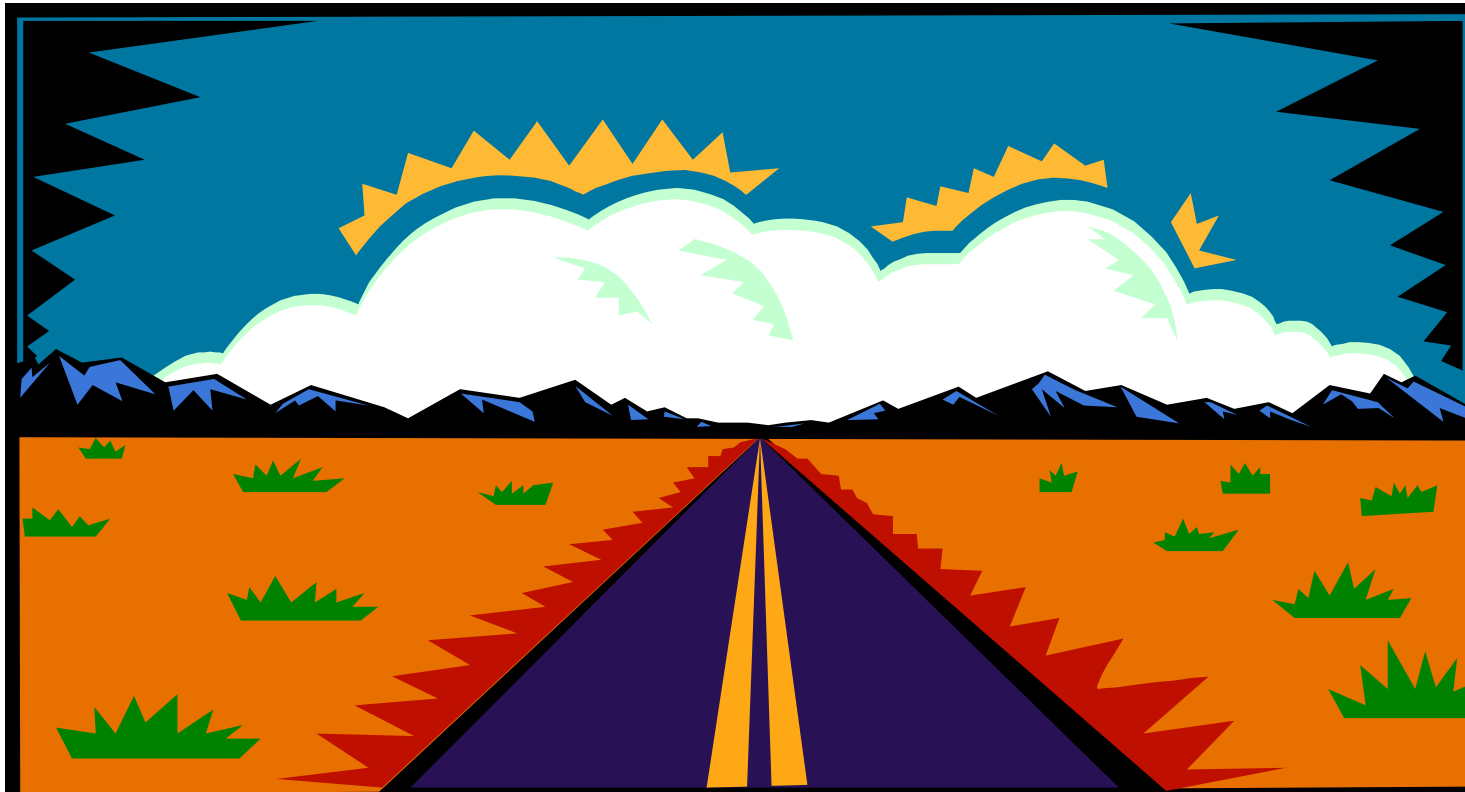


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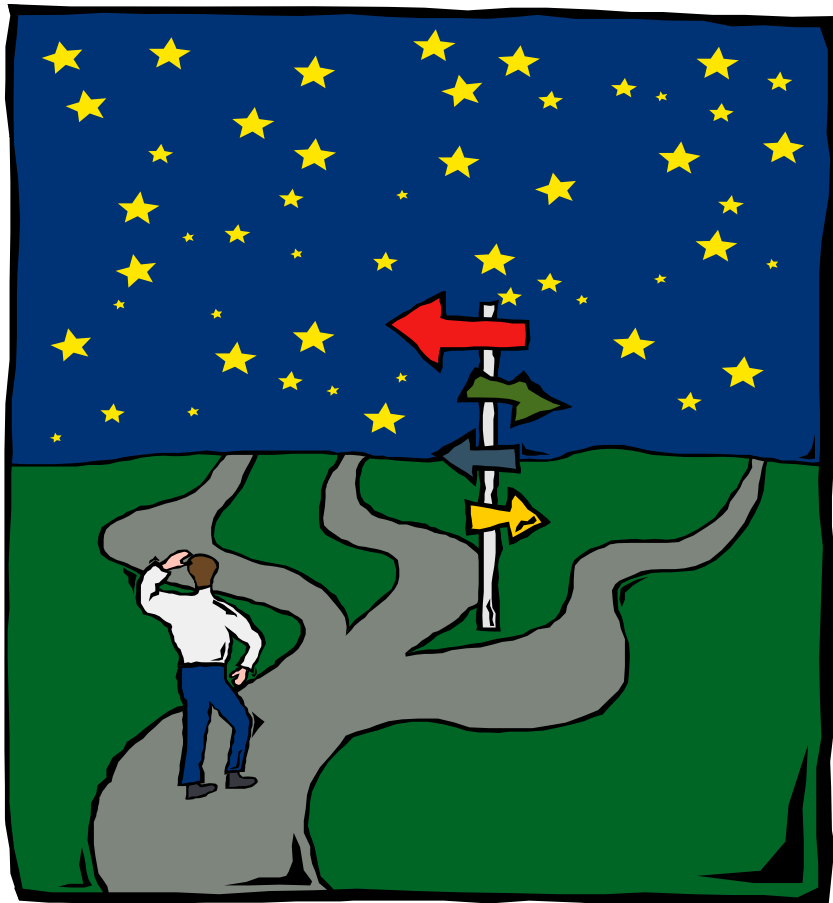
## **Strategies for Use of Antifungal Agents in Patients at High Risk for Fungal Infection**

1. Prophylaxis
2. Empirical therapy
  - persistent or recurrent neutropenic fever that is unresponsive to broad-spectrum antibacterial agents
3. Preemptive therapy
  - Lab markers, CT scan
4. Treatment

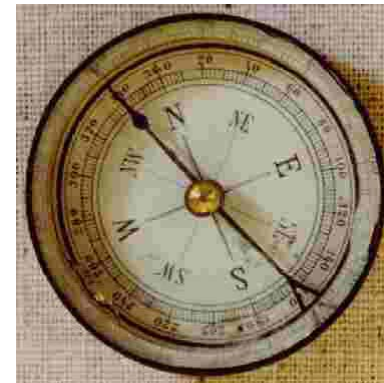
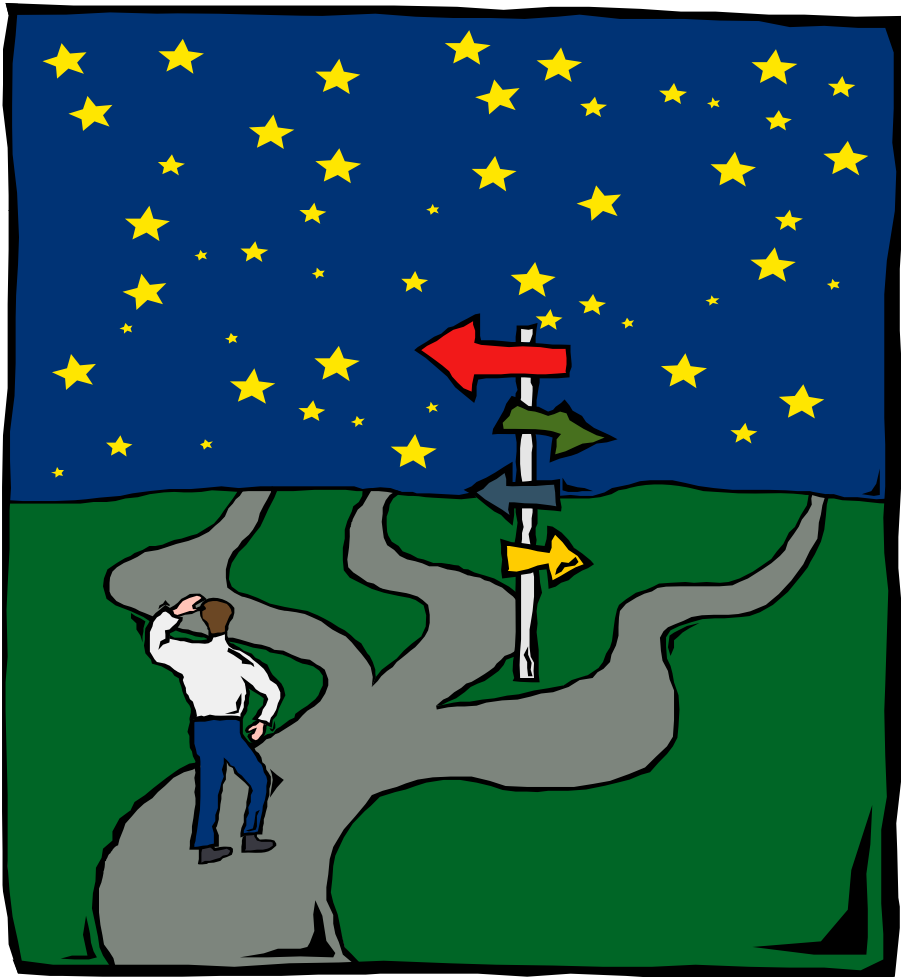
# Prophylaxis



# Empirical antifungal therapy



# Pre-emptive antifungal therapy

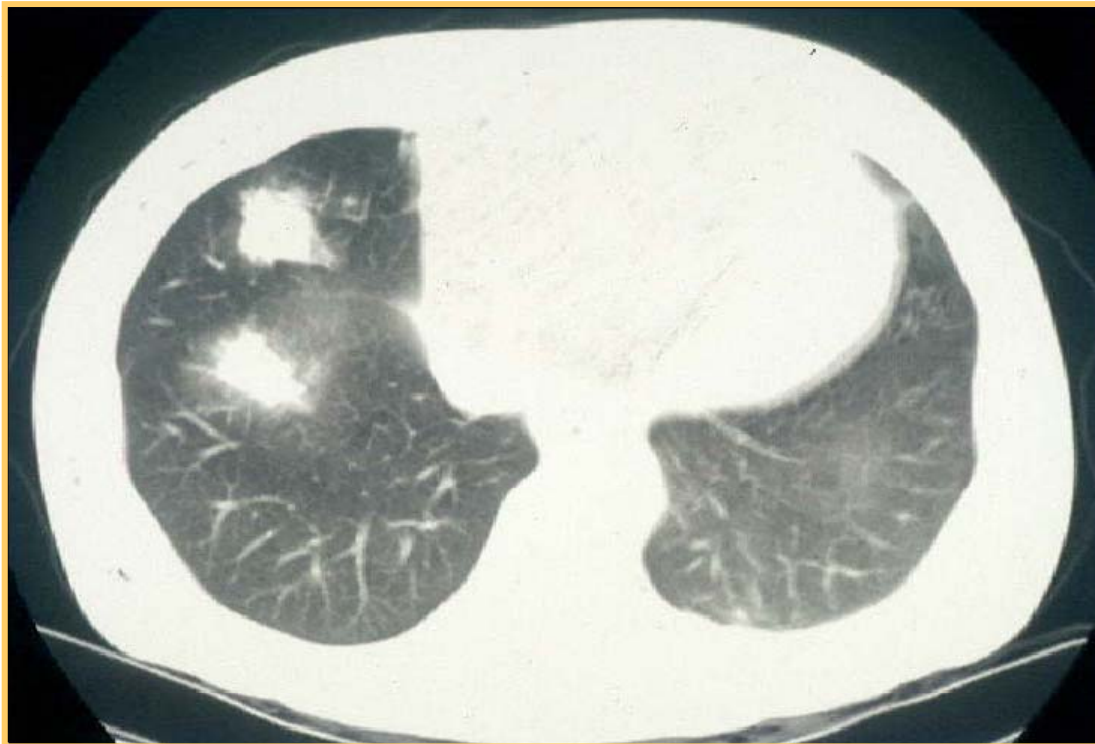




# Lab Markers for Early Detection of Fungal Infection

1. Galactomannan assay
2. B-glucan assay
3. PCR

## CT imaging





## **Key differences between antifungal prophylaxis vs. empirical and pre-emptive approaches**

Goal of prophylaxis is PREVENTION

Goal of empirical and pre-emptive approaches is EARLY TREATMENT because the markers are designed to detect early invasive disease

Scenario is different in pre-emptive anti-CMV therapy where detection of virus in blood identifies patients at high risk for developing CMV disease



# Fluconazole prophylaxis in HSCT recipients<sup>1</sup>

1. Mostly allogeneic
2. Fluconazole used until day 75
3. ↓ invasive fungal (*Candida*) infections
4. ↓ mortality
5. F/u analysis of patients enrolled in original study showed survival advantage in fluconazole arm extending to 9 years<sup>2</sup>
  - ↓ frequency of severe gut GVHD in fluconazole arm

<sup>1</sup>Slavin MA, et al. *J Infect Dis.* 1995;171:1545-52.

<sup>2</sup>Marr KA, et al. *Blood.* 2000;96:2055-61.

## **Fluconazole vs. Itraconazole in Allogeneic HSCT Recipients**

1. Fewer cases of invasive aspergillosis in itraconazole recipients, but no difference in overall survival
2. Increased toxicity with itraconazole
  - Gastrointestinal
  - Hepatic
  - increase in cyclophosphamide metabolites, which in turn correlated with hyperbilirubinemia and nephrotoxicity during the early transplant period

<sup>1</sup>Winston DJ et al. *Ann Intern Med.* 2003;138(9):705-13

<sup>2</sup>Marr KA et al. *Blood.* 2004;103(4):1527-33



## **Micafungin vs. Fluconazole Prophylaxis in HSCT During Neutropenia**

1. N= 882 (~50% allogeneic)
2. Treatment success was defined as the absence of fungal infection (suspected and proven) through 4 weeks following study drug
3. Overall success rate was significantly higher in micafungin (80.0%) versus fluconazole (73.5%) recipients
4. Superiority of micafungin driven by fewer micafungin recipients requiring modification of antifungal therapy due to persistent neutropenic fever
5. Frequency of breakthrough candidiasis was <1% in both arms.
6. One micafungin recipient and 7 fluconazole recipients developed invasive aspergillosis (p=0.07).
7. Safety and survival were similar

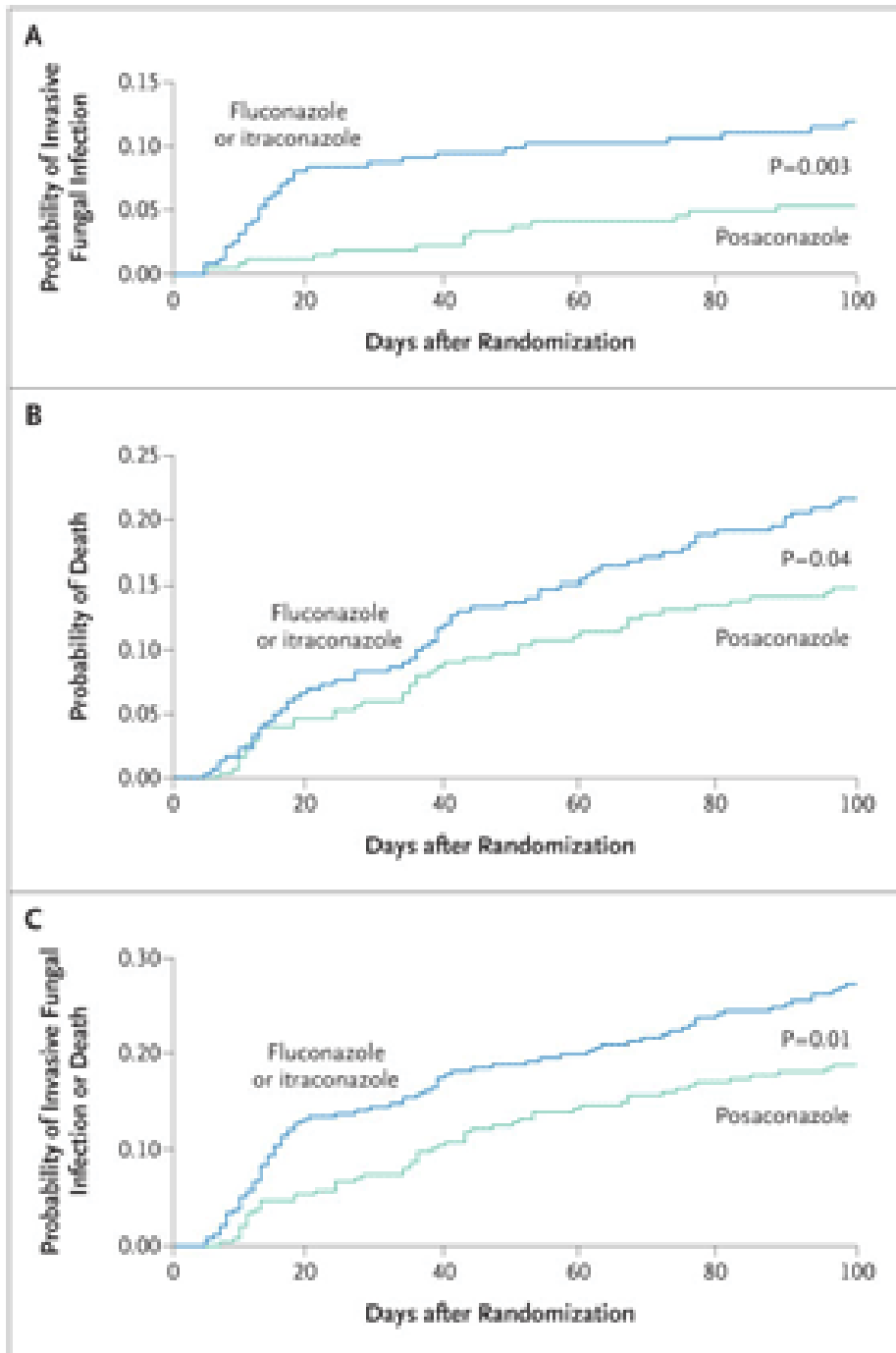
# Posaconazole prophylaxis

## 1. Neutropenia

- Prophylaxis with posaconazole led to fewer IFIs and less overall mortality compared to fluconazole or itraconazole in neutropenic patients with acute leukemia or myelodysplastic syndrome [Cornely et al. NEJM, 2007].

## 2. GVHD

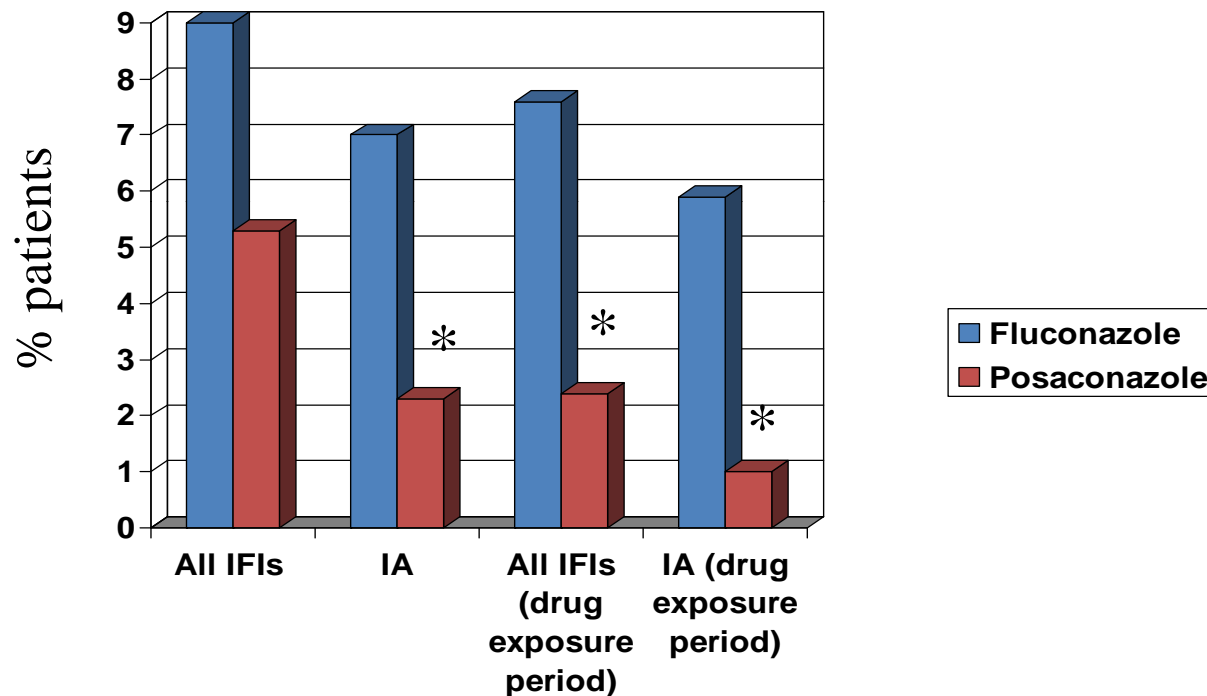
- Prophylaxis with posaconazole led to a reduction in the incidence of IA, in the total number of IFIs while on treatment, and in the number of deaths attributed to fungal infection [Ullman et al. NEJM, 2007].



1. Prophylaxis with posaconazole led to fewer IFIs and less overall mortality compared to fluconazole or itraconazole in neutropenic patients with AML or myelodysplastic syndrome
2. Serious adverse events (mostly GI) possibly or probably related to treatment occurred in 6% of posaconazole and in 2% fluconazole or itraconazole recipients (P=0.01).

Cornely et al. N Engl J Med, 2007

## Posaconazole vs. fluconazole for severe GVHD



1. Prophylaxis with posaconazole led to a reduction in the incidence of IA, in the total number of IFIs while on treatment, and in the number of deaths attributed to fungal infection
2. No significant difference in AEs

## Limitations

1. Some of the patients may have been receiving “pre-emptive therapy”, based on baseline + serum GM
2. Mould-active prophylaxis can reduce sensitivity of serum GM test
3. Variable bioavailability of posaconazole
  - Need for food
4. Potential for drug-drug interactions
5. What to do with suspected or documented breakthrough IFIs?

## The first pre-emptive antifungal study

1. N= 136 treatment episodes for high-risk neutropenic patients
2. screened by daily serum galactomannan and chest CT scans and BAL per study criteria
3. Only patients who met pre-specified criteria for probable or proven invasive fungal infection received liposomal amphotericin B; successful in reducing ampho use
4. 17 cases of IA and 1 case of zygomycosis in one patient
5. Seven (41%) deaths occurred in patients with positive serum galactomannan results.
  - Of these, 6 had autopsy-proven invasive aspergillosis.
  - However, only 2 patients were considered to have died directly due to invasive aspergillosis.
6. Could diagnosis of IA lead to a delay in subsequent chemo and HSCT?



**Results of a Randomized, Double-blind Trial of  
Fluconazole (FLU) vs. Voriconazole (VORI)  
for the Prevention of Invasive Fungal Infections (IFI) in 600  
Allogeneic Blood and Marrow Transplant (BMT) Patients**



**John R Wingard, Shelly L Carter, Thomas J Walsh, Joanne Kurtzberg,  
Trudy N Small, Iris D Gersten, Adam M Mendizabal, Helen Leather,  
Dennis L Confer, Lindsey R Baden, Richard T Maziarz, Edward A Stadtmauer,  
Javier Bolanos-Meade, Janice Brown, John F DiPersio, Michael Boeckh and  
Kieren A Marr**

## Double-blind controlled trial comparing fluconazole (+screening) with voriconazole (+screening)

- Study drug to be given for 100 days (or 180 days if on corticosteroids or CD4<200/ $\mu$ L if graft T-cell depleted)
  - Fluconazole 400 mg QD po or iv
  - Voriconazole 200 mg BID po or iv
- Galactomannan screening twice weekly for 60 days (then once weekly until day 100 if no GVHD or twice weekly if GVHD)
- Standardized empirical antifungal therapy permitted for suspected IFI limited to <14 days

**Primary endpoint: fungal-free survival (FFS) at 180 days**



## Microbiologically Documented Proven/Probable Fungal Infections Through Day 180

Fungal Genus	FLU	VORI
• Aspergillus*	16*	7*
• Candida	3	3
• Zygomycetes	3	2
• Other	1	1
Totals**	23**	13**

\*p = 0.05\*\* p = 0.11



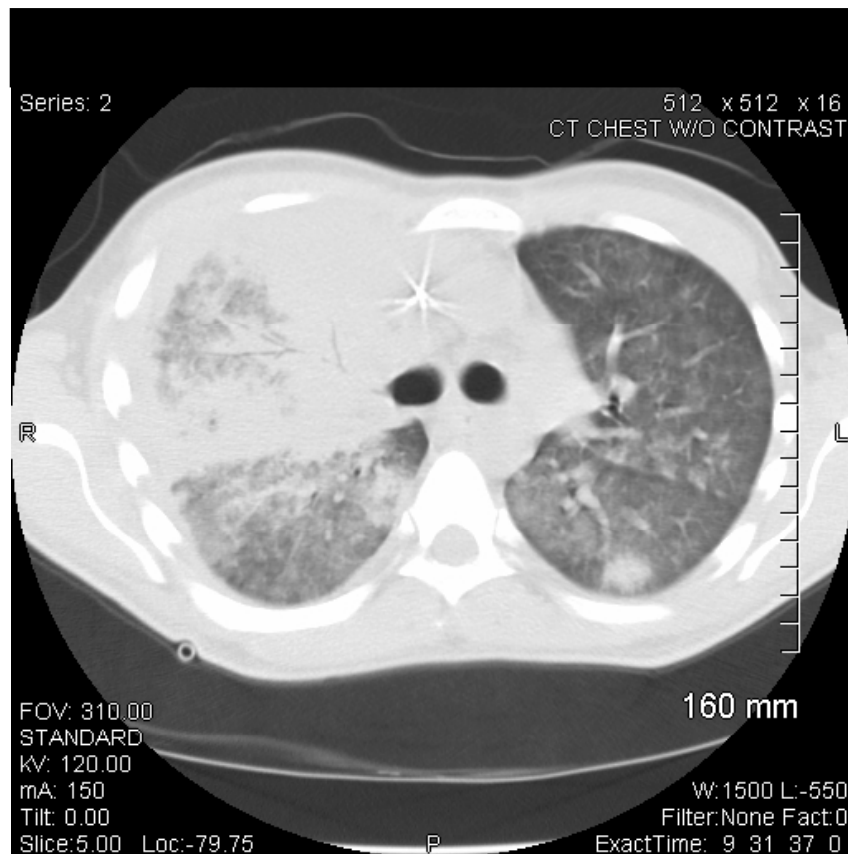
## Summary of CTN trial

- No differences in fungal-free or overall survival rates
- Trend to fewer *Aspergillus* infections in voriconazole arm
- Infections by Zygomycetes were not increased in the voriconazole arm
- Toxicities were similar

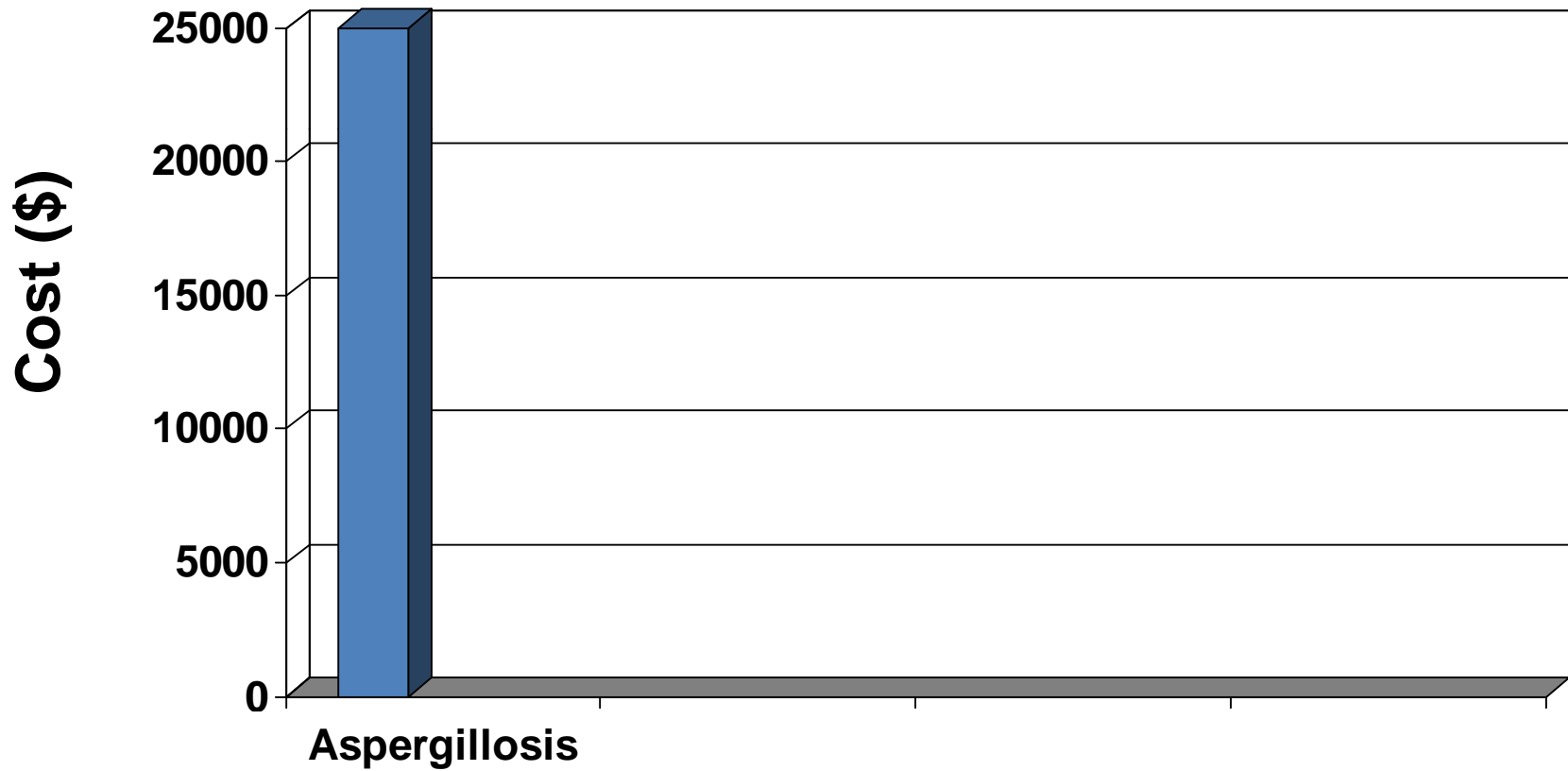
## **Prophylaxis with extended-spectrum azoles: general conclusions**

1. Effective in preventing invasive aspergillosis in high-risk patients
2. Increased overall survival with posa vs. fluc in AML and MDS
3. More likely to detect benefit of prophylaxis when targeted to highest risk patients (e.g., severe GVHD vs. all Allo HSCT recipients)
4. Modestly increased number of SAEs in mould-active azole vs. fluc in 1 of 3 studies (Cornely et al.); toxicity was similar in the other 2 studies

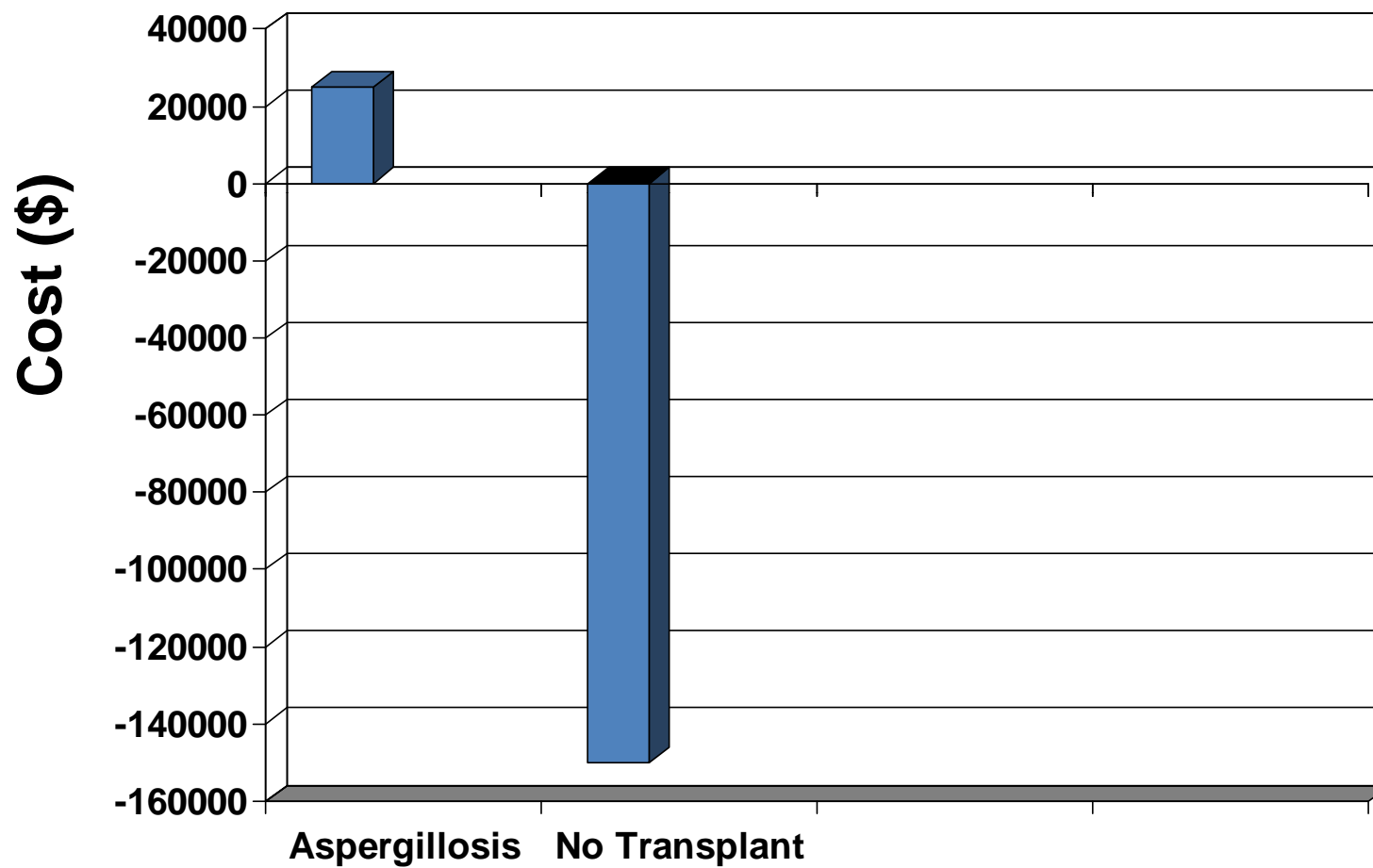
## A case study of cost-effectiveness of antifungal prophylaxis: What should we measure?



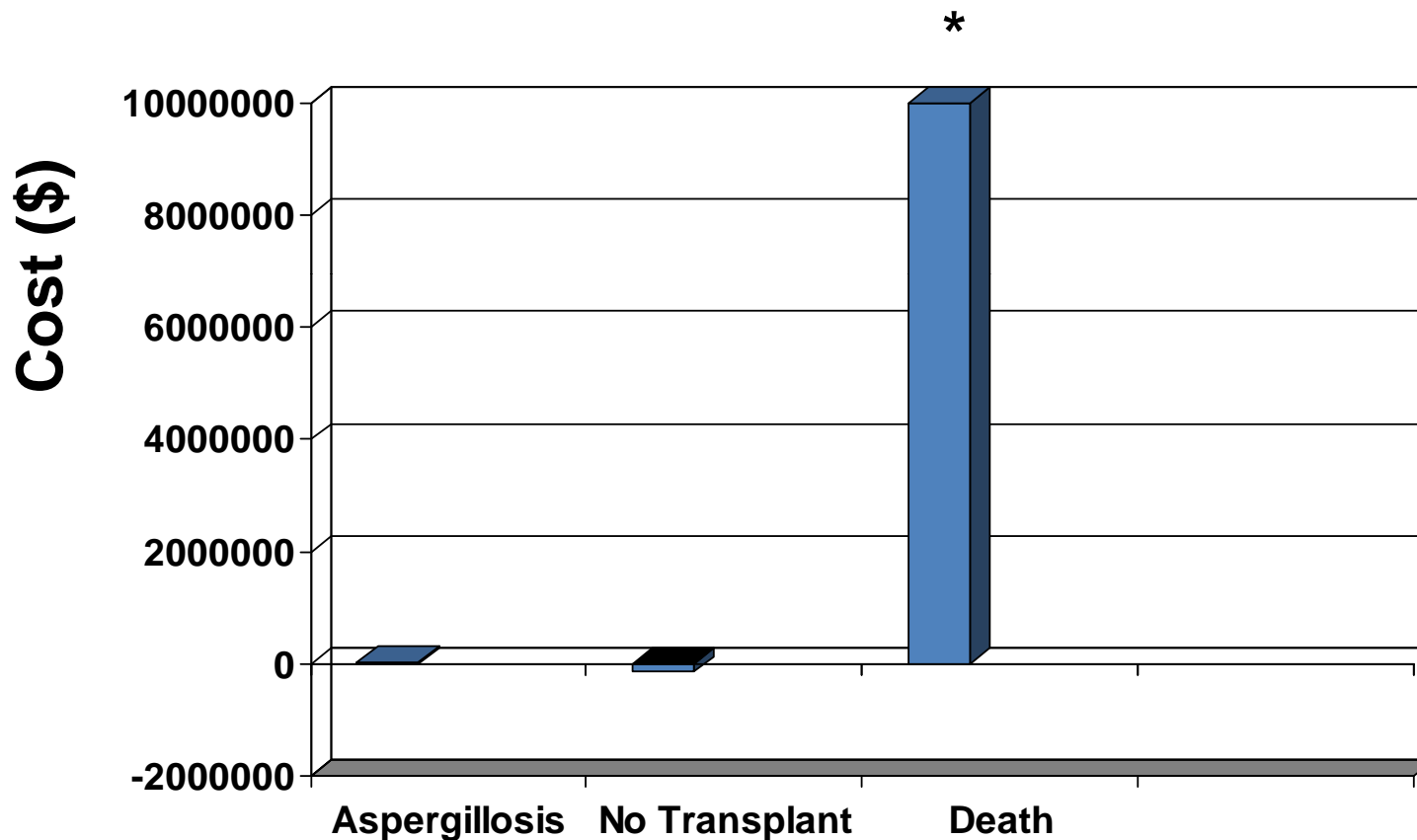
## Estimated cost of case of aspergillosis



## Estimated cost of case of aspergillosis

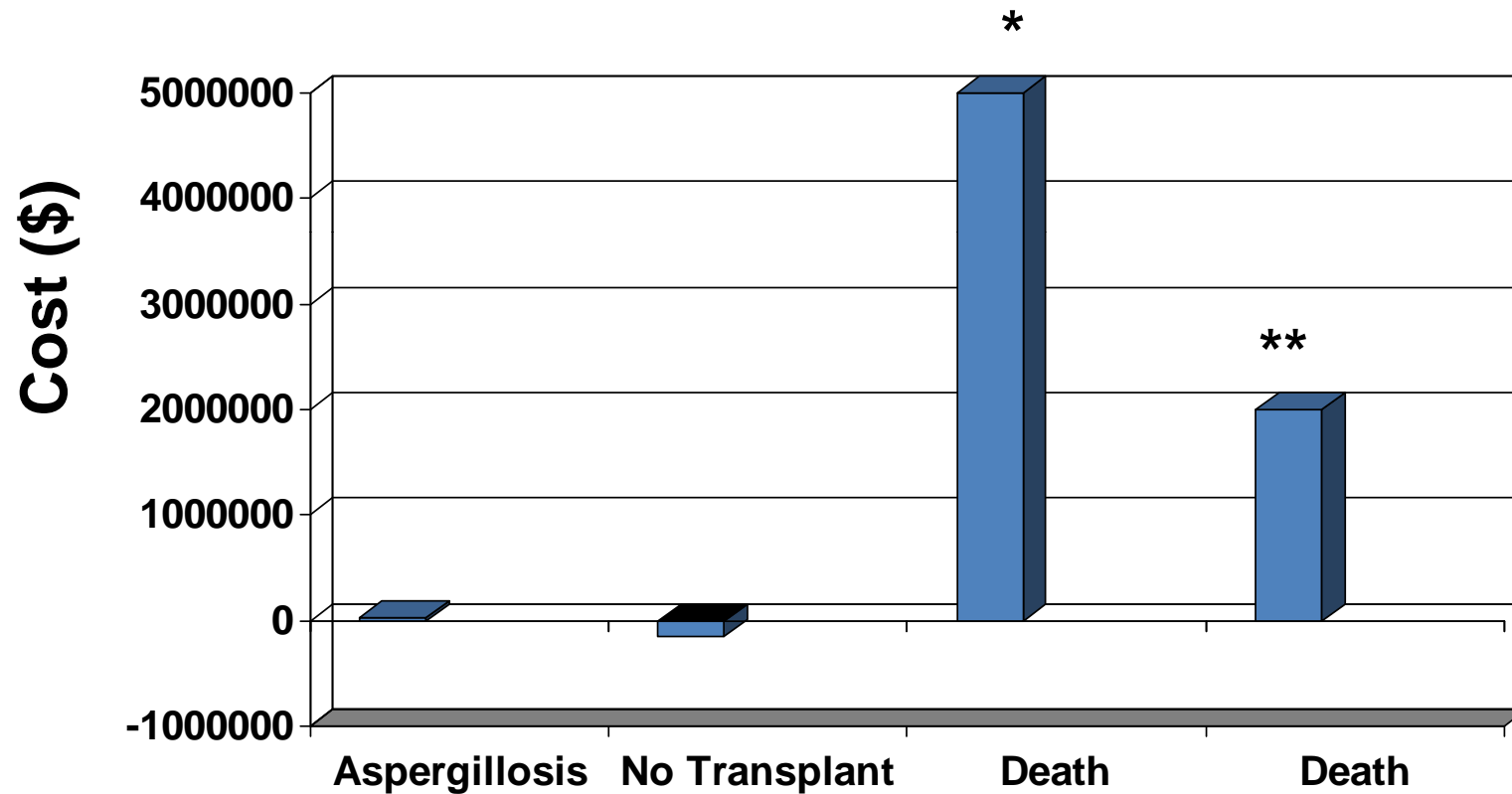


## Estimated cost of case of aspergillosis



\* Assuming 50 year life span following transplant and society assigning a modest monetary value of \$200,000 per statistical life-year

## Estimated cost of case of aspergillosis



\* Assuming 25 year life span following transplant

\*\* Assuming 10 year life span following transplant



## Cost per Life Saved for Selected Regulations

Regulation	Agency	Net costs per year*	Lives saved per year	Cost per life saved*
Head-impact protection	DOT	\$390 M–\$516 M	611–732	\$665,000–\$705,000
Child restraints	DOT	\$54 M–\$122 M	25–35	\$1.5 M–\$4.9 M
State NO <sub>x</sub> rule	EPA	\$1265 M†	152–342	\$3.7 M–\$8.3 M
Methylene chloride	OSHA	\$112 M	8.8	\$12.7 M
Enhanced surface water treatment	EPA	<\$0–\$95 M	14–64	<\$0–\$6.8 M

\* Dollars in 2001 values. † In 2007.

Kaiser J. Science, 2003; “How much are human lives and health worth?”

## **Proposition: Mould-active prophylaxis should be used in patients at high risk for invasive aspergillosis**

1. Host factors and local population data on frequency of IFIs guide decisions
  - High risk vs. Highest risk
2. Future research should focus on refining the definition of high risk based on genetic factors <sup>1,2</sup>
3. A reasonable goal for targeted extended-spectrum mould-active prophylaxis is to reduce the frequency of invasive aspergillosis to 1% among neutropenic patients with MDS/AML and allo HSCT recipients with significant GVHD

<sup>1</sup> Bochud et al. Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation, NEJM, 2008

<sup>2</sup> Zaas et al. Plasminogen Alleles Influence Susceptibility to Invasive Aspergillosis. PLoS Genet, 2008