MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Antifungal prophylaxis: Whom, what and when

Professor Yee-Chun Chen

Professor of Medicine

National Taiwan University Hospital and College of Medicine;

Investigator, National Institute of Infectious Diseases and Vaccinology

National Health Research Institutes, Taiwan

ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Presented at MMTN Vietnam Conference
1–3 December 2017, Ho Chi Minh City, Vietnam

Antifungal Prophylaxis: Whom, What and When

Yee-Chun Chen, M.D., PhD.

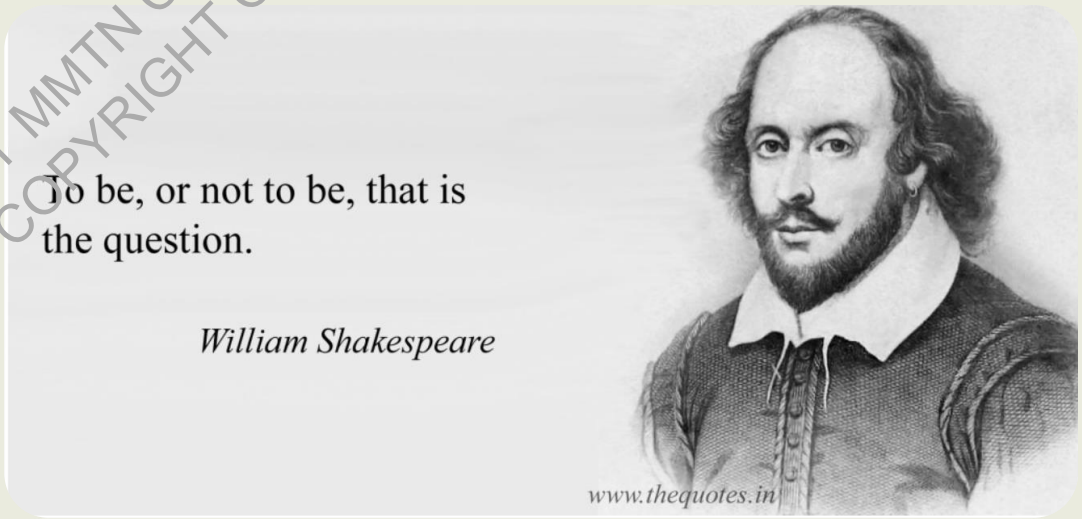
Department of Medicine, National Taiwan University Hospital and College of Medicine, Taiwan

Disclosure

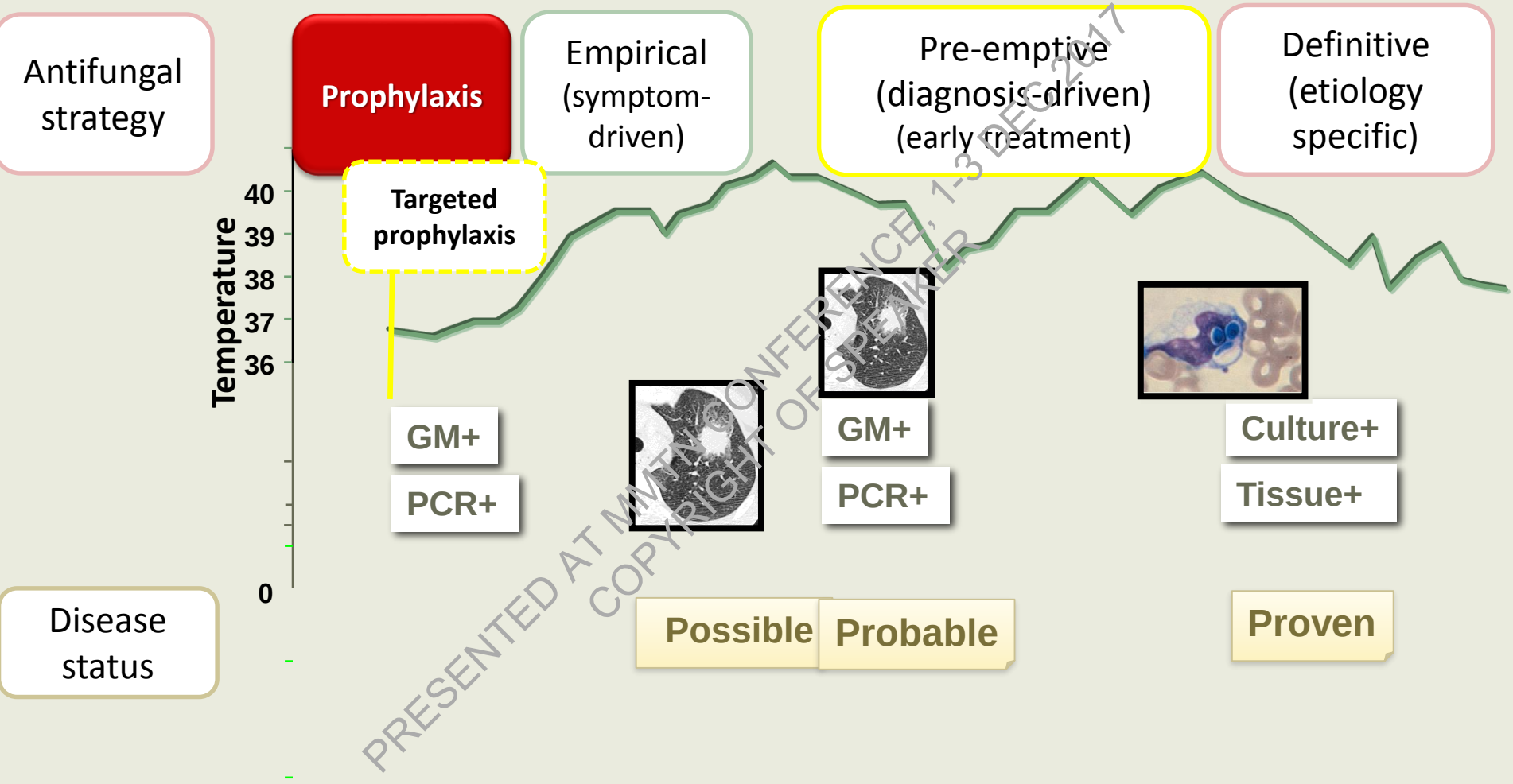
- received honoraria for speaking or advisory board membership from Pfizer, Gilead, Merck, or Astellus,
- has involved as a steering committee member of regional education programs for Pfizer and Gilead,
- received investigator-initiated research funds from Pfizer and Gilead,
- received research grants from Minister of Science Technology, Taiwan and National Health Research Institutes, Taiwan.

Contents

- **To be or not to be**
- **Recent advances**
- **The flip side**
- **Whom**
- **What**
- **Guidelines**
- **Conclusion**



Antifungal strategies



69% of patients with proven/probable invasive mold diseases had fever.

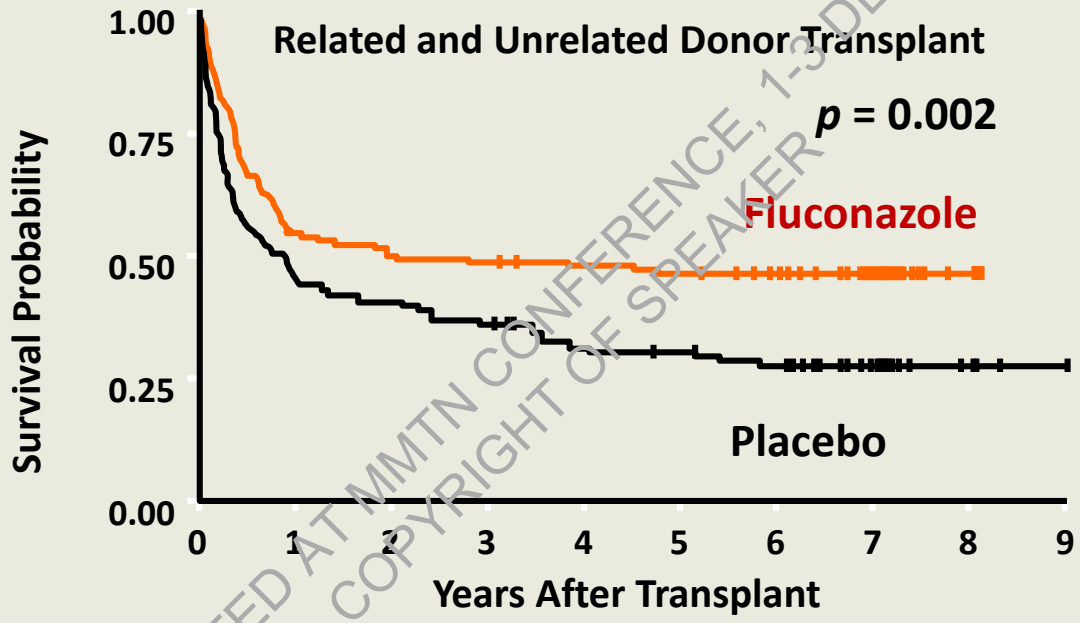
Porpon et al. Med Mycol 2017 doi: 10.1093/mmy/myx029

The Rationale for Prophylaxis

- The substantial morbidity and mortality associated with invasive fungal diseases (IFD)
- The difficulty in obtaining a timely diagnosis
- The suboptimal response of best available treatments
- The substantial additional resource use in patients with IFD
  - Diagnostic approaches and therapeutic monitoring
  - Slow resolution of infection => prolonged suppressive therapy
  - Risk of recurrence in the immunosuppressive period
- Delay in subsequent chemotherapy which compromises overall outcome

RECENT ADVANCES

Fluconazole Prophylaxis Prevents IFI and Improves Survival After HSCT



n = 355 autopsies	Fluconazole	No Fluconazole
Invasive Fungus	37%	43%
Aspergillus/Mucor	29%	18%
Candida	8%	27%
Hepatosplenic	3%	16%

incidence of IA
1987 – 6%
1993 – 11%

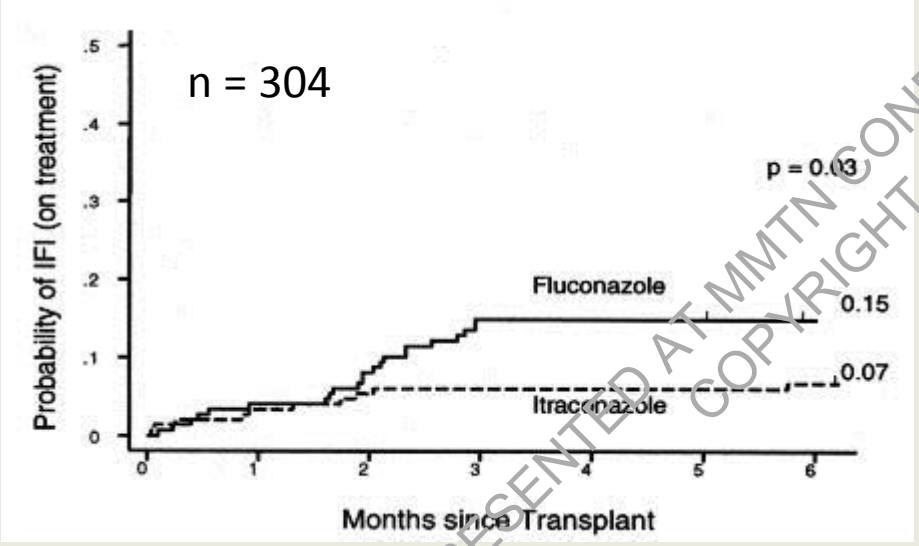
Slavin MA et al, J Infect Dis 1995;171:1545-5
Marr KA et al, Blood 2000;96:2055-61
Van Burik JA et al. Medicine 1998;77:246-54

Fluconazole *vs* Itraconazole prophyalxis

Allo-HSCT

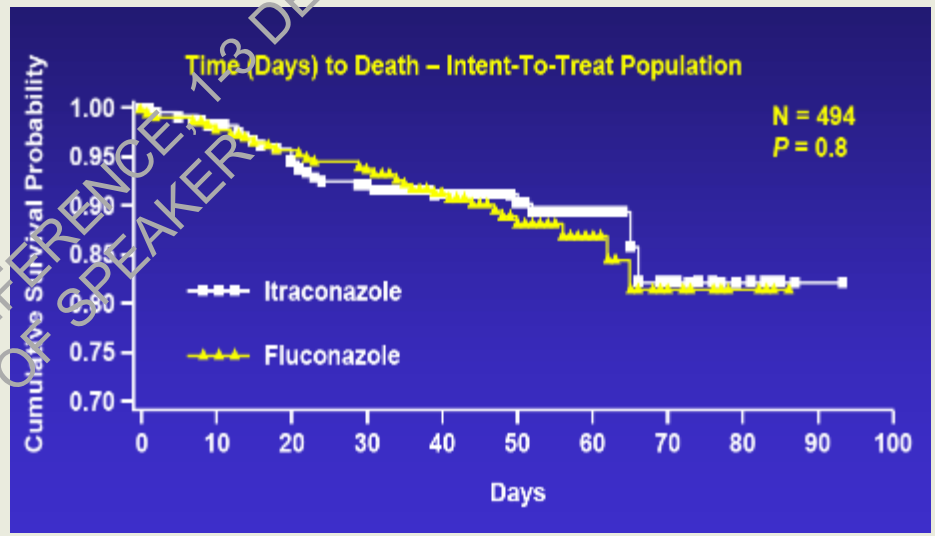
Cumulative incidence of proven/probable IFI while on-treatment

Discontinuation of itraconazole 36%



„Itraconazole appears to prevent IMI in the subset of patients who **tolerate** the drug“

Neutropenic patients

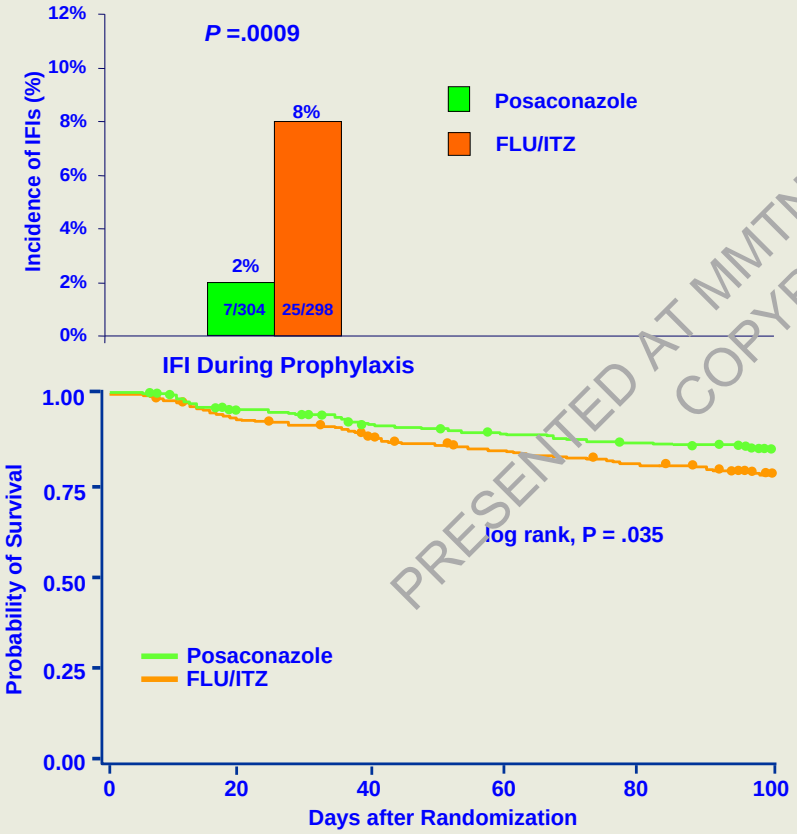


1. Marr KA et al. Blood 2004;103:1527-33
2. Glasmacher A et al. J Antimicrob Chemother 2006;57:317-25

Posaconazole Prophylaxis

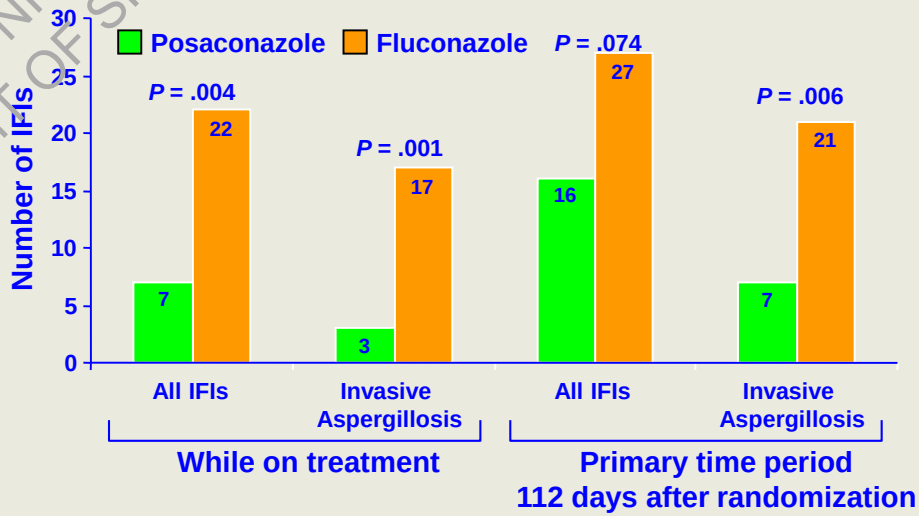
In AML/MDS with 3+7 induction:

- Posa vs. Itra/Flu (n= 308 vs. 298)
- Incidences of IFI decreased
- Survival benefits demonstrated



In Severe GVHD after allo-HSCT:

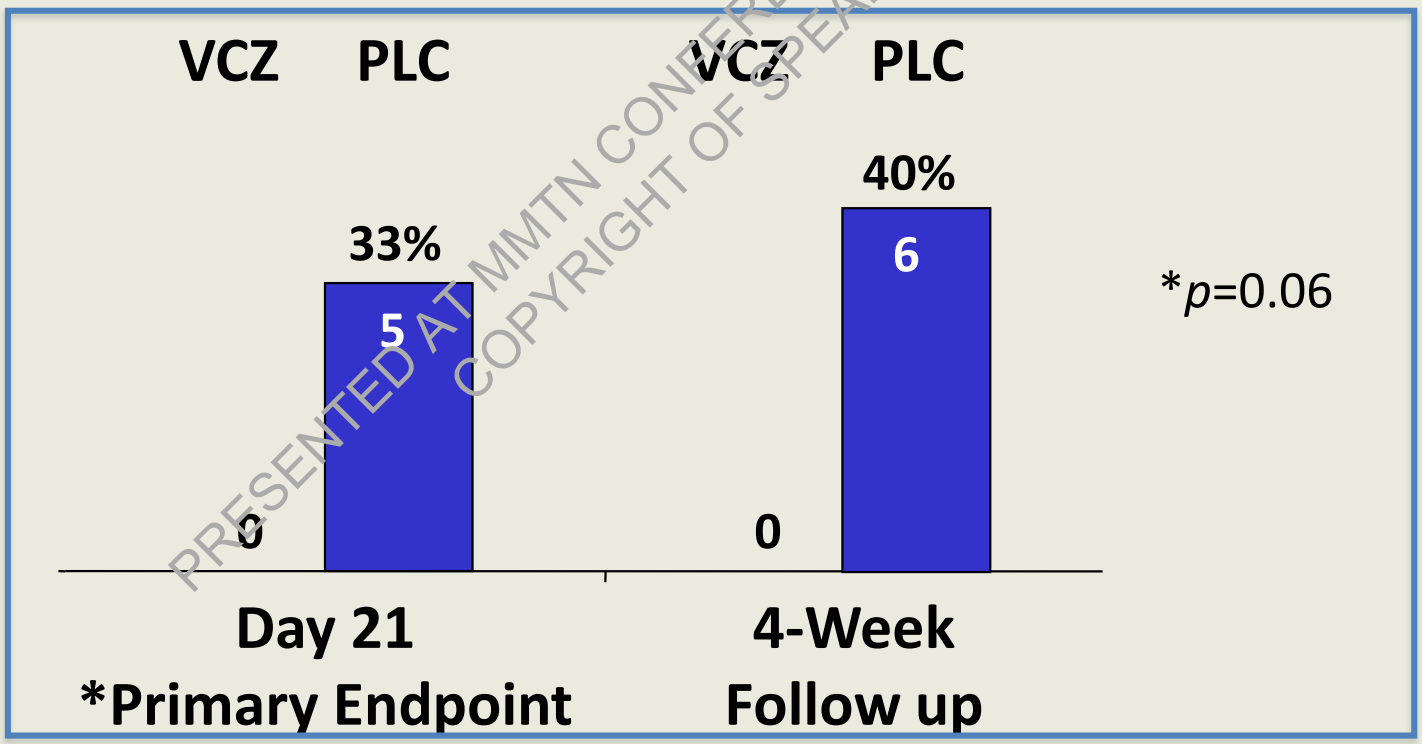
- Posa vs Flu (n=301 vs. 299)
- Incidences of IFI decreased
- Survival benefits NOT demonstrated



Cornely OA et al. *N Engl J Med*. 2007;356:348
Ullmann AJ et al, N Engl J Med 2007;356:335-47

Voriconazole Prophylaxis *vs* Placebo

- n = 25, first induction for AML
- Incidences of Lung Infiltrates
- Stopped because of ethical concern with placebo arm



VCZ, voriconazole; PLC, placebo control; AML, acute myelogenous leukemia

Vehreschild JJ et al, J Infect 2007;55:445-9.

Voriconazole vs. itraconazole in alloHSCT

- IMPROVIT Study
- Prospective, phase 3, randomized, open-label trial
- 47 transplant centers across 12 countries
- Survival benefits NOT demonstrated

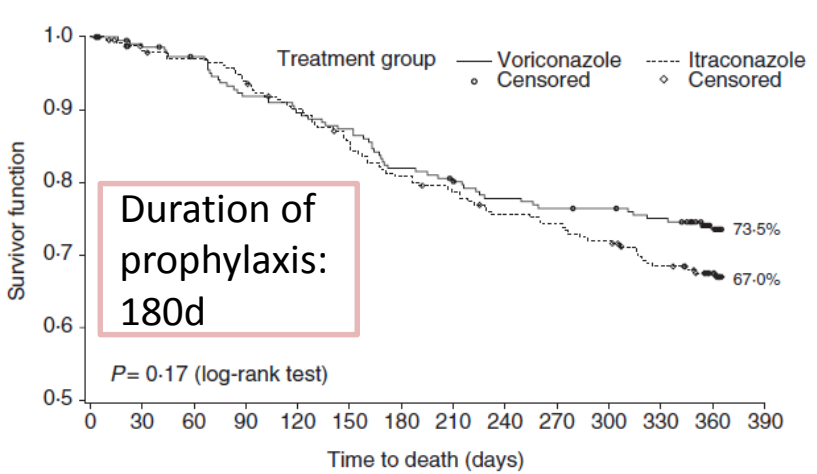
•Global **satisfaction** score at d14 (70% vs. 63%)** was a significant predictor of completion 100d prophylaxis
• Less use of other systemic antifungals (30% vs. 42%)**

Success of prophylaxis*	Voriconazole N=234	Itraconazole N=255	Differences (95% CI)
at d180	48.7%	33.2%	16.4% (7.7-25.1)**
at d100	54.0%	39.8%	15.4% (6.6-24.2)**

*Composite endpoints
1. **Survival** at day 180
2. No probable/proven breakthrough **IFI**
3. **Not discontinuation** of study drug for >14d during 100d prophylactic period

**P<0.05

Br J Hematol 2011;155:318-327

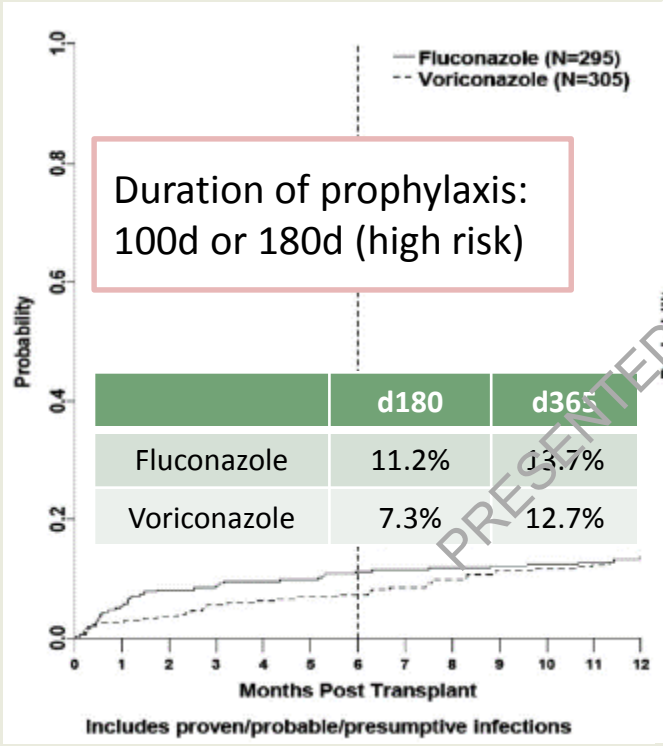


Voriconazole vs. fluconazole in allo-HSCT patients

- **BMT-CTN Study**
- Prospective, randomized, double-blind trial
- 35 transplant centers in the Blood and Marrow Transplant Clinical Trials Network
- Adult and pedi

AML (independent risk factor of IFI)
- Fewer IFIs (8.5% vs. 21%; p=0.04)
- Improved FFS (78% vs. 61%; p=0.04)
- No difference in OS (81% vs. 72%; p=0.32)

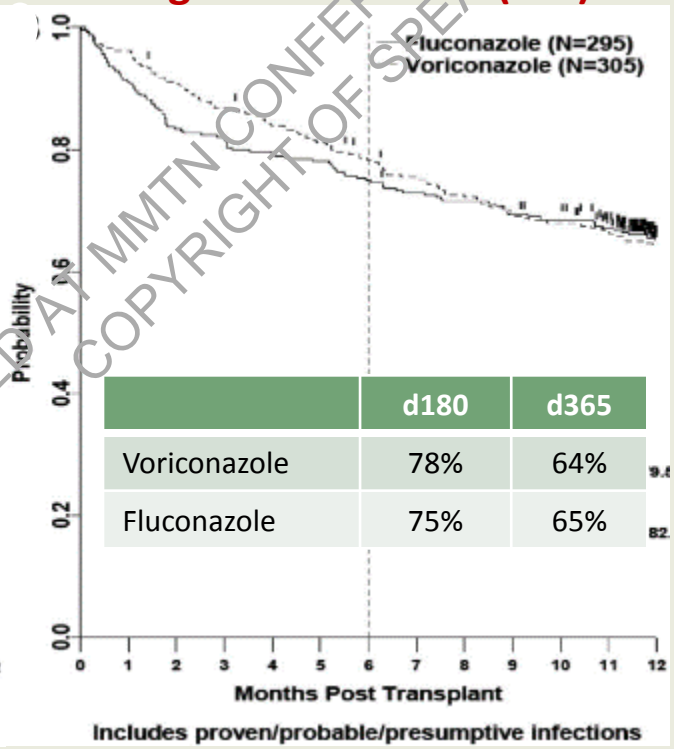
Cumulative incidence rates of IFIs



Duration of prophylaxis:
100d or 180d (high risk)

	d180	d365
Fluconazole	11.2%	13.7%
Voriconazole	7.3%	12.7%

Fungal-free survival (FFS)



	d180	d365
Voriconazole	78%	64%
Fluconazole	75%	65%

Structured monitoring

- GM twice-weekly until d60 then once-weekly until d100
- GM twice-weekly until d100 if GVHD under steroid therapy
- Radiological studies and invasive diagnostic procedure while IFI was suspected: Chest CT, Sinus CT, Bronchoalveolar lavage or biopsy

Empirical L-AmB or caspofungin as short as possible and for up to 14 days

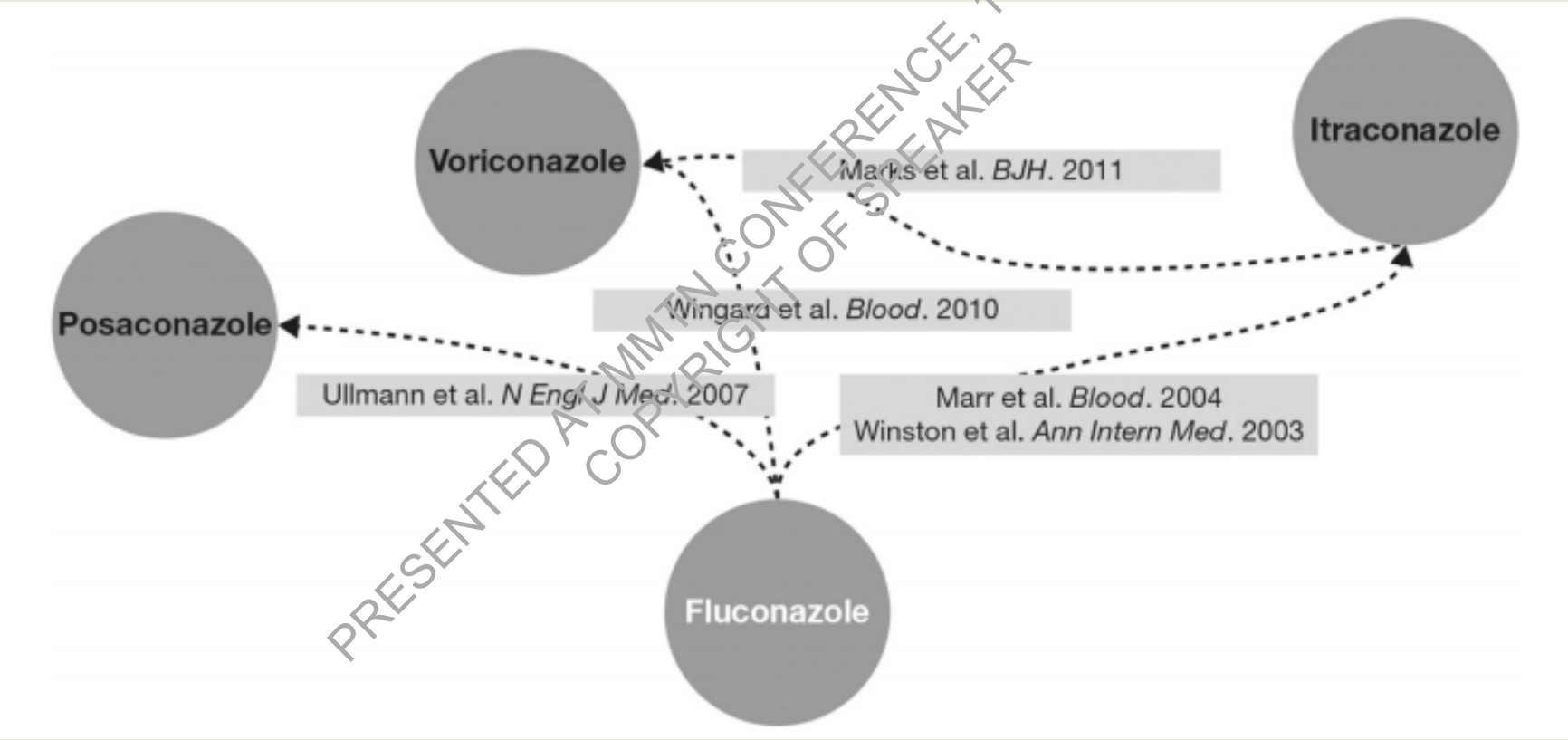
Wingard J et al, Blood 2010;116:5111-8

Mould-active compared with fluconazole prophylaxis to prevent invasive fungal diseases in cancer patients receiving chemotherapy or HSCT

- A meta-analysis that included 20 randomized trials
- reduced the risk of invasive aspergillosis compared with fluconazole prophylaxis
- reduced the risk of invasive fungal infection–related mortality compared with fluconazole prophylaxis (RR 0.67, 95% CI 0.47-0.96).
- no difference in overall mortality
- associated with an increased risk of adverse events leading to antifungal discontinuation

HSCT, haematopoietic stem-cell transplantation
Ethier MC, et al. Br J Cancer. 2012;106:1626.

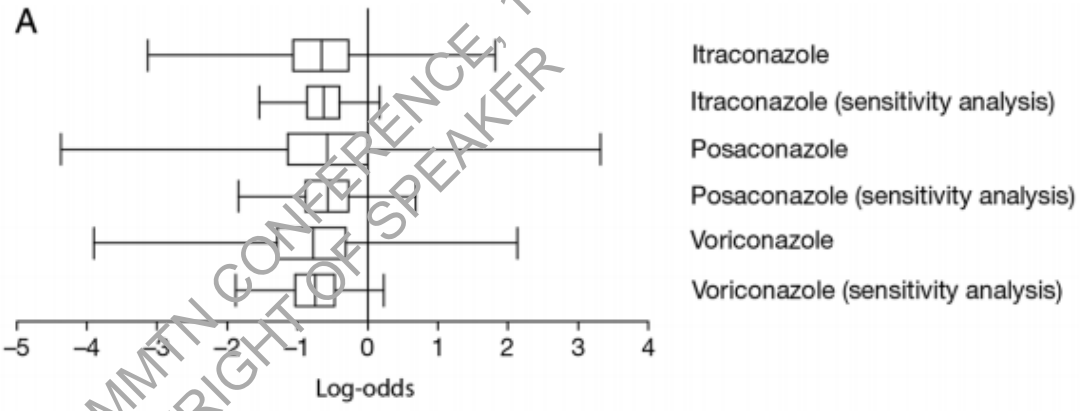
Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in alloHSCT recipients



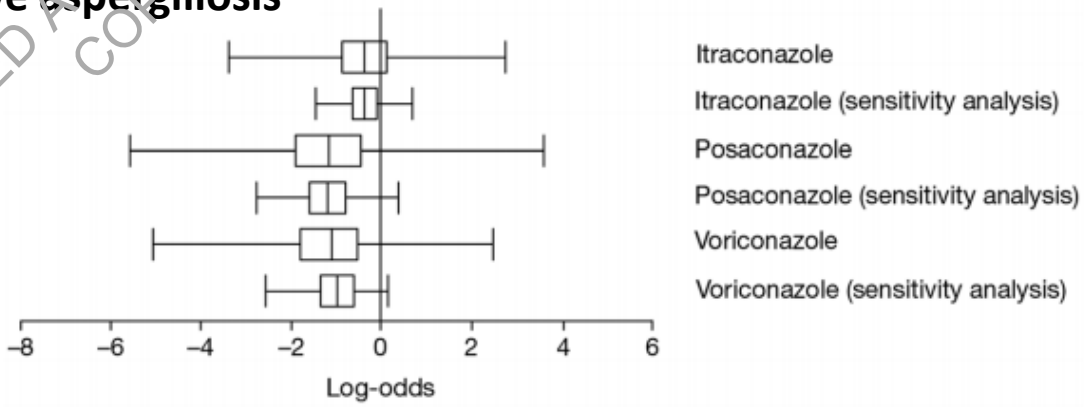
Five RCTs, 2147 patients alloHSCT, allogeneic haematopoietic stem-cell transplantation
Bow EJ, et al. BMC Infect Dis. 2015;15:128

Treatment effect of mould-active compared with fluconazole prophylaxis in allogeneic hematopoietic cell transplant recipients

Proven/probable invasive fungal infection



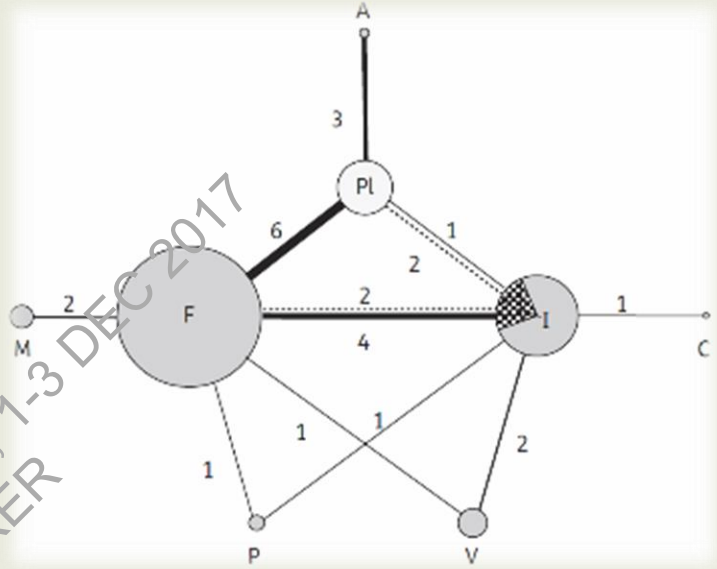
proven/probable invasive aspergillosis



Five RCTs, 2147 patients
Bow EJ, et al. BMC Infect Dis. 2015;15:128

All-cause mortality was similar across all mould-active agents

Mixed treatment comparison of systemic antifungal prophylaxis in neutropenic patients receiving therapy for haematological malignancies



- A systematic review of 25 studies identified
- Antifungal prophylaxis was more effective than no prophylaxis in reducing IFI risk.
- The IFI risk after voriconazole or posaconazole was lower than after fluconazole or itraconazole tablets.
- Posaconazole was also found to be more effective than no prophylaxis in reducing all-cause mortality.

Pechlivanoglou et al. J Antimicrob Chemother 2014; 69: 1–11

Resistance, Toxicity, Cost, Breakthrough infections

THE FLIP SIDE

Antifungals are associated with a number of potential drug interactions, please consult the pharmacist for advice

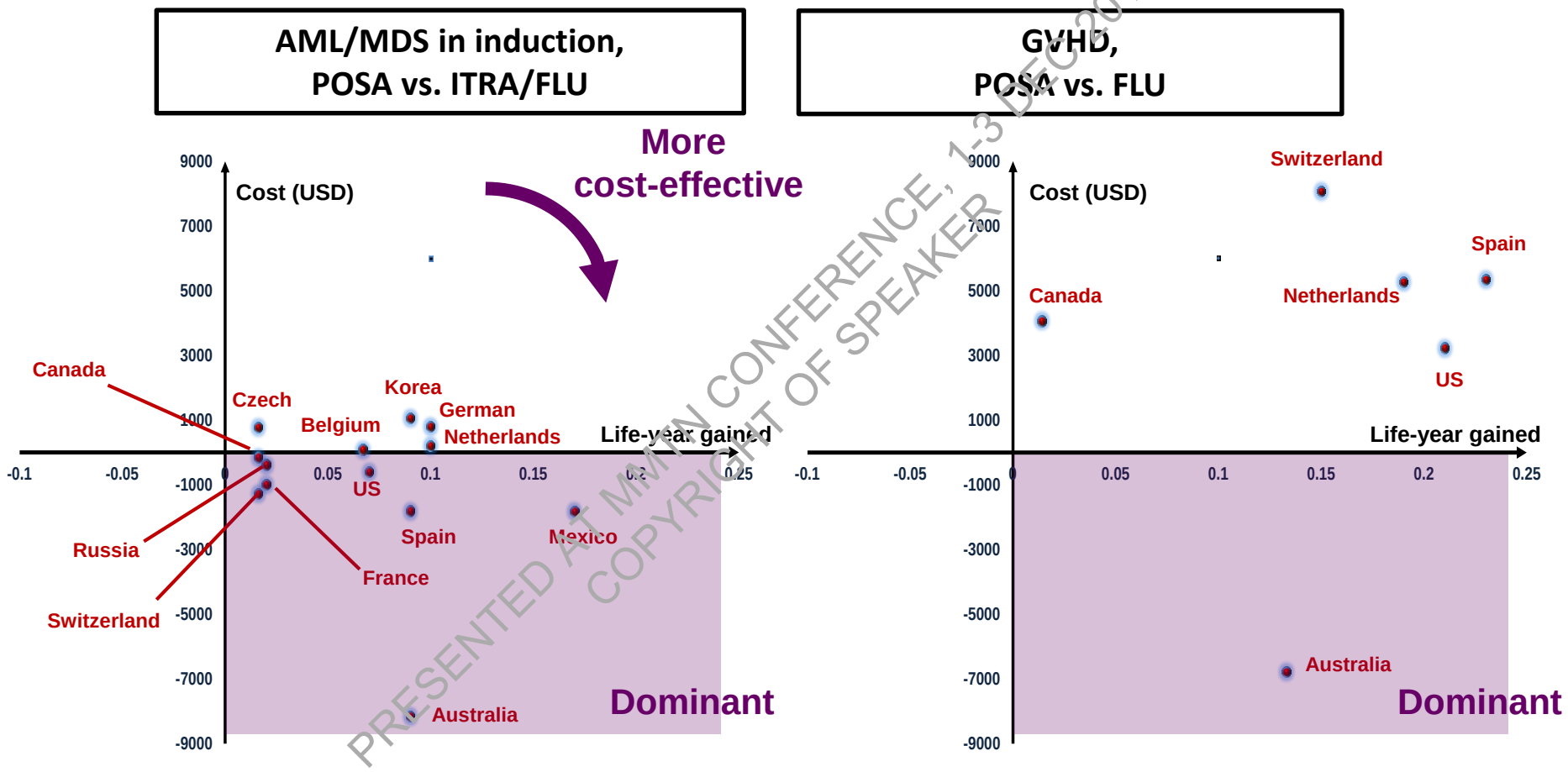
Antifungal	Affected Drug(s)	Notes
Posaconazole	Ciclosporin, tacrolimus, sirolimus, statins, Rifampicin, Midazolam, Phenytoin (and other anticonvulsants), busulfan, thiotepa	Ciclosporin/tacrolimus dose adjustments may be required
Voriconazole	Ciclosporin, tacrolimus, Phenytoin, rifabutin, rifampicin, efavirenz, busulfan, thiotepa	Ciclosporin/tacrolimus dose adjustments may be required.
Ambisome	Increased risk of nephrotoxicity when given with other nephrotoxic drugs i.e. ciclosporin, tacrolimus, aminoglycosides. Can increase cardiotoxicity of digoxin due to Ambisome-induced hypokalaemia. Increased risk of hypokalaemia when used with corticosteroids and/or diuretics	Monitor renal function and electrolytes including potassium and magnesium levels
Micafungin	May increase levels of sirolimus, nifedipine or itraconazole	
Fluconazole	Warfarin, ciclosporin, tacrolimus, rifabutin, phenytoin, sulphonylureas, theophylline	

Breakthrough Candidemia in alloHSCT recipients, Japan

- Out of 768 allo-HSCT cases, 26 developed BC.
- Etiologies identified: *C. parapsilosis* (9 strains), *C. glabrata* (4 strains), *C. guilliermondii* (3 strains), and the other *Candida* species (6 strains).
- Agents used: micafungin (17 cases), liposomal AmB (5), itraconazole (2), and voriconazole (2).
- 85% of the causative *Candida* species of micafungin breakthrough were susceptible to micafungin. 75% of the strains were wild type for the administered agents.
- Systemic steroid administration and longer (≥ 5 days) severe neutropenic phase were independent risk factors of the breakthrough candidemia.

Antimicrob Agents Chemother 2017, doi:10.1128/AAC.01791-16

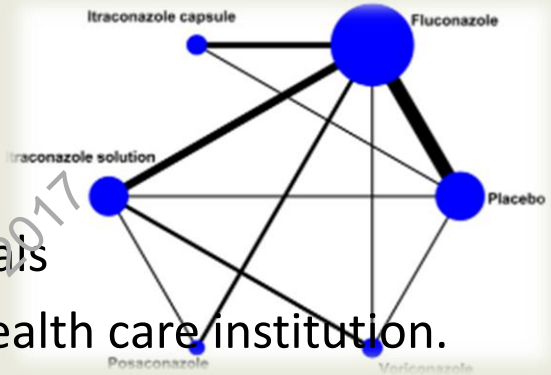
Plotted cost-effective plane for using posaconazole as antifungal prophylaxis in different countries



- **Prophylaxis does NOT always cost more.**
- **Prophylaxis for higher-risk populations does NOT always do better.**
- **Disease- and country-specific cost-effectiveness is required.**

2016 Taiwan guidelines. Data from Pharmacoeconomics 2011;29:251-68

Costs and health outcomes



- Network meta-analysis of 21 randomized controlled trials
- Resource use and costs obtained from the Singapore health care institution.
- All triazoles except itraconazole capsule were effective in reducing invasive fungal infections (IFIs) .
- Posaconazole was more efficacious in reducing IFIs and all-cause deaths than were fluconazole and itraconazole.

AML

Treatment	Total cost (SGD)	Effectiveness[a] No. of IFIs	No. of IFIs avoided	LY	LY saved	ICER Per IFI avoided	Per LY saved
Fluconazole	4,186.91	0.100		5.197			
Itraconazole capsule	5,748.09	0.135	−0.035	5.134	−0.063	Dominated	Dominated
Itraconazole solution	4,172.47	0.066	0.034	5.258	0.061	Dominant	Dominant
Posaconazole	4,909.45	0.037	0.063	5.310	0.113	11,469	6,394
Voriconazole	14,095.61	0.049	0.051	5.288	0.091	194,288	108,887

HSCT

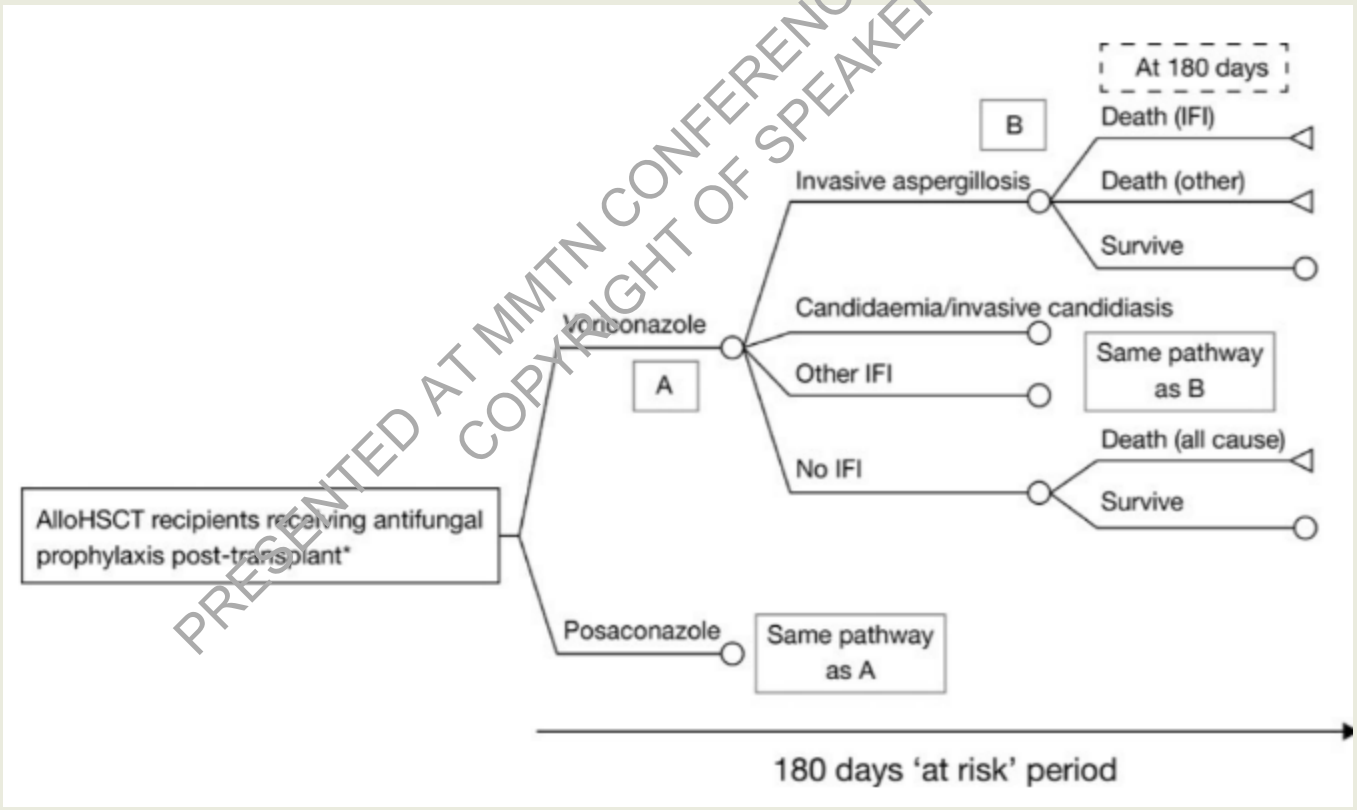
Treatment	Total cost (SGD)	Effectiveness[a] No. of IFIs	No. of IFIs avoided	LY	LY saved	ICER Per IFI avoided	Per LY saved
Fluconazole	4,271.27	0.100		6.247			
Itraconazole capsule	5,893.90	0.135	−0.035	6.172	−0.075	Dominated	Dominated
Itraconazole solution	4,697.85	0.066	0.034	6.320	0.073	12,546	5,844
Posaconazole	5,960.76	0.037	0.063	6.383	0.136	26,817	12,423
Voriconazole	17,442.68	0.049	0.051	6.357	0.110	258,263	119,740

[a] IFI, invasive fungal infection; LY, life-years; ICER, incremental cost-effectiveness ratio.

Zhao et al. Antimicrob Agents Chemother 2015;60:376

Economic evaluation of azoles as primary prophylaxis in Spanish patients undergoing alloHSCT

Cost-effectiveness analysis decision-analytic model structure from the perspective of the Spanish National Health System



Solano et al. Mycoses 2017 Feb;60(2):79-88.

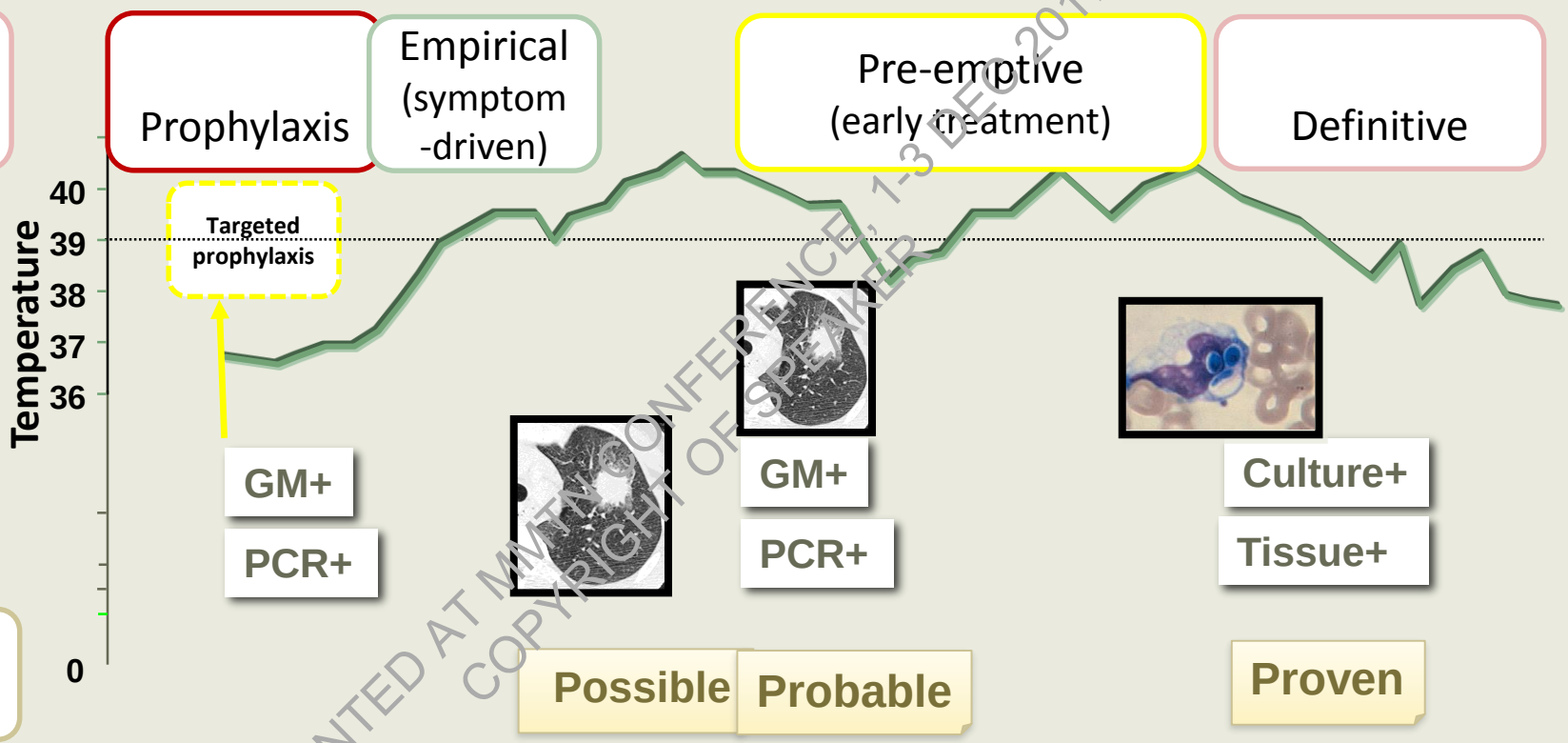
Economic evaluation of azoles as primary prophylaxis in Spanish patients undergoing alloHSCT (cont.)

- Generic itraconazole was the least costly AFP (€162) relative to fluconazole (€500), posaconazole oral suspension (€8628) or voriconazole (€6850).
- Compared with posaconazole, voriconazole was associated with the lowest number of breakthrough IFIs (36 vs 60); thus, the model predicted fewer deaths from breakthrough IFI for voriconazole (24) than posaconazole (33), and the lowest predicted costs associated with other licensed antifungal treatment and IFI treatment in a cohort of 1000.
- Voriconazole resulted in cost savings of €4707 per patient compared with posaconazole. Itraconazole demonstrated a high probability of being cost-effective.
- As primary AFP in alloHSCT patients 180 days posttransplant, voriconazole was more likely to be cost-effective than posaconazole regarding cost per additional IFI and additional death avoided.

Solano et al. Mycoses 2017 Feb;60(2):79-88.

Limited targets/options of current antifungal agents

Antifungal strategy	Prophylaxis	Empirical (symptom -driven)	Pre-emptive (early treatment)	Definitive
Disease status	Possible	Probable		Proven
Antifungal approved	**Fluconazole** **Itraconazole** **Posaconazole** (AML, GVHD) **Micafungin** (HSCT) **Voriconazole** (HSCT, GVHD)	**AmB** **Caspofungin** **L-AmB** (neutropenia)	**Molds: Vori, AmB, etc.** **Candida: echinocandin, azoles, etc.**	



Risk stratification is used to help target antifungal prophylaxis to those who would most benefit from it

WHOM

High-risk disease population for IFI

Increase in risk

- Chronic granulomatous disease
- Allologous HSCT with graft versus host disease
- Myelodysplastic syndrome treated with remission induction therapy
- Acute myeloblastic leukemia treated with remission induction therapy
- Lung or heart-lung transplantation
- Small bowel transplantation
- Liver transplantation
- Allogeneic HSCT without graft versus host disease
- Acute myelobalstic leukemia during consolidation therapy
- Acute lymphoblastic leukemic
- Heart transplantation
- Chronic lymphocytic leukemia
- Myelodysplastic syndrome
- Multiple myeloma
- Chronic obstructive pulmonary disease with acute exacerbation
- AIDS
- Non-Hodgkin's lymphoma
- Autologous hematoploietic stem cell transplantation
- Kidney transplantation
- Solid tumors
- Auto-immune disorders

High

Intermediate

Low

Herbrecht R, et al 2012 Ann. N.Y.Acad.Sci

Mold and Yeast Infections in Patients with Hematological Malignancies

Incidence of IFI varied by primary diseases

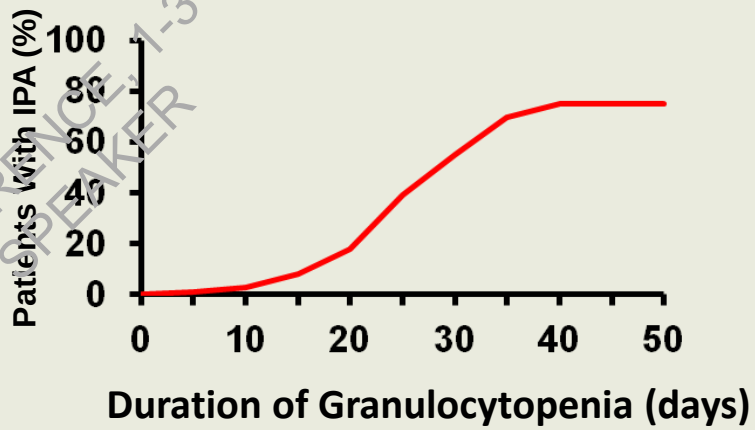
HM	*No. of patients*	*No. of IFI (incidence)*	*Molds*		*Yeasts*	
			No. cases	*Incidence %*	*No. cases*	*Incidence %*
AML	3012	373 (12%)	239	7.9	134	4.4
ALL	1173	77 (6.5%)	51	4.3	26	2.2
CML	596	15 (2.5%)	14	2.3	1	0.2
CLL	1104	6 (0.5%)	5	0.4	1	0.1
NHL	3457	54 (1.6%)	30	0.9	24	0.7
HD	844	6 (0.7%)	3	0.35	3	0.35
MM	1616	7 (0.5%)	4	0.3	3	0.2
Total	11802	538 (4.6%)	346	2.9	192	1.6

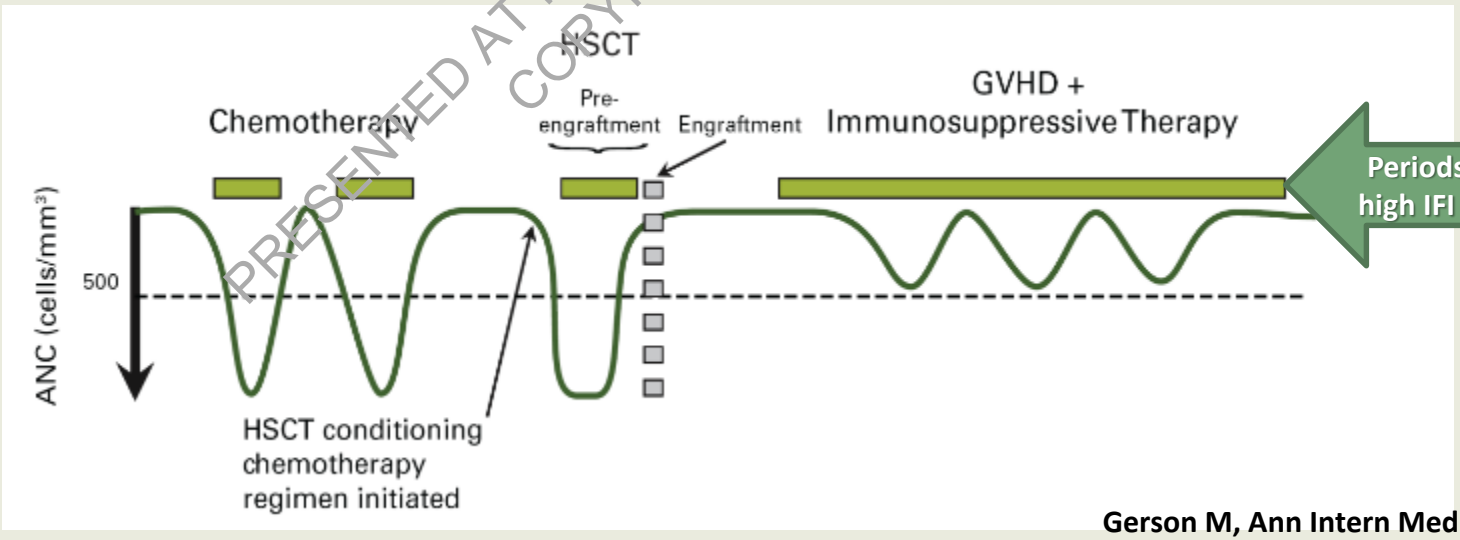
- n = 3228 (1249 allo, 1979 auto) pts from 11 Italian HSCT centers
- Incidence of proven/probable IA: 7.8% in alloHSCT
- Attributable mortality in alloHSCT patients: 77.2%

Pagano L et al (Italian Multicenter Study), Haematologica 2006;91:1068-75; Clin Infect Dis 2007;45:1161-70

Neutropenia remains the most important risk factor

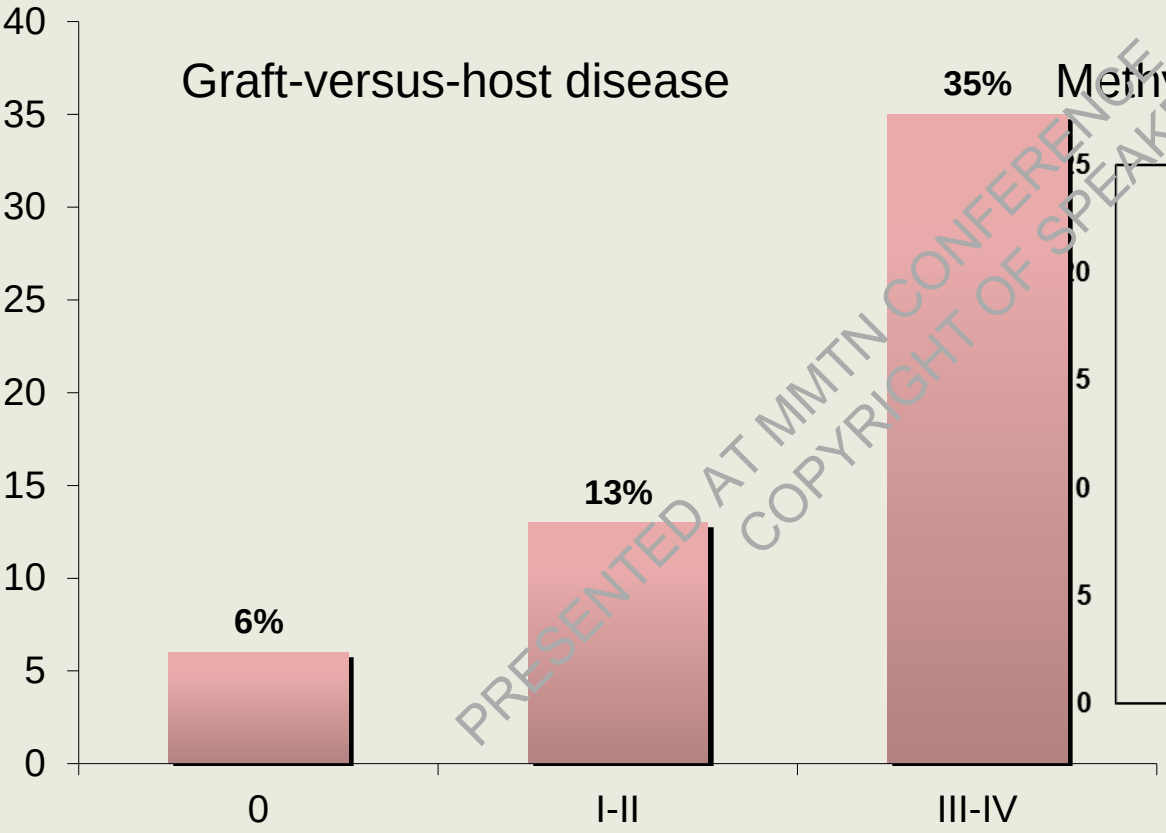
- Periodic in nature
- 2nd-wave of infection
  - Neutropenia > 7 days..
    (difference in induction?)

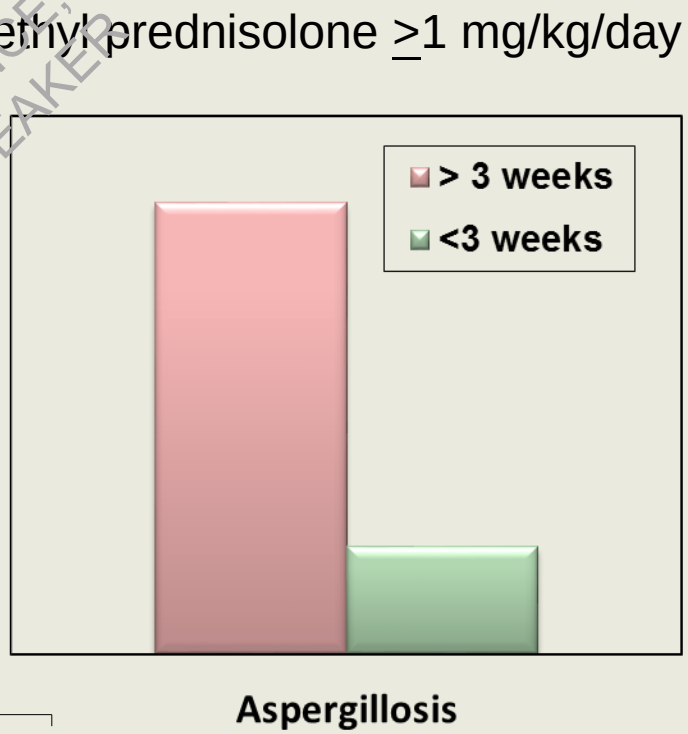




Gerson M, Ann Intern Med 1984;100:345

GVHD is a major risk factor





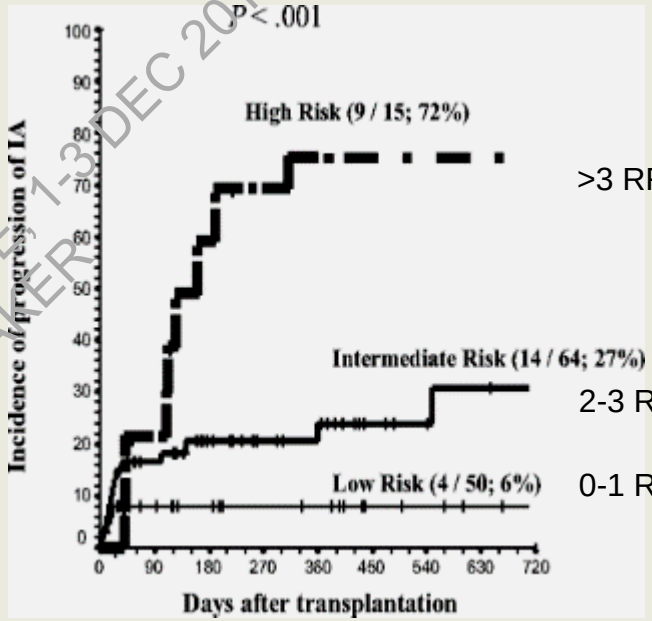
Jantunen E, Bone Marrow Transplant 1997;19:801

Grow W, Bone Marrow Transplant 2002;29:15

Prior IA is a risk factor

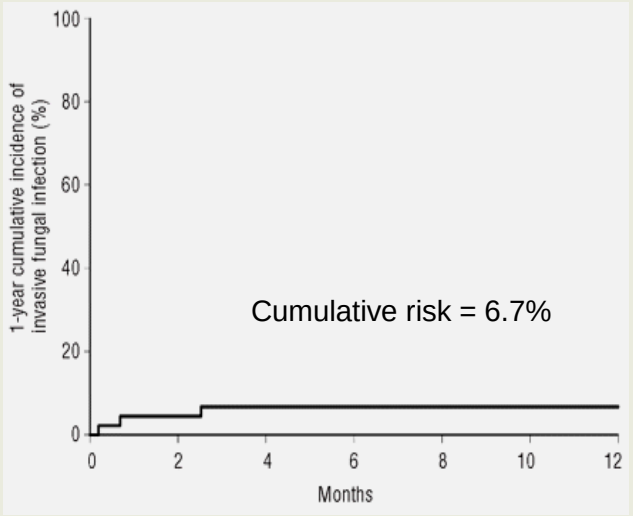
- **Recurrence risks**
  1. Longer neutropenia
  2. Advanced underlying disease
  3. Short interval from IA to transplant (<6 wks)
  4. Ablative conditioning regimen
  5. CMV disease
  6. Marrow or cord blood as graft
  7. Acute GVHD

Martino R, Blood 2006; 108: 2928



- **Voriconazole reduce the risk for recurrence, the VOSIFI study**
  - 45 pts with prior IFI (31 IA, 5 *Candida*, 6 other)
  - 2 relapses (1 *Candida*, 1 *Scedosporium*) & 1 new mucormycosis

Cordonnier C, Haematologica 2010;95:1762



Changes in population at risk of IFI in hematology

Change in patient population	Reasons/Treatment
Prolonged survival in immunocompromised condition (elder, relapsed/refractory…)	Better supportive care
Higher risk in transplantation	Haploidentical HSCT; Cord blood transplantation; CD34-selected or T-cell depleted graft
T-cell immunosuppression	New immunosuppressants (FK-506, etc); Chemotherapy agents (fludarabine, alemtuzumab, etc)

Clin Microbiol Inf 2008;14(s4):5

Risks can vary even with the same disease

	Auberger et al 2008	Hahn-Ast et al 2010	$Malagola et al 2008	Hammond 2010	Neofytos et al 2013	Kurosawa 2012[18]	NTUH 2015
Regions	Austria	German	Italy	US	US	Japan (Hokkaido)	Taiwan
Year	1995-2004	1995-2006	1997-2002	2004-2006	2005-2010	2006-2008	2004-2009
Study design	Prospective Single-center	Retrospective Single-center	Prospective Multi-center	Retrospective Single-center	Prospective Single-center	Retrospective Multi-center	Prospective Single-center
Disease	All HMs	All HMs	Fresh AML	Fresh AL	Fresh AML	All HMs (597 SCT)	Fresh and relapsed AL
Patient number	1095	592 (1693 C/T)	224	231	254	2821	401 (507 C/T)
Systemic antifungal prophylaxis	Fluconazole Itraconazole Lip-AmB	Oral AmB Itraconazole	Not remarked	No	No	Various	No
Chemotherapy regimens	C/T* Auto-SCT, Allo-SCT	C/T* Auto-SCT	Fludarabine-based induction	Standard induction	Standard induction	C/T* SCT	Induction
IFI Incidence							
All fungi	15.0%	8.8%	4%@(induction) 2%@(consolidation)	5.9% (30 days) 11.1% (100 days)	48.4%	1.3%@(for all) 0.4%@(for C/T)	11.4%@ 32.1%&
Candida					5.5%		
Mold					42.5%		
Mortality%							
All-cause	72.0%			42%	23.7% (6 months)		28.2%
IFI-attributed	25.1%	40.9%	60% (induction) 80% (consolidation)			22.2% (for C/T) 50% for SCT	25.8%

Tang JL et al. PLoS One. 2015;10:e0128410

Pretreatment risks assessment for IFDs

Immunogenetic status

Toll-like receptors polymorphism
C-type lectin receptor polymorphism
Mannose binding lectin polymorphism
Plasminogen polymorphism
Others

Underlying conditions

Neutropenia
Progressive cancer
GvHD
Anticancer chemotherapy
Steroids
T-cell suppressors

Primary diseases

Hematological malignancy
Allo HSTCT, solid organ transplant
Solid tumors, others

Environmental factors

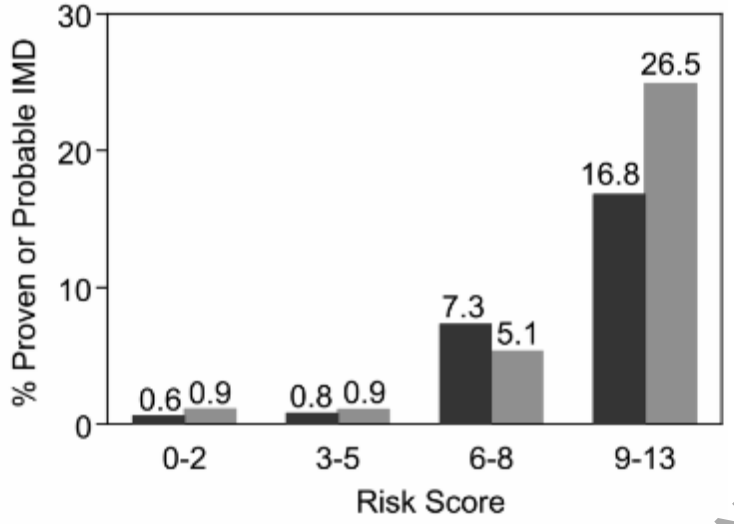
Geo-climate
Construction work
Tobacco or cannabies use
Contaminated food or spices
Pets, potted plants, and gardening
No HEPA filtered air during HSCT

Other factors

Diabetes
Iron overload
Trauma, burns
Renal impairment
Metabolic acidosis
Prior respiratory disease

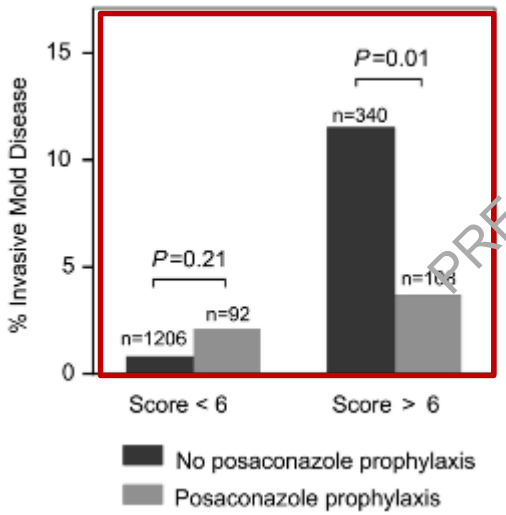
Pagano L, et al, Haematologica 2006;91; Clin Infect Dis 2007;45:1161; Drugs 2007;67:1567; Herbrecht R, et al 2012 Ann. N.Y.Acad.Sci; Johnson MD et al. CID 2012;54:502; Smeekens SP et al. EMBO Mol Med 2013;5:805; Cunha C, et al. NEJM 2014;370:5:421

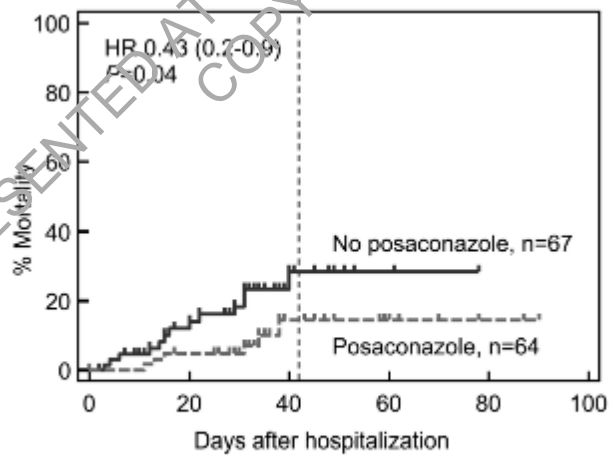
A Risk Prediction Score for Invasive Mold Disease in Patients with Hematological Malignancies



Variable	Frequency in patients with IMD (%)	β-coeff	Wald χ^2	*P* value	Hazard Ratio(95% CI)	Points
Duration of neutropenia	590 (41)	1.72	21.99	< 0.001	5.60 (2.72-11.50)	4
Previous IMD	31 (9)	1.71	12.42	< 0.001	5.55 (2.14-14.41)	4
Malignancy status	755 (50)	1.53	19.46	< 0.001	4.64 (2.34-9.19)	3
Lymphocytopenia or lymphocyte dysfunction	415 (31)	0.90	9.57	0.002	2.45 (1.39-4.34)	2

doi: 10.1371/journal.pone.0075531.t004





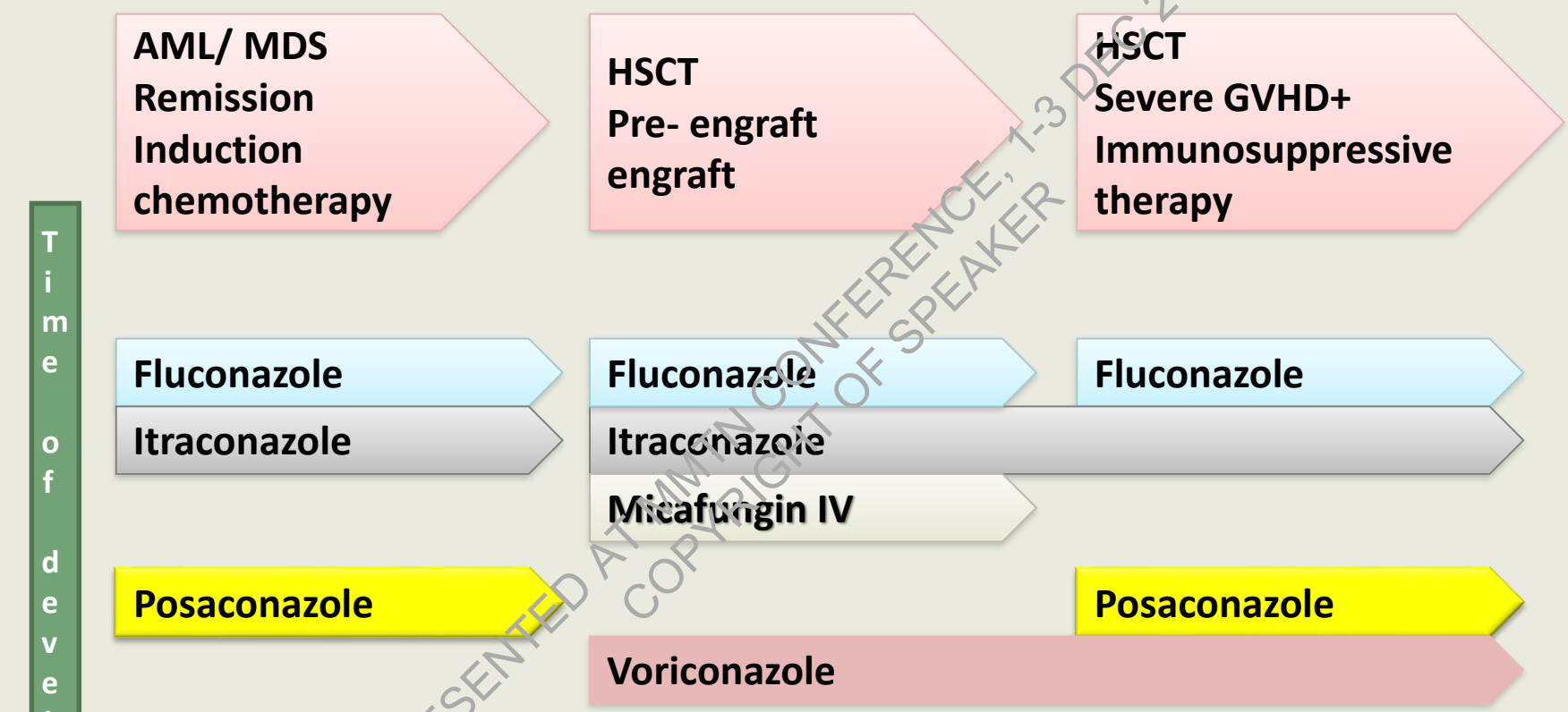
Impact of posaconazole prophylaxis on the incidence and mortality of invasive mold disease

Stanzani et al. PLoS ONE 2013;8(9): e75531.

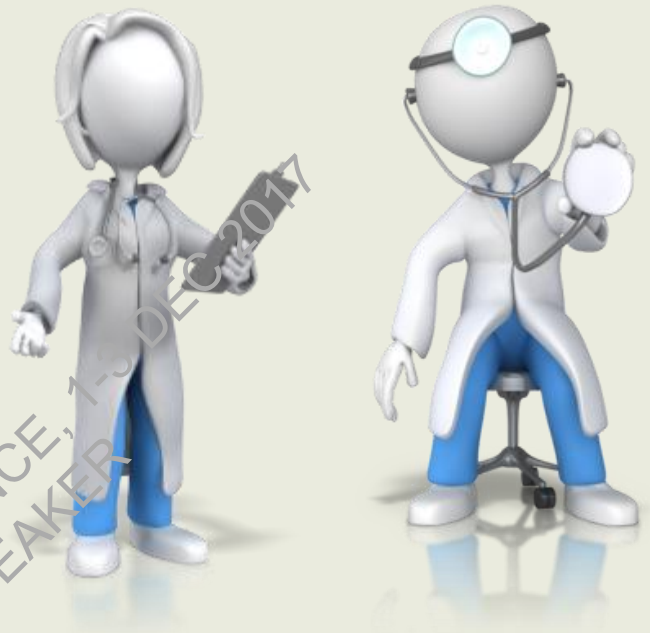
Science or art?

WHAT

Systemic antifungal prophylaxis



Factors to be considered: efficacy, drug-drug interaction, toxicity, bioavailability, compliance, and cost



Systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances.

GUIDELINES

J Microbiol Immunol Infect
2006;39:523-525

Guidelines for the use of antifungal agents in patients with invasive fungal infections in Taiwan

Infectious Diseases Society of Taiwan; Medical Foundation in Memory of Dr. Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; and CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccine

J Microbiol Immunol Infect 2010;43(3):258-263

Contents lists available at ScienceDirect

Journal of Microbiology, Immunology and Infection

Journal homepage: http://www.e-jmii.com

Guideline

Guidelines for the Use of Antifungal Agents in Patients with Invasive Fungal Infections in Taiwan — Revised 2009

The Infectious Diseases Society of Taiwan; The Hematology Society of Taiwan; Taiwan Society of Pulmonary and Critical Care Medicine; Medical Foundation in Memory of Dr Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; and CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines.

Journal of Microbiology, Immunology and Infection

Available online 25 July 2017

open access

In Press, Accepted Manuscript

Review Article

2016 Guideline Strategies for the Use of Antifungal Agents in Patients With Hematological Malignancies or Hematopoietic Stem Cell Transplantation Recipients in Taiwan

Bor-Sheng Ko [a], Wei-Ting Chen [b], Hsiang-Chi Kung [c], Un-In Wu [c], Jih-Luh Tang [a], Ming Yao [a, d], Yee-Chun Chen [c, d] ✉, Hwei-Fang Tien [a, d], Shan-Chwen Chang [c, d], Yin-ching Chuang [e], Dong-Tsamn Lin [f]

The Infectious Diseases Society of Taiwan; The Hematology Society of Taiwan; The Taiwan Society of Blood and Marrow Transplantation

Medical Foundation in Memory of Dr Deh-Lin Cheng, Foundation of Professor Wei-Chuan Hsieh for Infectious

Journal of Microbiology, Immunology and Infection

Available online 25 July 2017

open access

In Press, Accepted Manuscript

Review Article

2016 Guidelines for the Use of Antifungal Agents in Patients with Invasive Fungal Diseases in Taiwan

Hsiang-Chi Kung [a], Po-Yen Huang [b], Wei-Ting Chen [c], Bor-Sheng Ko [d, c], Yee-Chun Chen [a, c] ✉, Shan-Chwen Chang [a, e], Yin-Ching Chuang [f]

The Infectious Diseases Society of Taiwan

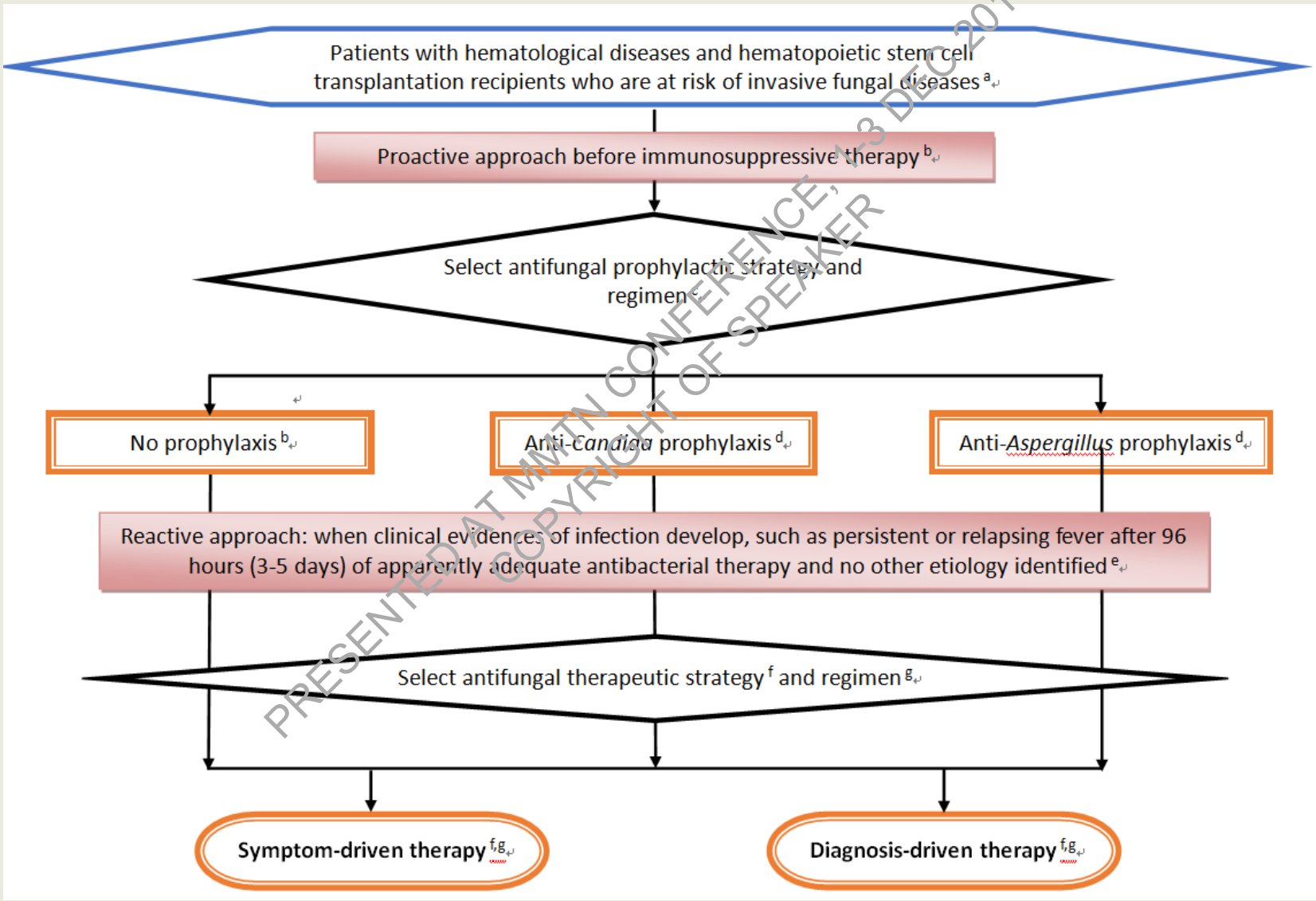
Medical Foundation in Memory of Dr. Deh-Lin Cheng, Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education, CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines

From Evidences to Guidelines

- Grading the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong).
- The strengths of recommendations are based on, but not limited to:
  1. quality of evidence.
  2. balance between benefits (e.g., treatment efficacy and benefit of early intervention) and harms (e.g., potential toxicity and drug-drug interaction and negative impact of delay in intervention);
  3. disease burdens,
  4. resources and cost.

Ko BS et al. 2016 guideline strategies for the use of antifungal agents in patients with hematological malignancies or hematopoietic stem cell transplantation recipients in Taiwan. *J Microbiol Immunol Infect* 2017 Jul 25. pii: S1684-1182(17)30145-7. doi: 10.1016/j.jmii.2017.07.005. [Epub ahead of print]

A risk-adapted and dynamic antifungal strategy



2016 Taiwan guidelines

Selection of antifungal strategy

Factor	Prophylaxis	Empirical (symptom-driven)	Pre-emptive (diagnosis-driven)	Target (definitive)
Proactive assessment				
Epidemiology: local incidences and risk of IFD	High			Low
Diagnostics tools in facility: availability, accessibility, performance, and turn-around time	Poor			Good
Accessibility to healthcare setting during high risk period	Poor			Good
Therapeutics: compliance, bioavailability, direct toxicity and drug-drug interaction	Easy			Complex
Cost-effectiveness	High			Low

2016 Taiwan guidelines

General recommendations

- Strategies to reduce risk of invasive fungal diseases through modifying risk factors such as control of underlying diseases or conditions, environmental control to reduce exposure to fungi, and patient education for personal hygiene and food safety are important before adapting prophylactic strategy.
- Prophylactic use of anti-mold agents reduces the yields of galactomannan antigen assay and molecular diagnostics.
- Prophylactic strategy may increase the uncertainty or difficulty of managing subsequent fungal infections
- If the risk of invasive mold diseases is low, may use fluconazole as antifungal prophylaxis and combine with a mould-directed diagnostic approach.
- Duration of therapy is based on recovery from neutropenia or immunosuppression.

Primary prophylaxis

Diagnosis or status of the hosts	Primary	Alternative	Comments
AML and MDS patients receiving induction chemotherapy	Nystatin (S/L)*	Posaconazole (S/H) Itraconazole (W/H) Fluconazole 50-400 mg (W/H) AmB-d (W/H)	Clinical trials for fluconazole showed various results. continued until myeloid reconstitution has occurred.
Allogeneic HSCT, initial neutropenic phase	Nystatin (S/L) Fluconazole 400 mg iv or po (S/H) Micafungin 50 mg (W/H)	Voriconazole 200 mg (4 mg/kg) bid po (W/H) Itraconazole (W/H) AmB-d (W/H)	
Allogeneic HSCT, GVHD phase	Nystatin (S/L) Posaconazole (S/H) Voriconazole (S/H)	Itraconazole (W/H) Fluconazole (W/H) AmB-d (W/H)	Prophylactic use of anti-mold agents is recommended in patients with severe GVHD under treatment with high dose steroid or equivalent immunosuppressants

*Grading of recommendation (strong, weak)/evidence (high-, low-quality)
2016 Taiwan Guideline

Secondary Antifungal Prophylaxis

- Second prophylaxis is strongly recommended in patients with previously defined IFD during a period of myelosuppression (eg, during induction chemotherapy in AML patients) (S/L).
- The choice of agent depends on etiology of prior infection, and in part upon the need to avoid drug interactions while chemotherapy is being given.
  - Voriconazole is the first-line agent for *Aspergillus* spp and has been best studied as secondary prophylaxis, but mold-active azoles are usually not given concomitantly with certain chemotherapy regimens with hepatically metabolized drugs.

Secondary Antifungal Prophylaxis

- Duration:
  - at least until myeloid reconstitution has occurred
  - follow-up imaging and fungal markers obtained 2~4 weeks after antifungal prophylaxis has been discontinued to ensure that reactivation has not occurred.
  - Patients undergoing repeated courses of myelosuppressive chemotherapy should generally continue secondary prophylaxis until completion of the course of chemotherapy.

Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by IDSA. Clin Infect Dis. 2011;52(4):e56.

Introduce concept of health economics and provides data translated from local disease burdens

Patient population	Study design	Study period	Study number	IFD category	IFD incidence	NNT	Reference
Adult AML[6] Induction chemotherapy	Prospective, Single center	2004-2009	298 patients	Proven/ Probable	10.7%	12[a]	Tang JL, et al[6]
				Proven/ Probable/ Possible	34.6%	3[a]	
Adult AML[68] Induction chemotherapy	Retrospective, Single center	2010-2014	39 patients	Proven/ Probable	17.9%	6[a]	Yang XY, et al[68]
Pediatric AML[69]							
Induction chemotherapy	Prospective, Single center	2010-2012	28 courses	Proven/ Probable	17.9%	6	Yeh TC et al[69]
Post-remission high dose			76 courses		7.9%	13	
Post-remission modest dose			56 courses		1.8%	56	
Pediatric ALL[69]							
Induction chemotherapy	Prospective, Single center	2010-2012	62 courses	Proven/ Probable	14.5%	7	Yeh TC, et al[69]
Consolidation chemotherapy			59 courses		0%	NA	
Re-induction chemotherapy			59 courses		1.7%	59	

Abbreviations: IFD, invasive fungal diseases; NNT, number needed to treat.

[a] NNT is calculated on the inverse of the absolute risk reduction with antifungal prophylaxis, [67] and the incidence of IFDs with antifungal prophylaxis is based on the data from the study by Cornely, et al.[47]

Ko BS, et al. *J Microbiol Immunol Infect* 2017;S1684-1182(17)30145–7.

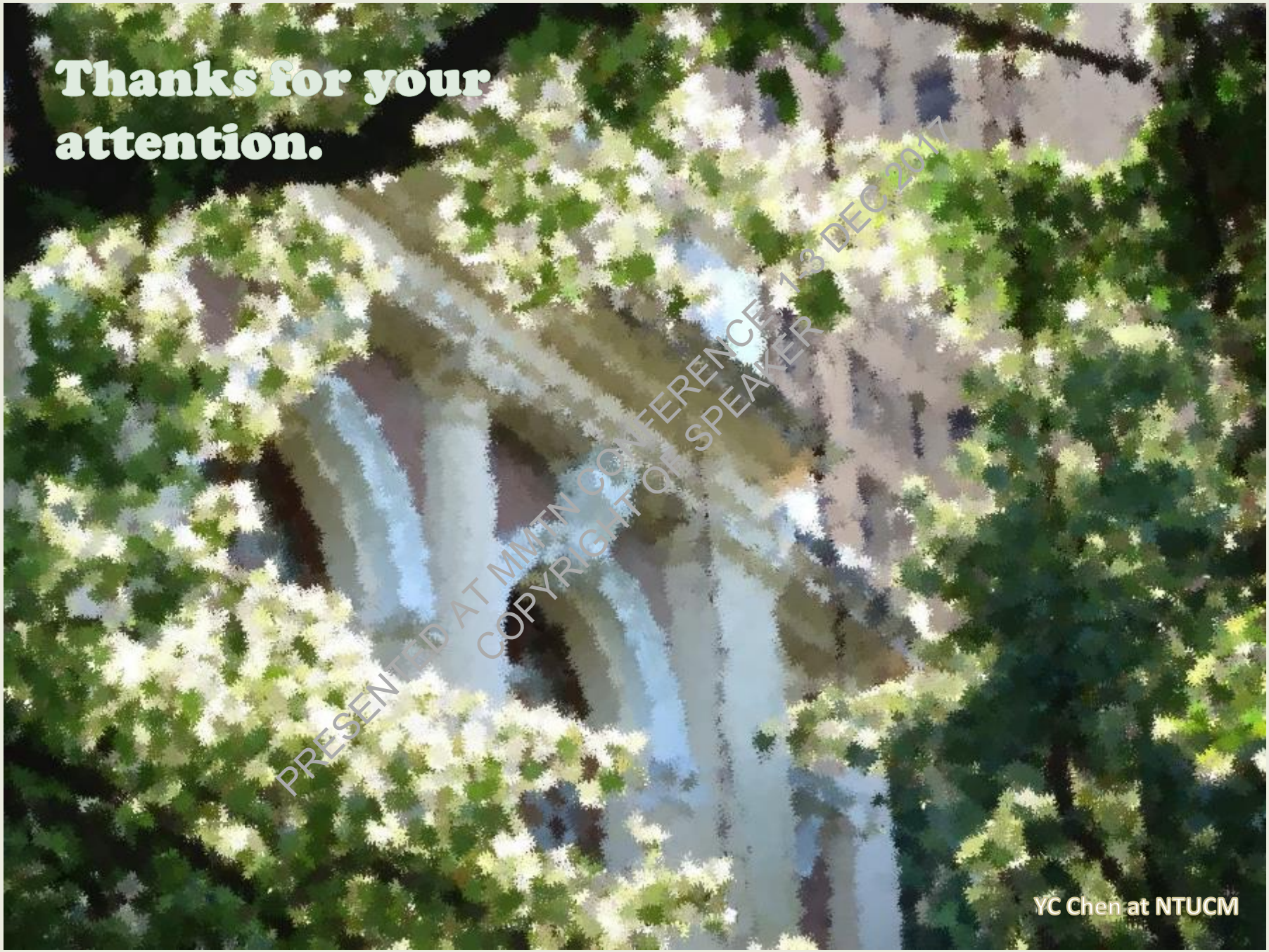
Tang JL, et al. *PLoS One* 2015;10:e0128410;
Yang XY, et al. *J Microbiol Immunol Infect* 2017;
Yeh TC, et al. *Cancer* 2014;120:1255.

ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia;
IFD: invasive fungal disease; NNT: number needed to treat.

Conclusion

Summary

- Debates remain regarding the universal systemic primary prophylaxis due to concerns of resistance, toxicity, cost and breakthrough infections.
- Primary prophylaxis has been proven to be cost-effective in selected high-risk patients with hematologic malignancies.
- Selection of prophylactic strategy should be individualized based on risk-benefit assessment at each hospital, or, even for each patient, after considering factors such as: epidemiology, diagnostics, therapeutics and cost-effectiveness.
- Selection of a prophylactic agent should be based on knowledge of the host, the agents, and the strategies available. Consideration should be given to the efficacy, bioavailability, toxicity, drug drug interaction, compliance, and cost.


Thanks for your attention.
PRESENTED AT MMTN CONFERENCE, 13 DEC 2017
COPYRIGHT OF SPEAKER
YC Chen at NTUCM