MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

5 controversies in mycology

Dr Methee Chayakulkeeree
Associate Professor
Division of Infectious Diseases and Tropical Medicine
Faculty of Medicine Siriraj Hospital, Mahidol University
Bangkok, Thailand

ASIA FUNGAL WORKING GROUP
an ISHAM working group

Siriraj Infectious Diseases

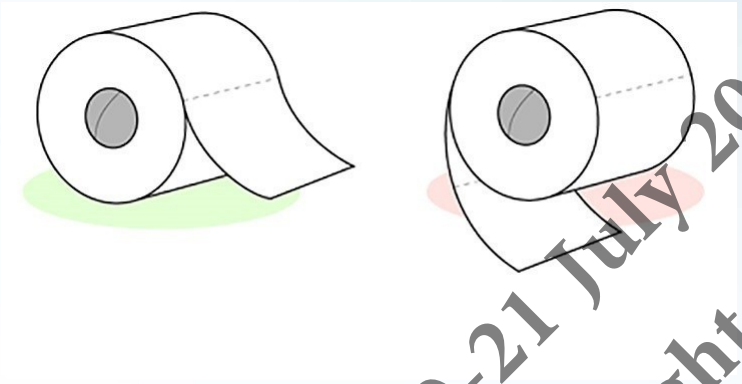
5 Controversies in Mycology

Methee Chayakulkeeree, MD, PhD, FECMM
Division of Infectious Diseases and Tropical Medicine
Department of Medicine, Faculty of Medicine Siriraj Hospital
MAHIDOL UNIVERSITY

SiID
Siriraj Infectious Disease

How do you place your toilet paper?

1. **2.**



Response from AFWG Faculty

- Prophylaxis, empirical and diagnostic-driven treatment in ICU and hematological patients (5 responses)
- Combination antifungal therapy (3 responses)
- Colonization vs. infection (2 responses)
- Identification and susceptibility in all isolates? (2 responses)
- Duration of treatment (1 response)
- TDM (1 response)
- Miscellaneous: echinocandins, immunotherapy

Topics

- Who should receive antifungal prophylaxis?
- Should we use antifungal prophylaxis in all high-risk individuals?
- Preemptive and empirical antifungal therapy in neutropenic patients, which one is better?
- Should we suggest empirical antifungal therapy in high-risk ICU patients?
- What is the place for combination antifungal therapy?

Topics

- Who should receive antifungal prophylaxis?
- Should we use antifungal prophylaxis in all high-risk individuals?
- Preemptive and empirical antifungal therapy in neutropenic patients, which one is better?
- Should we suggest empirical antifungal therapy in high-risk ICU patients?
- What is the place for combination antifungal therapy?

Primary Antifungal Prophylaxis in High-Risk Hematological Patients

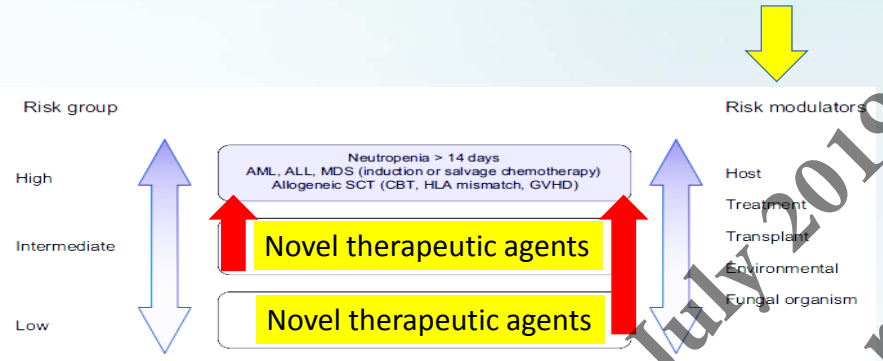
Antifungals	Population	IFD	Survival	Ref.
Posaconazole vs. Fluco/Itra	Neutropenia (AML, MDS during induction)	Posa (2%) < fluco/itra (5%)* • IA: 1% vs. 7%* • SE: 6% vs 2%*	Posa > fluco/itraco (84% vs78%)*	Cornely OA., et al. NEJM 2007
Posaconazole vs. Fluconazole	Allo HSCT with Severe GvHD	• Overall posa ~ fluco (5.3 % vs. 9.0%) • Invasive aspergillosis: posa (2.3%) < fluco (7.0%)*	Posa ~ fluco (75% vs. 72%) SE: similar (36% vs. 38%)	Ullmann AJ., et al. NEJM 2007
Voriconazole vs. Fluconazole	Allo HSCT	• IFI: 7.3% vs. 11.2% (similar) • IA: 9% vs. 17% (similar)	Similar (80% vs. 81.2%)	Wingard JR., et al. Blood 2010
Voriconazole vs. Itraconazole	Allo HSCT	• IFI: 1.3% vs. 2.1% (similar)	Similar (81.9% vs. 80.9%)	Marks DI., et al. BJH 2011

* Statistical significant

NCCN Guidelines Version 1.2019 Risk for Cancer-Related Infections

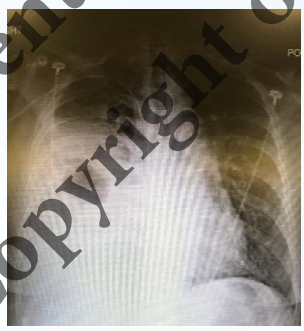
Overall Infection Risk	Disease/Therapy Examples
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 days
Intermediate	• Autologous HSCT • Lymphoma • Multiple myeloma • CLL • Purine analog therapy (fludarabine, clofarabine, nelarabine, cladribine) •Anticipated neutropenia 7-10 days
High	• Allogeneic HSCT including cord blood • Acute leukemia - Induction - Consolidation/maintenance • Alemtuzumab therapy • GVHD treated with high dose steroids (>20 mg daily) • Anticipated neutropenia greater than 10 days

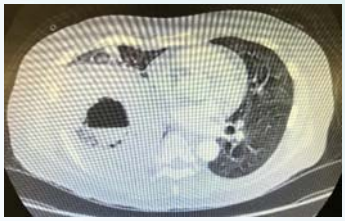
Risk of Invasive Fungal Diseases in Hematological Patients



Zabalza A. et al. Therapeutic Advances in Hematology 2013;4

Pulmonary Mucormycosis and Aspergillosis in Patient Receiving Ibrutinib

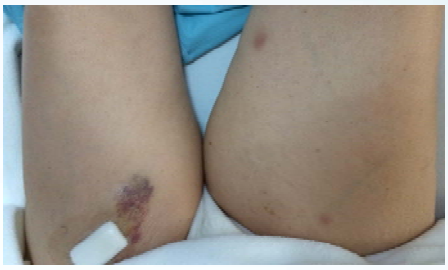


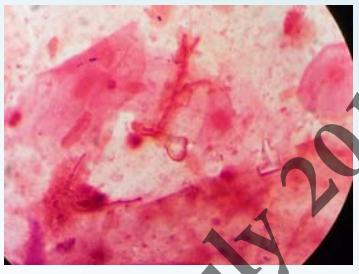


A 67-year-old woman, CLL, receiving ibrutinib

- Lung cavity RLL and bilateral infiltrates
- Galactomannan-negative
- BAL culture: *A. fumigatus* and *C. tropicalis*
- TBBx: broad non-septate hyphae

Skin Lesion in A Patient with myelofibrosis Treated with Ruxolitinib (Jakafi)





Disseminated Aspergillosis

- *Aspergillus fumigatus*
- *Aspergillus granulosus* (breakthough posaconazole)

Invasive Fungal Diseases in Acute Lymphoid Leukemia

- 350 episodes of febrile neutropenia in 153 patients
- 31 IFD (8.9%)

Invasive fungal disease	No.
Proven	23
Invasive candidiasis/candidemia	10
Invasive fusariosis	5
Fungemia due to *Exophiala jeanselmei*	3
Other[a]	5
Probable	8
Invasive aspergillosis	8
Total	31

[a]Other: aspergillosis, mucormycosis, trichosporonosis, fungemia due to *Phialemonium* spp., fungemia due to *Rhodotorulla* spp.: 1 case each.

Nicolato A, et al. Leukemia & Lymphoma 2016, 57:9, 2084-9

Incidence of Fungal Infections in Lymphoproliferative Disorders

Reference	Years of observation	All Cases	Cumulative incidence of fungal infections				
			CLL	HL	NHL	INHL	MM
Francis *et al.* 2006[7]	1995-2005	280	11 (3.9%)	/	/	/	/
Pagano *et al.* 2006[1]	1999-2003	7021	6 (0.5%)	6 (0.7%)	54 (1.6%)	/	7 (0.5%)
Offidani *et al.* 2011[8]	2003-2009	202	/	/	/	/	1 (0.5%)
Kurosawa *et al.* 2012[9]	2006-2008	1840	/	1 (1.1%)	4 (0.3%)	/	3 (0.8%)
Wongso *et al.* 2013[6]	1993-2008	3564	/	12 (0.34%)	/	/	
Moreira *et al.* 2013[10]	1999-2009	174	3 (1.7%)	/	/	/	
Stanzani *et al.* 2013*[11]	2009-2012*	787	2.6 (4%)	/	6 (1.5%)**	/	4.6 (1.4%)
Nosari *et al.* 2014[2]	2004-2012	1355	11 (4%)	2 (1.2%)	27 (4.3%)	/	2 (0.7%)
Takaoka *et al.* 2014[12]	2006-2012	696	/	/	16 (2.3%)	/	/
Sun *et al.* 2015[13]	2011	1769	3 (3.13%)	0%	17 (1.54%)	/	3 (0.7%)
Teng *et al.* 2015[5]	2009-2011	719	4 (7.8%)	2 (3.6%)	8 (4.3%)	3 (0.7%)	7 (2.8%)
Teh *et al.* 2015[14]	2009-2011	372	/	/	/	/	9 (2.4%)
Li *et al.* 2015[15]	2006-2012	143	/	/	/	/	15 (10.8%)
Liu *et al.* 2016[16]	Jan 2011-Aug 2011	443	/	/	/	/	17 (3.8%)
This report 2016	2006-2014	1191	4 (1.3%)	7 (3.7%)	11 (3.1%)	2 (2%)	14 (5.8%)

CLL: Chronic lymphocytic leukemia; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; iNHL: indolent non-Hodgkin lymphoma; MM: multiple myeloma. *Stanzani: only prospective cohort; **NHL: excluding patients who received allogeneic or autologous HSCT.

Tisi MC, et al. haematologica 2017; 102:e108

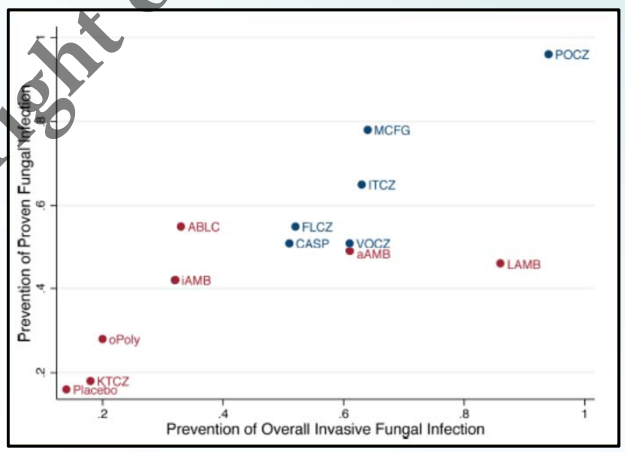
Topics

- Who should receive antifungal prophylaxis?
- Should we use antifungal prophylaxis in all high-risk individuals?
- Preemptive and empirical antifungal therapy in neutropenic patients, which one is better?
- Should we suggest empirical antifungal therapy in high-risk ICU patients?
- What is the place for combination antifungal therapy?

ECIL-5 Guidelines for Antifungal Treatment

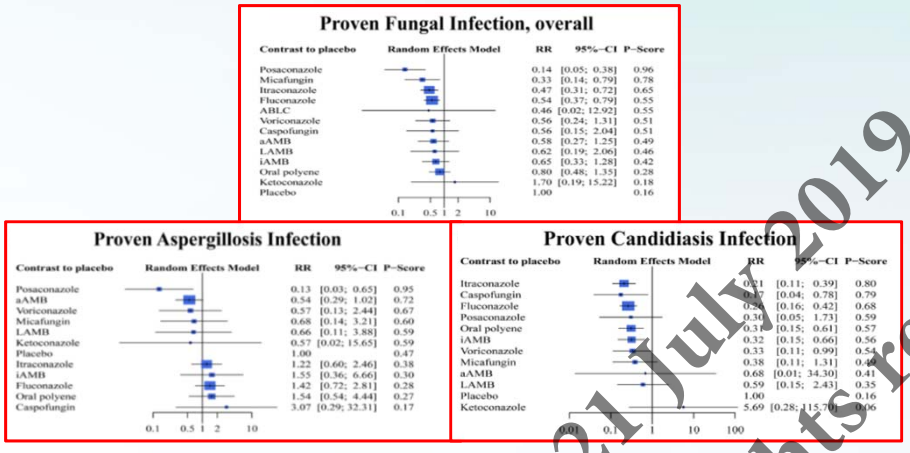
Drug	Prophylaxis			
	Allo-HSCT neutropenic		Allo-HSCT GvHD	AML/MDS with CMT
	Low risk for molds	High risk for molds		
AMB	CIII (aerosol+fluco)	BII (aerosol+fluco)	-	Against
Liposomal AMB	CII	CII	CII	CII (IV), BI (aerosol+fluco)
ABCD	-	-	-	CII
ABLD	-	-	-	CII
Fluconazole	**AI**	AIII-against	AIII-against	BI
Itraconazole oral solution	BI	BI	BI	BI
Posaconazole	BII	BII	**AI**	**AI**
Voriconazole	BI	BI	BI	BII
Caspofungin	-	-	-	CII
Micafungin	BI	CI	CII	CII

Cumulative Probability of Prophylactic Antifungals for Overall and Proven IFD



Lee CH, et al. Antimicrob Agents Chemother 2018; 62:e00355-18

Risk Ratio of IFD in Different Antifungal Prophylaxis



Lee CH, et al. Antimicrob Agents Chemother 2018; 62:e00355-18

Primary Antifungal Prophylaxis in High-Risk Hematological Patients

NNT = 17 (aspergillosis)

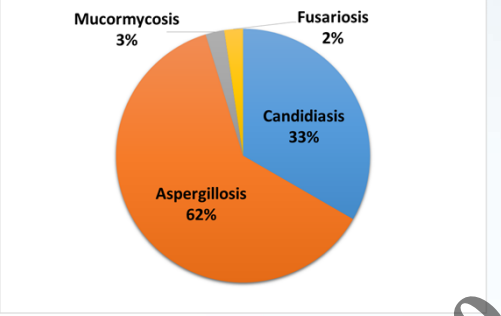
NNT = 34

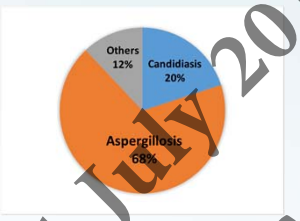
NNT = 17

Antifungals	Population	IFD	Survival	Ref.
Posaconazole vs. Fluco/Itra	Neutropenia (AML, MDS during induction)	Posa (2%) < fluco/itra (5%)* • IA: 1% vs. 7%* • SE: 6% vs 2%*	Posa > fluco/itraco (84% vs78%)*	Cornely OA., et al. NEJM 2007
Posaconazole vs. Fluconazole	Allo HSCT with Severe GvHD	• Overall posa ~ fluco (5.3 % vs. 9.0%) • Invasive aspergillosis: posa (2.3%) < fluco (7.0%)*	Posa ~ fluco (75% vs. 72%) SE: similar (36% vs. 38%)	Ullmann AJ., et al. NEJM 2007

Prevalence of IFD in Febrile Neutropenic Cancer Patients: Thailand (Single Center)

- Total 37 fungal infection episodes from 233 patients with 310 episodes of febrile neutropenia (**12% overall**)
- Hematologic malignancies = **14%,** AML = **17%**
- AML receiving induction chemotherapy = **20.5%**

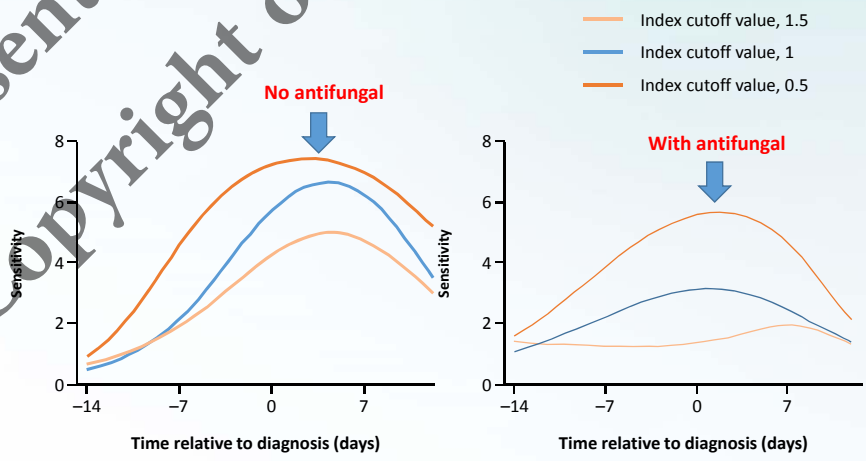




SEIFEM 2004 Study 11,802 patients

Pagano L. et al. Haematologica 2006; Phikulsod et al. Southeast Asian J trop Med public Health 2017;49:159-69

Mold-Active Antifungal Agents Decrease Sensitivity of Serum Galactomannan



Marr KA et al. Clin Infect Dis 2005;40:1762–9

Consideration for Use of Antifungal Prophylaxis

- Only in high risk patients
- Use mold-active agents
- Epidemiology of IFD in hematological patients in each country?
- Cost-effective?
- Choice of diagnostic tools?
- Ability to deal with breakthrough infection?

Topics

- Who should receive antifungal prophylaxis?
- Should we use antifungal prophylaxis in all high-risk individuals?
- Preemptive and empirical antifungal therapy in neutropenic patients, which one is better?
- Should we suggest empirical antifungal therapy in high-risk ICU patients?
- What is the place for combination antifungal therapy?

Definition

- Empirical therapy
  - An early approach in patients with persistently febrile neutropenia unresponsive to antibiotic therapy
- Pre-emptive/diagnostic-driven therapy
  - Treatment usually based on the presence of specific clinical signs and/or fungal biomarkers
  - There is no consensus on the definition and there may be overlap with empirical and targeted therapy

Drgona L. et al. Eur J Clin Microbiol Infect Dis 2014; 33:7–21

2010 IDSA Guidelines: Use of Antimicrobial Agents in Neutropenic Patients with Cancer

Antifungal Therapy

High risk

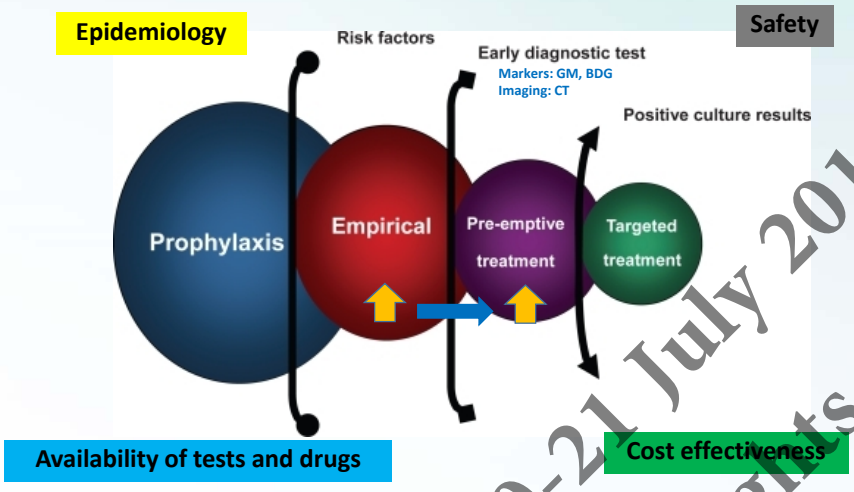
- ***Empirical Treatment***: if persistent fever for 4-7 days (A-I)
  - Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving anti-mold prophylaxis, but switch to a different class give IV should be considered
- ***Preemptive Treatment***: alternative (B-II)

Low risk

- Not recommended (A-III)

Freifeld AG., et al. CID 2011:52: e56-e93

Antifungal Strategies for Treatment of IFIs



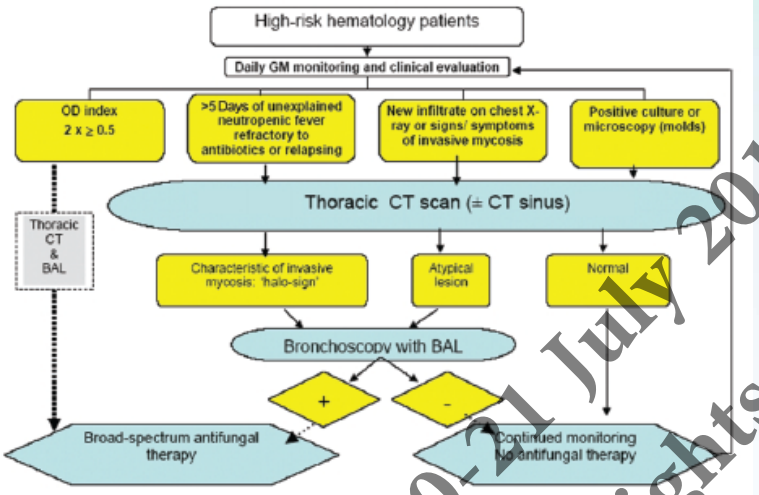
Zaragoza R, et al. Ther Clin Risk Manag (2008)

Empirical vs Preemptive Treatment

- Galactomannan and CT-based preemptive antifungal therapy in neutropenic patients at high risk for IFI: A prospective feasibility study
  - 12-week survival for patients with IFI = 63.6% (63.1% for IA)

Maertens J., et al. Clin Infect Dis 2005:41:1242-50

Diagnosis-Driven Strategy for Antifungal Treatment



Maertens J., et al. Clin Infect Dis 2005:41:1242-50

Empirical versus preemptive antifungal therapy: A randomized, controlled trial

- Total 293 patients
  - 150 in the empirical treatment arm
  - 143 in the preemptive treatment arm
- No difference in survival and length of hospital stay
- Survival by intention-to-treat analysis
  - Empirical treatment 97.3%
  - Preemptive treatment 95.1%
  - Difference -2.2 (95%CI = -5.9 to 1.4) = **Non-inferiority**
- Preemptive treatment decreased antifungal costs by 35%
- Invasive fungal infections
  - Preemptive (13 of 143) > empirical (4 of 150)
  - Most occurred during induction therapy

Cordonnier C., et al. CID 2009:48:1042-51

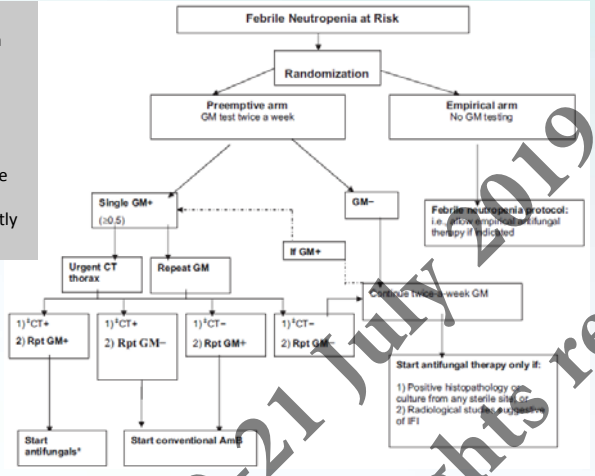
Galactomannan-guided preemptive vs. empirical antifungals in the persistently febrile neutropenic patient: a prospective randomized study☆

Ban Hock Tan [a,*], Jenny Guek Hong Low [a], Nidhi L. Chlebicka [a], Asok Kurup [a], Foong Koon Cheah [b], Raymond Tzer Pin Lin [c], Yeow Tee Goh [d], Gee Chuan Wong [d]

- Total 52 patients
  - 27 episodes preemptive arm
  - 25 episodes empirical arm
- 12-week survival
  - 85.2% preemptive arm
  - 84% empirical arm

Conclusion

- A preemptive approach may reduce empirical antifungal use without compromising survival in persistently febrile neutropenic patients



Tan BH., et al. Int J Infect Dis 2011:15:e350-6

Preemptive Antifungal Therapy for Febrile Neutropenic Patients in China

Preemptive treatment group, antifungal therapy initiated if

- **Clinical** or **imaging** suggested pneumonia, acute sinusitis, stage III mucositis, infectious shock, IFD-related skin damage, central nerve system symptoms due to unknown reason, periorbital inflammation, abscess of liver or spleen, severely diarrhea, colonization by aspergilloma
- **(1,3)-b-D-glucan or galactomannan** -positive

End point	Empirical (n=138)		Preemptive (n=130)		Difference (95%CI)	P value
Survival rate	134	(97.1%)	123	(94.6%)	−2.5 (−5.9 to 1.4)	0.305
Death cases	4	(2.9%)	7	(5.4%)	–	–
IFD cases	3	(2.2%)	12	(9.2%)	−7.0 (−12.3 to −1.7)	0.012
Baseline IFD						
Aspergillus	2	0	6	0	–	–
Candida	0	0	2	0	–	–
Breakthrough IFD						
Aspergillus	1	0	2	0	–	–
Candida	0	0	2	0	–	–
IFD related mortality	1	(0.7%)	3	(2.3%)	1.6 (−1.9 to 1.3)	0.573

Yuan W. et al. Med Sci Monit 2016; 22: 4226-32

Diagnosis-Driven (Preemptive) Antifungal Therapy

Advantages

- Minimized unnecessary use of antifungal agents
  - Reduce cost
  - Reduce toxicities

Limitations

- Available of galactomannan assay (twice a week)
- Available of HRCT within 24 hours when requested (at least < 7 days after positive galactomannan)
- Issue of false positive and false negative GM
- Biomarker for candidiasis may need to be included (BDG)

Topics

- Who should receive antifungal prophylaxis?
- Should we use antifungal prophylaxis in all high-risk individuals?
- Preemptive and empirical antifungal therapy in neutropenic patients, which one is better?
- Should we suggest empirical antifungal therapy in high-risk ICU patients?
- What is the place for combination antifungal therapy?

Risk Factors of Candidemia in ICU

Healthcare-related

- Critical illness, especially long-term ICU stay
- Abdominal surgery, especially with anastomotic leakage
- Broad-spectrum antibiotics
- Central vascular catheter / total parenteral nutrition
- Hemodialysis
- Solid organ transplantation
- Glucocorticoid / chemotherapy

Host-related

- Acute necrotizing pancreatitis
- Hematologic malignancies
- Solid-organ tumors
- Neonates - low birth weight, and preterm infants
- Candida colonization, particularly if multifocal (colonization index >0.5 or corrected colonization index >0.4)

1. Kullberg, BJ., and Arendrup, MC. N Engl J Med 2015;373:1445-56
2. Chakrabarti, A. Intensive Care Med. 2015, 41, 285–295

Candida Scores

Leon score[1]

- Non-neutropenic ICU patients

Total score = 1x (Multifocal *Candida* colonization)
+ 1x (Surgery)
+ 1x (Total parenteral nutrition)
+ 2x (Severe sepsis)

- Present = 1, Absent = 0

- Positive: Total score ≥ 3
- Sensitivity 81%
- Specificity 74%

Ostrosky-Zeichner score[2]

Major criteria
- ICU stay ≥ 4 days and
- Systemic ATB therapy or Central venous catheter

Minor criteria
- Total parenteral nutrition
- Any dialysis
- Any major surgery
- Pancreatitis
- Steroid use
- Immunosuppressive drug use

- Positive: 2 major + 2 minor criteria
- Sensitivity 34%
- Specificity 90%

1 Leo´n C, *et.al*; Crit Care Med 2009 ; 2 Ostrosky-Zeichner L, *et.al*; Eur J Clin Microbiol Infect Dis 2007

Evaluation of *Candida* scores at Siriraj Hospital, Bangkok

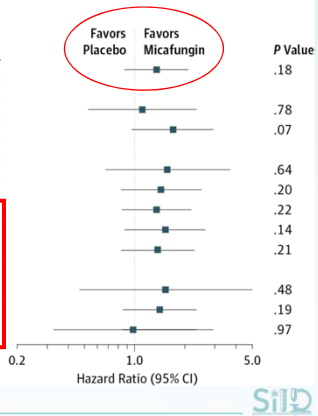
	Leon score		Ostrosky score	
	Our setting	Original study	Our setting	Original study
Sensitivity (%)	46.8	81.0	29.2	34.0
Specificity (%)	84.9	74.0	82.6	90.0
PPV (%)	63.8	NR	44.9	9.0
NPV (%)	73.8	NR	70.7	79.0

NR = Not reported

The EMPIRICUS Study

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure

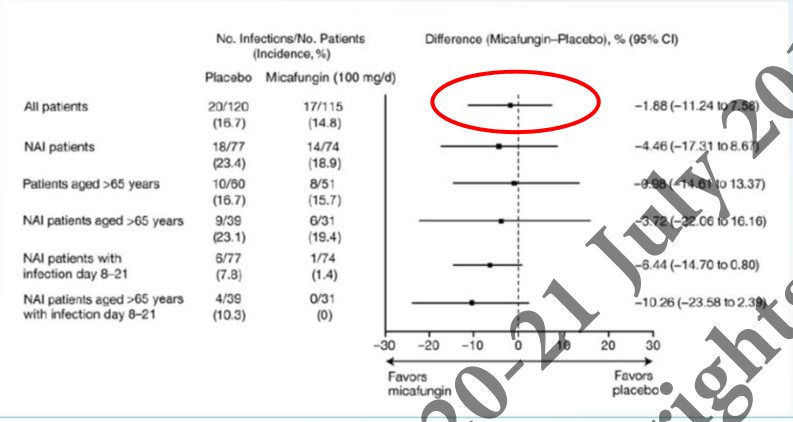
	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	87	128	74	123	1.35 (0.87-2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53-2.33)	.78
>8	36	62	22	55	1.69 (0.96-2.94)	.07
Admission category						
Surgical	22	34	16	31	1.56 (0.67-3.70)	.64
Medical	65	94	58	92	1.43 (0.83-2.50)	.20
Colonization index ≥0.5[a]	68	101	58	99	1.35 (0.84-2.17)	.22
Corrected colonization index ≥0.4[b]	52	76	45	80	1.52 (0.87-2.63)	.14
Candida score ≥3	64	96	47	85	1.37 (0.83-2.27)	.21
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	14	25	1.52 (0.47-5.00)	.48
>80	58	91	47	84	1.41 (0.85-2.33)	.19
≤80	29	37	27	39	0.98 (0.30-2.94)	.97



Timsit JF, et al. JAMA. 2016;316(15):1555-1564

INTENSE Study

Adults who presented with a generalized or localized intra-abdominal infection (community-acquired or nosocomially acquired) requiring surgery and an ICU stay



Knitsch W, Vincent JL, Utzolino S, et al. Clin Infect Dis 2015;61:1671-8

Septic ICU Patients: Empirical antifungal treatment ?

Development of diagnostic tests with a high PPV are mandatory before future randomized controlled trials of pre-emptive/empiric antifungal treatment.

Empiric antifungal treatment may be considered in high risk patients BUT should be re-evaluated after 72–96 hours depending on results from blood cultures or intraoperative specimen and response to treatment to limit unnecessary long treatment courses.

Osthoff M. Thorac Dis 2017;9:E269-E273

Topics

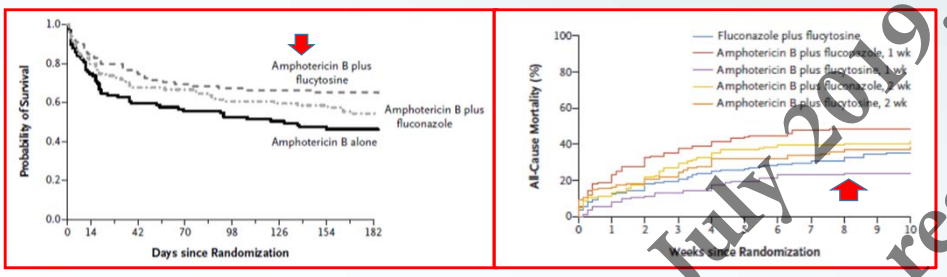
- Who should receive antifungal prophylaxis?
- Should we use antifungal prophylaxis in all high-risk individuals?
- Preemptive and empirical antifungal therapy in neutropenic patients, which one is better?
- Should we suggest empirical antifungal therapy in high-risk ICU patients?
- What is the place for combination antifungal therapy?

Combination Antifungal Therapy

- Cryptotoccal meningoencephalitis
  - Amphotericin B plus flucytosine (5-FC) for induction
  - Duration of induction treatment reduced from 2 to 1 week (ACTA Trial)
- Others – still controversial
  - Invasive candidiasis
  - Invasive aspergillosis
  - Mucormycosis

Molloy SF, et al. N Engl J Med 2018;378:1004-17

Combination Therapy in Cryptococcal Meningitis



Day JN, et al. N Engl J Med 2013;368:1291-1302; Molloy SF, et al. N Engl J Med 2018;378:1004-17

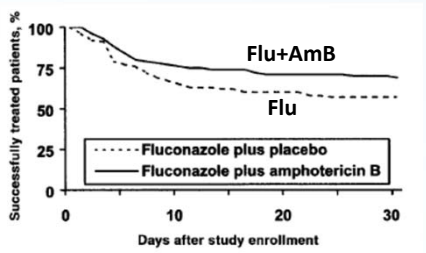
Combination Antifungal Treatment in Invasive Candidiasis

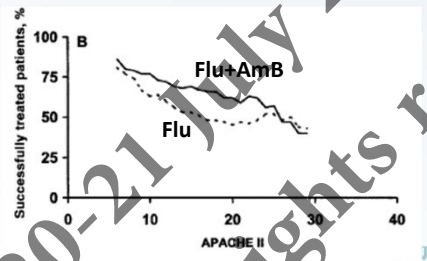
- IDSA: AmB with or without 5-FC
  - Native valve *Candida* endocarditis
  - *Candida* CNS infection
  - Azole-resistant *Candida glabrata* infection
  - Ascending pyelonephritis
  - Fluconazole-resistant *Candida* endophthalmitis
- Candidemia
  - An RCT comparing fluconazole vs. fluconazole+AmB in non-neutropenic candidemia other than *C. krusei*
- Echinocandin/azole
  - In vitro and in vivo study showed synergism in *Candida albicans* but no clinical trial

Pappas PG, et al. Clin Infect Dis 2016;62:e1-50, Campitella M, et al. J Clin Med Res 2017;9:451-6

Fluconazole vs. Fluconazole/AmB in Candidemia

- Randomized placebo-control trial (N = 219)
  - Fluconazole 800 mg/d (n = 107)
  - Fluconazole 0.7 mg/Kg/d (n = 112)
- Fluconazole group - higher APACHE II (16.8±0.6 vs. 15.0±0.7; ***p* = .039**)
- Day30 success rates = 57% (Flu) and 69% (Flu+AmB) *p* = .08
- Overall success rates 56% (Flu) and 69% (Flu+AmB) ***p* = .043**
- Failed to clear infection 17% (Flu) and 6% (Flu+AmB) ***p* = .02**



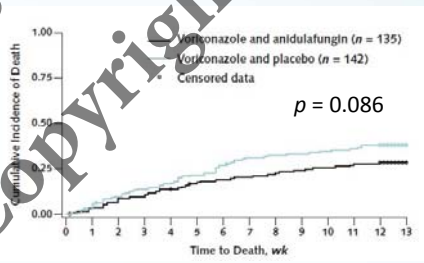


Rex JH, et al. Clin Infect Dis 2003; 36:1221–8

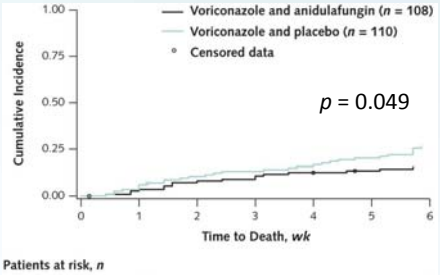
Voriconazole vs. Voriconazole/Anidulafungin for Invasive Aspergillosis

- Randomized placebo-control trial (N = 454; Modified ITT 277 analyzed)
- Multicenter trial

Overall-modified ITT



Subgroup GM positive



Patients at risk, *n*

Voriconazole and anidulafungin	96	88
Voriconazole and placebo	94	79

Voriconazole plus caspofungin was **NOT** better than voriconazole alone in hematological patients with aspergillosis

Read II, et al. Int J Antimicrob Agents 2015;45:283-8.

Marr KA. et al. Ann Intern Med. 2015;162:81-89

Mucormycosis

- Only small case series or restrospective study
- No prospective RCT
- Combination of AmB and caspofungin or posaconazole are recommended for refractory mucormycosis (ESCMID/ECMM Guidelines)

Cornel OA, et al. Clin Microbiol Infect 2014;20(Suppl 3):5-26

Q and A