MMTN
MEDICAL MYCOLOGY
TRAINING NETWORK

Candidemia: Lessons learnt from Asian studies for intervention

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ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

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Candidemia: Lessons learnt from Asian studies for intervention

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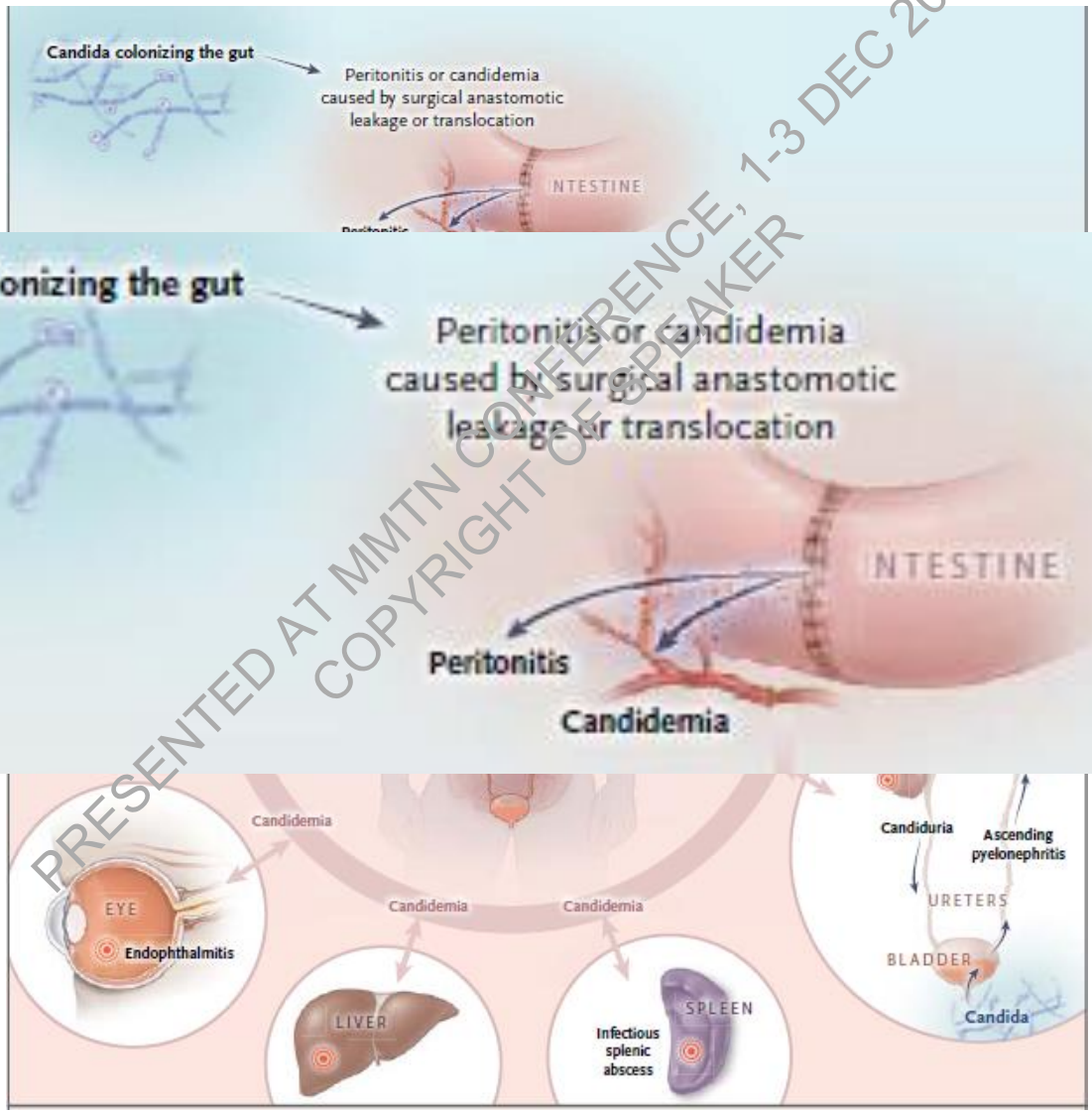
Candidemia

- Affects >250,000 people/year worldwide with > 50,000 deaths
- Incidence reported to be between 2 and 14 cases per 100,000 persons in population-based studies and 6.87 cases per 1000 ICU patients
- Mostly in ICUs and those with extreme age
- Cited as the 4th most common bloodstream infection
- Mortality 25-60%

1. Arendrup MC. Curr Opin Crit Care 2010; 16: 445-52
2. Cleveland AA, et al. PLoS One 2015; 10: e0120452
3. Wisplinghoff H, et al. Clin Infect Dis 2004; 39: 309-17

Pathogenesis of Invasive Candidiasis



Disseminated Candidiasis

Skin lesions

Chorioretinitis

Hepatosplenic abscess

Risk Factors for Candidemia

Healthcare-related

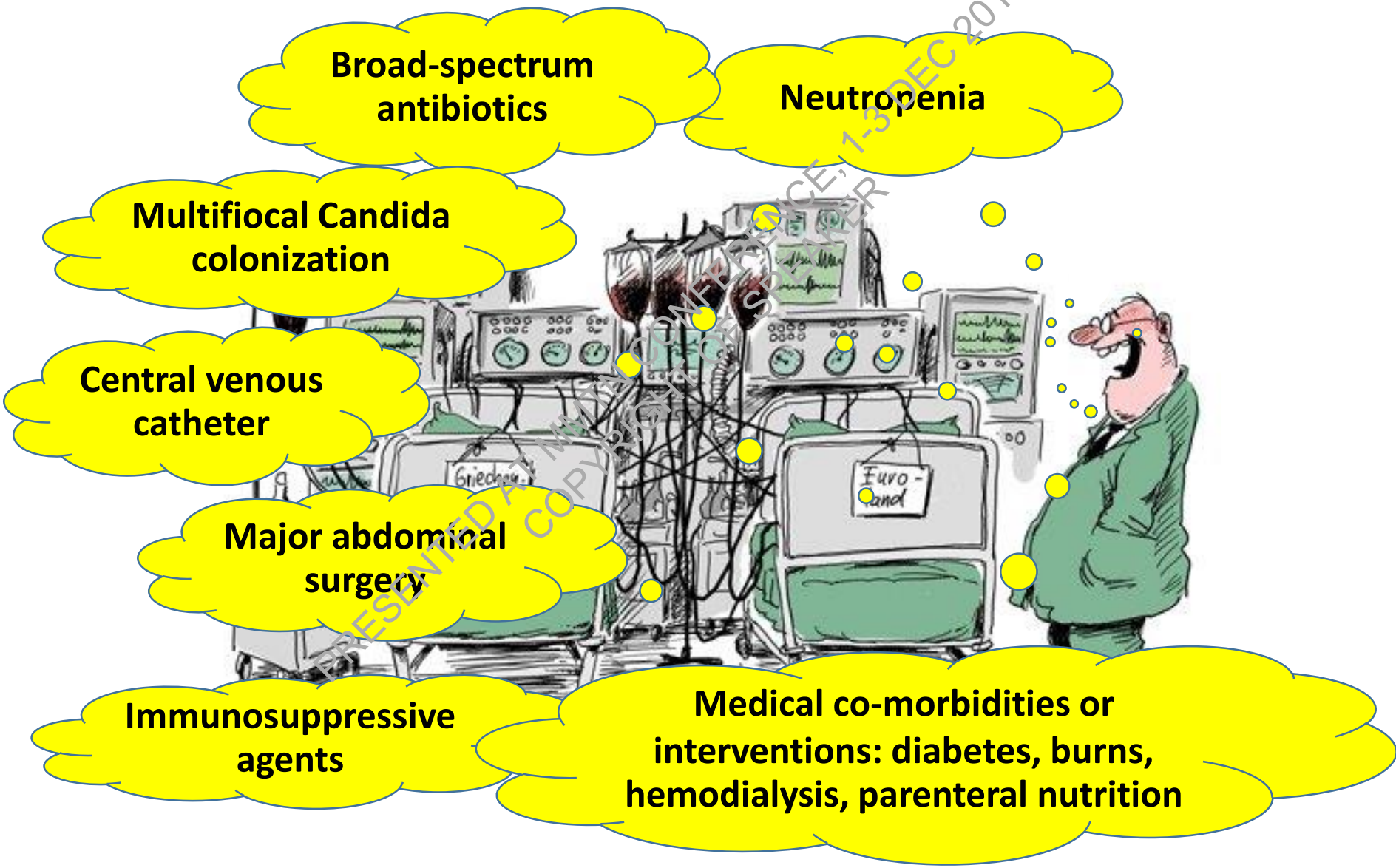
- Critical illness, especially long-term ICU stay
- Abdominal surgery, especially with anastomotic leakage
- Broad-spectrum antibiotics
- Central vascular catheter / total parenteral nutrition
- Hemodialysis
- Solid organ transplantation
- Glucocorticoid / chemotherapy

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

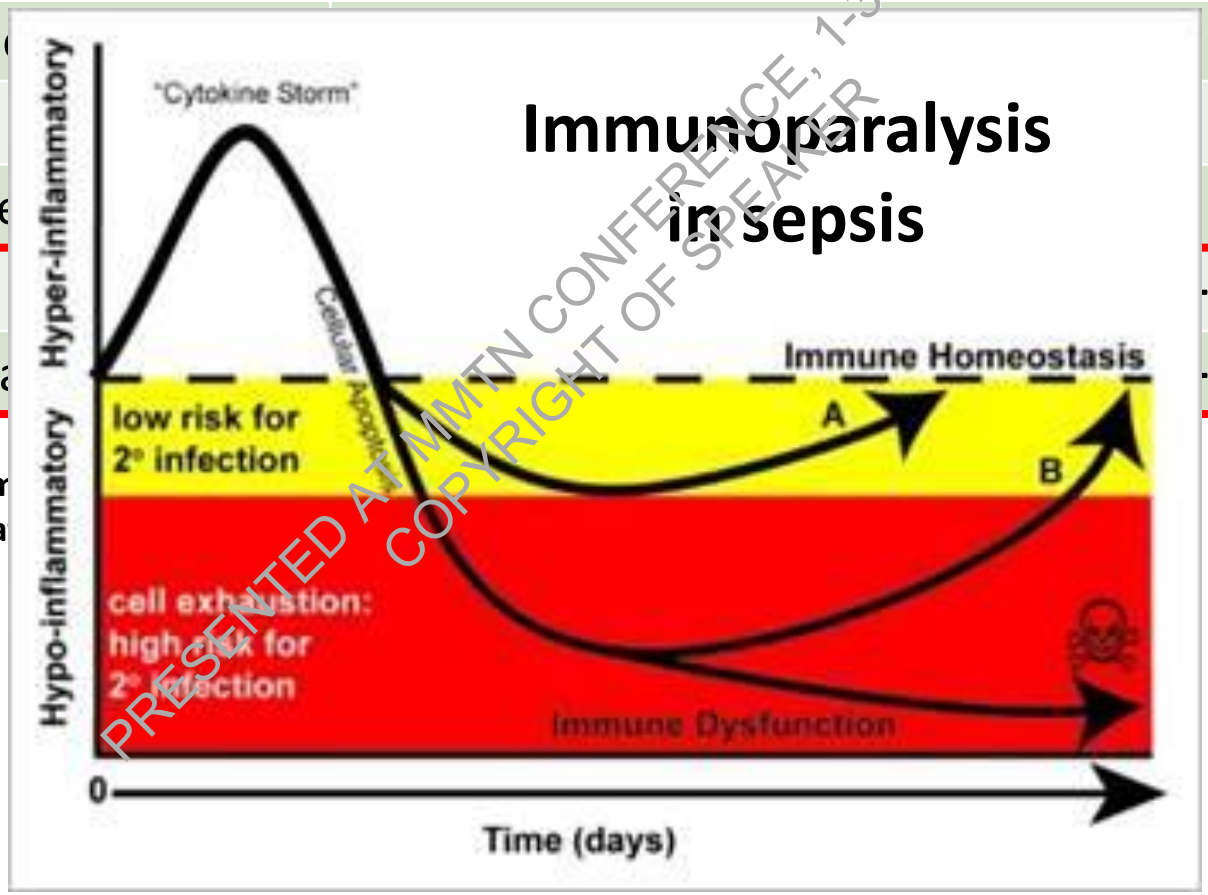
ICU Patients



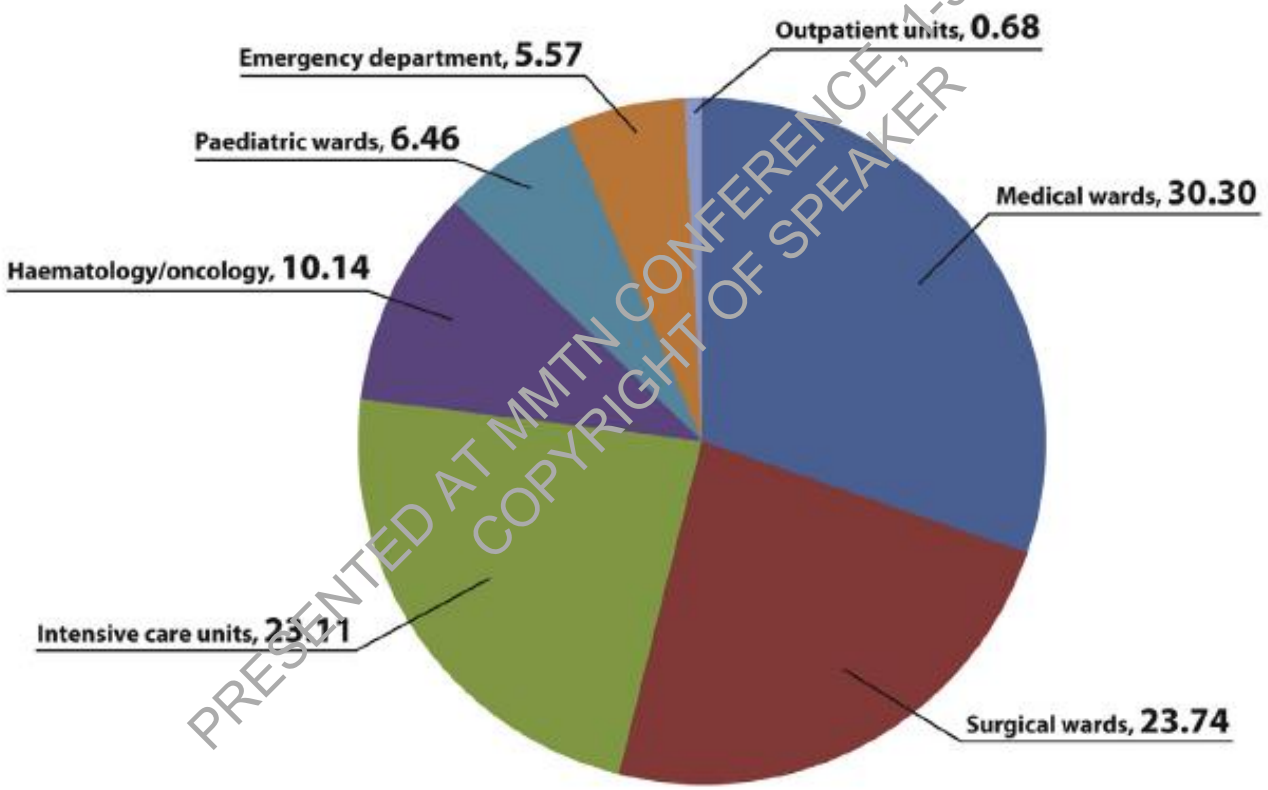
Invasive Fungal Diseases

	Aspergillus	*Candida*
Allogeneic		
AML		
SOT (depe		
ICU		
Abdomina		

AML, acute m
HSCT, haema



Candidemia in Asia



Tan BH., et al. Clin Microbiol Infect 2015; 21: 946–953

Risk Factors for Candidemia in Developing Countries

- The risk factors and underlying diseases for candidemia are **SIMILAR** in both developed and developing countries
- A multi-center study from India, candidemia occurred in
  - Younger age
  - Less co-morbidities
  - Much earlier post-ICU admission (median 8 days post-ICU admission compared to 23 days in USA)
- May be due to early colonization of Indian patients

Chakrabarti, A. Intensive Care Med. 2015, 41, 285–295

Incidence of Candidemia in Asian Countries and Developed Countries

Relatively higher incidence in Asian countries

Countries	Cases
USA	0.30
Canada	0.45
UK	1.87
Australia	0.21
Sweden	0.32
Switzerland	0.049

*per 1000 discharges/admissions

Countries	Cases
Overall Asia	0.39-14.2
China	0.38
India	1.94
Thailand	1.31
Singapore	0.12-0.33
Taiwan	2.93
Hong Kong	0.25

1. Kaur H. and Chakrabarti A. J. Fungi 2017, 3, 41; doi:10.3390/jof3030041
2. Tan BH., et al. Clin Microbiol Infect 2015; 21: 946–953

Candidemia in Asian and Developed Countries

- Incidence increased 5 fold globally in the last 10 years
- Developing countries → 4–15 times higher than developed countries
- The incidence of candidemia
  - Asia: from 0.026 to 4.2 cases per 1000 admissions
  - Developed countries: from 0.03 to 1.87 cases per 1000 admissions
  - ICUs of developing countries: 2.2 to 41.0 cases per 1000 admissions
  - ICUs of developed countries: 0.24–6.87 cases per 1000 admissions
- Over all crude mortality rate
  - Developed countries < 50%
  - Developing countries >50%

Kaur H. and Chakrabarti A. J. Fungi 2017, 3, 41; doi:10.3390/jof3030041

Why More Candidemia in Asians

- Limited awareness in fungal diseases
- Overuse and/or misuse of antibiotics and corticosteroid
- Suboptimal infection control
  - Lack of infrastructure, staff training, sanitation, surveillance programs, and compliance of healthcare workers
- Management largely based on clinical assessment and empirical therapy
  - Lack of accurate diagnostic methods and species identification
  - Inefficient implement of guidelines
- Immunogenetics
  - The majority of patients in the ICU do not acquire invasive candidiasis, even if they share similar risk factors
  - Single nucleotide polymorphisms (SNPs) in toll-like receptor 1–interferon-γ pathway – associated with candidemia → No data in Asians

1. Kaur H. and Chakrabarti A. J. Fungi 2017, 3, 41; doi:10.3390/jof3030041
2. Plantinga TS, et al. J Infect Dis 2012; 205: 934-43

Antifungal Susceptibility

Species
C. albicans
C. tropicalis
C. parapsilosis
C. glabrata
C. krusei

S-DD, Susceptible dose-dependent; I, Intermediate; S, Susceptible

Prior azole exposure is important !

Modified from CID 2009: 48:503-35

Antifungal Susceptibility

Species						Echino-candins
C. albicans						S
C. tropicalis						S
C. parapsilosis						S to R
C. glabrata						S
C. krusei						S
C. lusitaniae						S
C. guilliermondii						S to R
C. auris	R	R	R	R	R	S to r

S-DD, Susceptible dose-dependent; I, Intermediate; S, Susceptible

Prior azole exposure is important !

Modified from CID 2009: 48:503-35

Candida Studies in Asia

Tan BH., et al. Clin Microbiol Infect 2015; 21: 946–953

ORIGINAL ARTICLE MYCOLOGY

Incidence and species distribution of candidaemia in Asia: a laboratory-based surveillance study

B. H. Tan[1], A. Chakrabarti[2], R. Y. Li[3], A. K. Patel[4], S. P. Watcharananan[5], Z. Liu[6], A. Chindamporn[7], A. L. Tan[8], P.-L. Sun[9], U.-I. Wu[10] and Y.-C. Chen[11,12], on behalf of the Asia Fungal Working Group (AFWG)

1) Department of Infectious Diseases, Singapore General Hospital, Singapore, 2) Department of Medical Microbiology, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, India, 3) Department of Dermatology, Peking University First Hospital, Research Centre for Medical Mycology, Peking University, Beijing, China, 4) Department of Infectious Diseases, Sterling Hospital, Ahmedabad, India, 5)Division of Infectious Disease, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand, 6)Department of Infectious Diseases, Peking Union Medical College Hospital, Beijing, China, 7 Department of Microbiology, Faculty of Medicine, King Chulalongkorn Memorial Hospital Chulalongkorn University, Bangkok, Thailand, 8)Department of Pathology, Singapore General Hospital, Singapore, 9)Department of Dermatology, Mackay Memorial Hospital, 10)Department of Medical Research, National Taiwan University Hospital, 11)Department of Medicine, National Taiwan University Hospital and College of Medicine, Taipei and 12)National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Miaoli County, Taiwan

25 centers in 6 countries:
China, Hong Kong, Singapore, India, Taiwan, Thailand

From July 2010 to June 2011

1601 episodes of candidemia
1910 isolates

Tan TY., et al. Med Mycol 2016; 54: 417-7

Medical Mycology, 2016, 54, 471–477
doi: 10.1093/mmy/myv114
Advance Access Publication Date: 11 February 2016
Original Article

Original Article

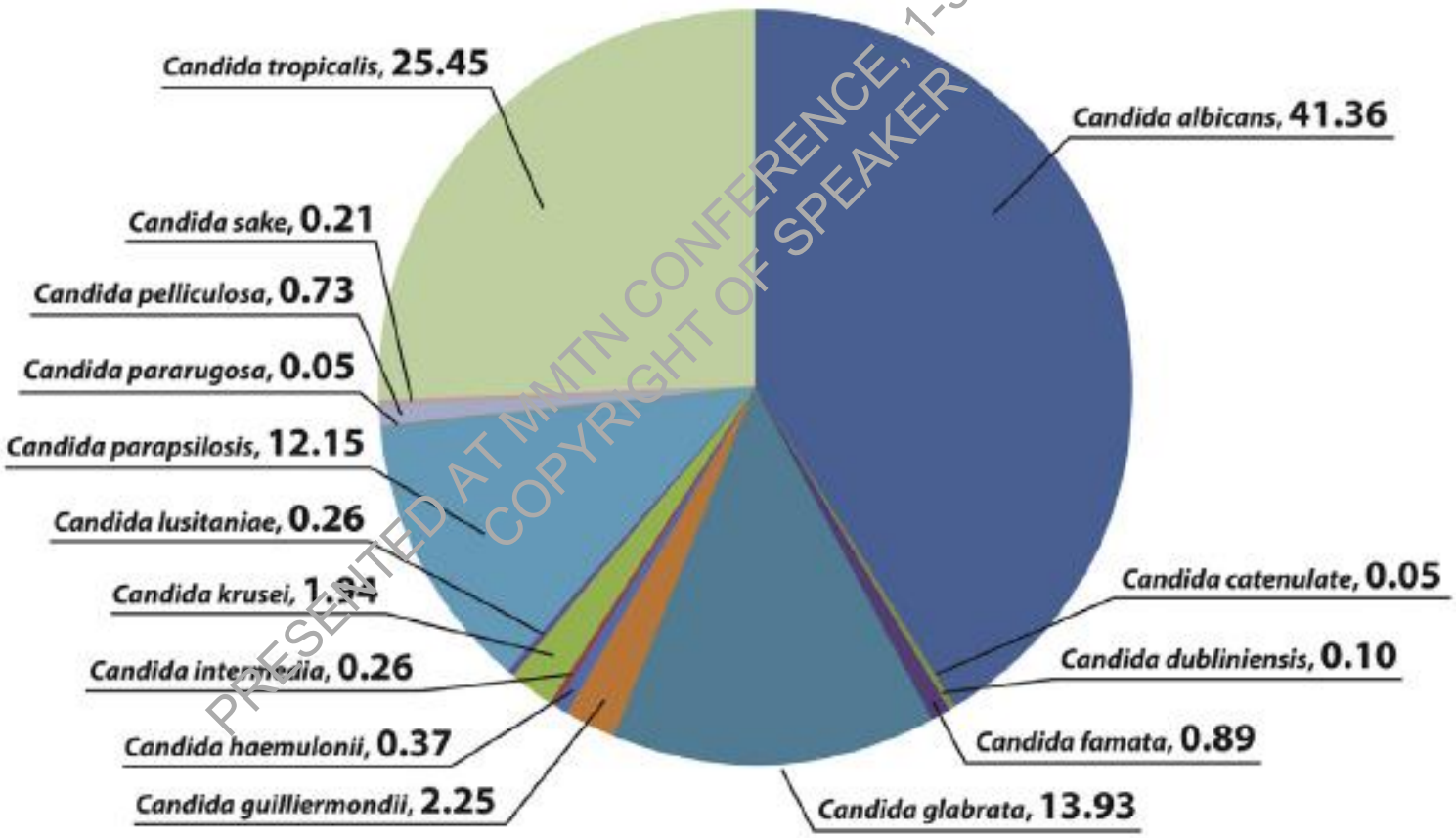
Antifungal susceptibility of invasive *Candida* bloodstream isolates from the Asia-Pacific region

Thean Yen Tan[1,*], Li Yang Hsu[2], Marissa M. Alejandria[3], Romanee Chaiwarith[4], Terrence Chinniah[5], Methee Chayakulkeeree[6], Saugata Choudhury[7], Yen Hsu Chen[8,9,10], Jong Hee Shin[11], Pattarachai Kiratisin[6], Myrna Mendoza[12], Kavitha Prabhu[5], Khuanchai Supparatpinyo[4], Ai Ling Tan[13], Xuan Thi Phan[14], Thi Thanh Nga Tran[14], Gia Binh Nguyen[15], Mai Phuong Doan[15], Van An Huynh[16], Su Minh Tuyet Nguyen[16], Thanh Binh Tran[17] and Hung Van Pham[17]

10 centers in 7 countries:
Brunei, Korea, Philippines, Singapore, Taiwan, Thailand, Vietnam

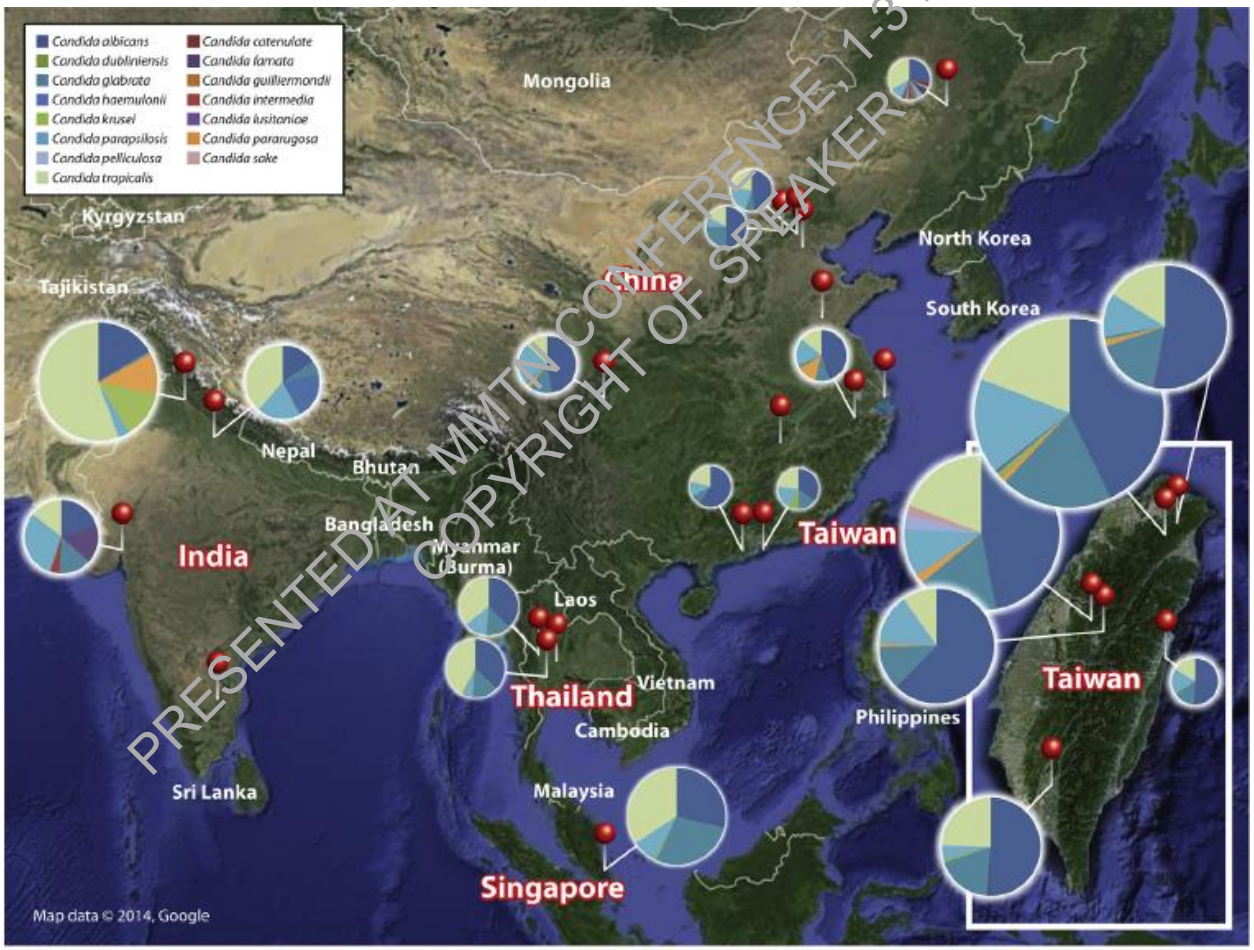
From 2013-2015
861 isolates

Species Distribution of *Candida* in Asia



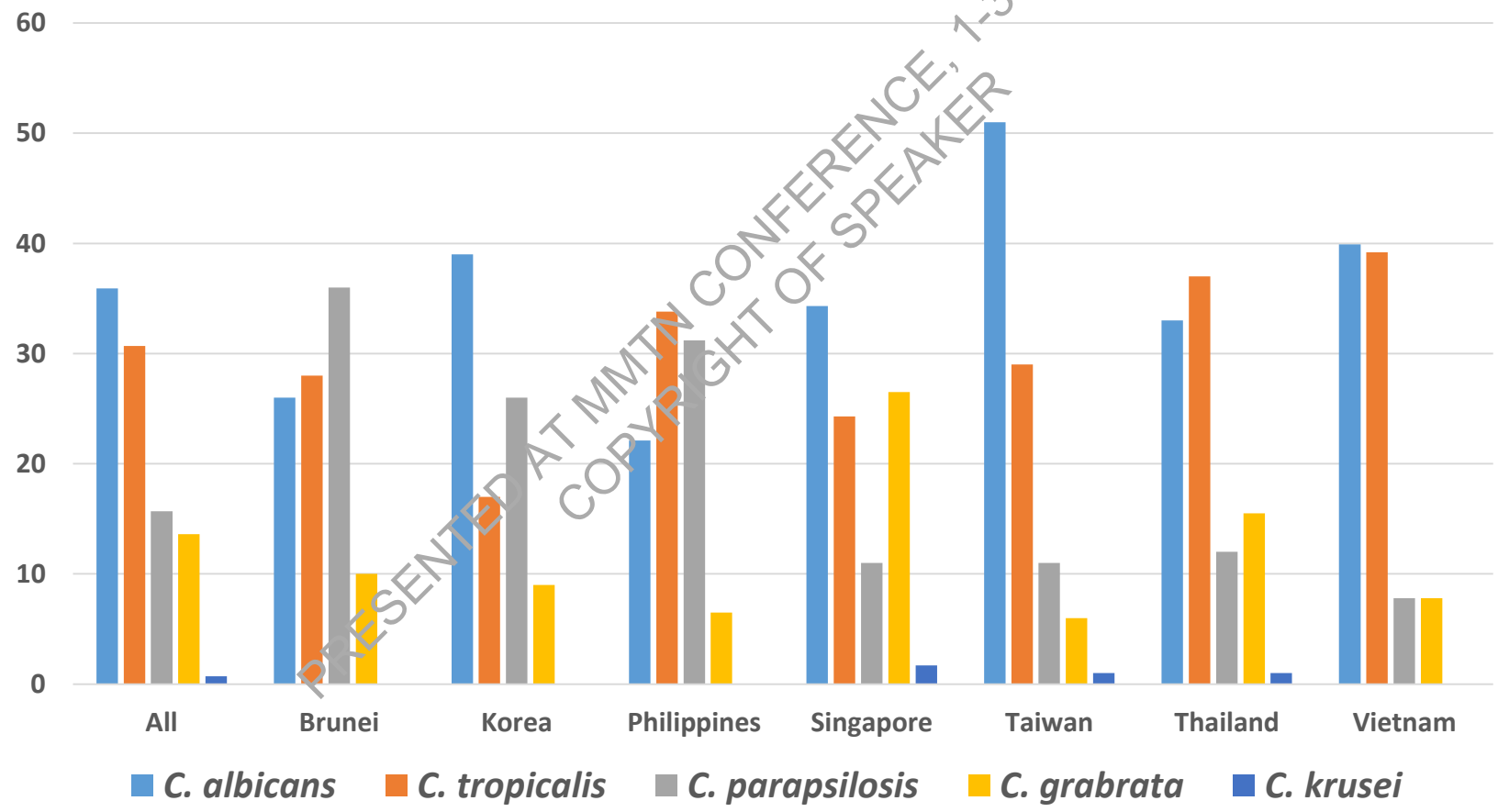
Tan BH., et al. Clin Microbiol Infect 2015; 21: 946–953

Species Distribution of *Candida* in Asia



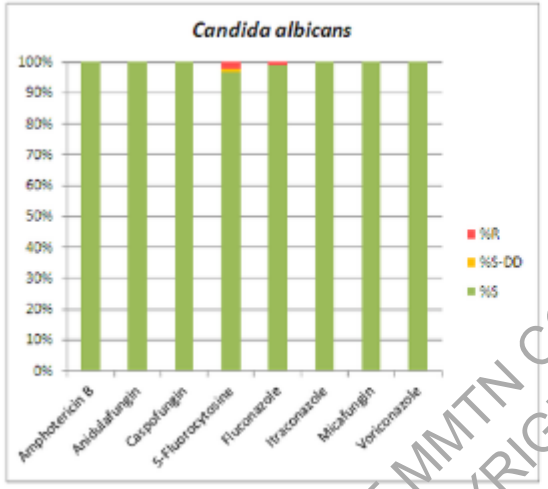
Tan BH., et al. Clin Microbiol Infect 2015; 21: 946–953

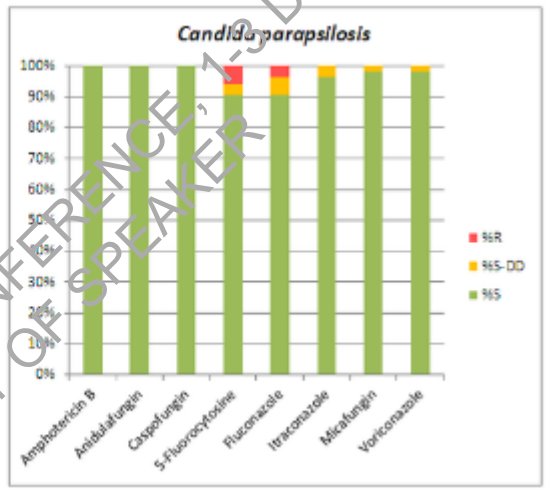
Species Distribution of *Candida* in Asia

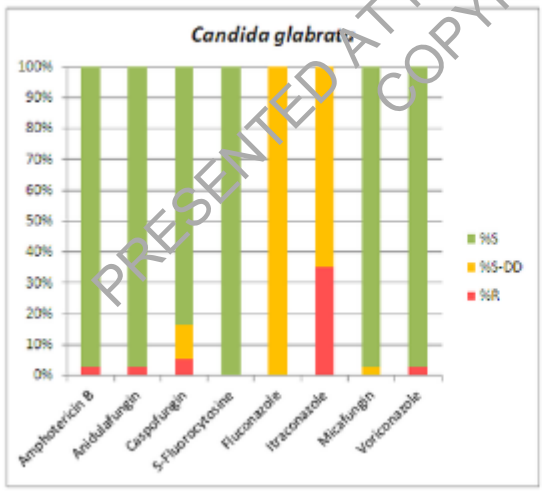


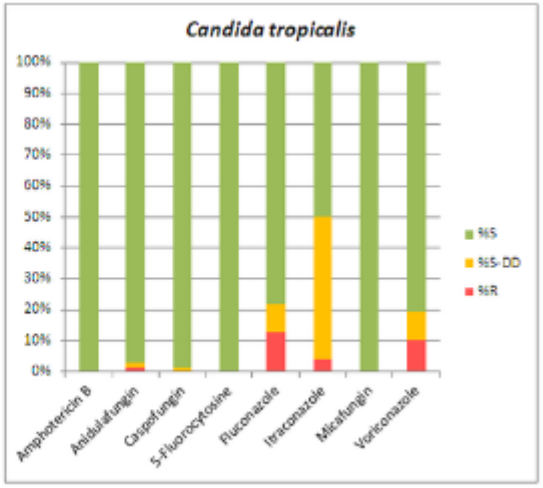
Tan TY., et al. Med Mycol 2016; 54: 417-7

Antifungal Susceptibility of *Candida* in Asia









Tan TY., et al. Med Mycol 2016; 54: 417-7

Antifungal Susceptibility of *Candida* Species

Species	Fluco-nazole	Itra-conazole	Vori-conazole	Posa-conazole	Ampho-tericin B	Echino-candins
C. albicans	S	S	S	S	S	S
C. tropicalis	S to R	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S to R
C. glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S to I	S
C. krusei	R	S-DD to R	S	S	S to I	S
C. lusitaniae	S	S	S	S	S to R	S
C. guilliermondii	S to R	S to R	S to r	S to r	S	S to R
C. auris	R	R	R	R	R	S to r

S-DD, Susceptible dose-dependent; I, Intermediate; S, Susceptible

Previous fluconazole exposure is important

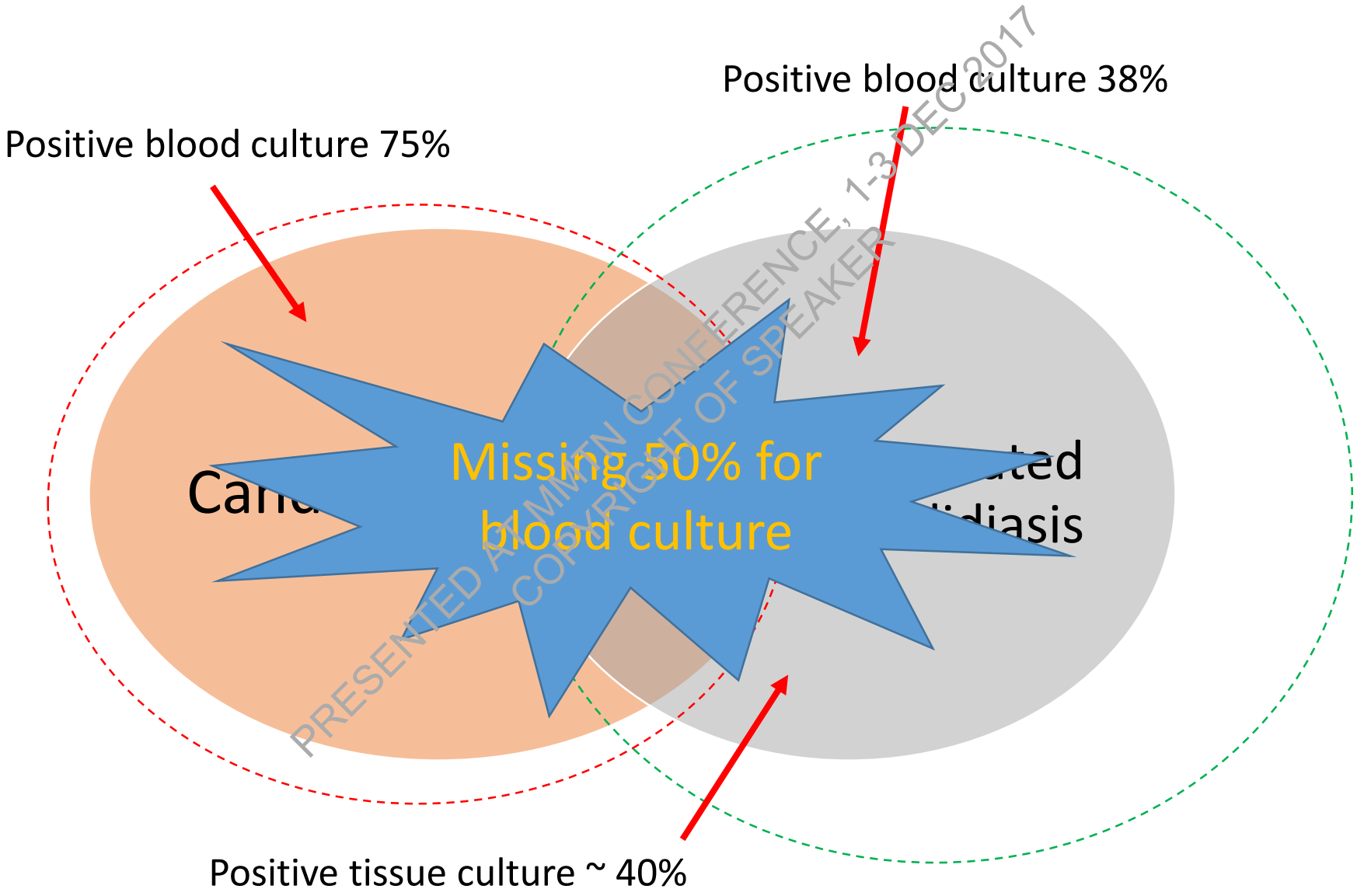
Modified from Clin Infect Dis 2009: 48:503-35

Candida auris: An Emerging Fungal Pathogen

- Found in 16 countries in 4 continents within 5 years
- Canada, Colombia, Germany, India, Israel, Japan, Kenya, Kuwait, Norway, Pakistan, Spain, South Africa, South Korea, the United Kingdom, and Venezuela, United States
- Cause of emergence
  - Unkown
  - May be antifungal selective pressure
  - DNA fingerprint study suggested that it emerged independently in multiple regions

1. Satoh K, et al. Microbiol Immunol 2009;53:41–4, 2. Lee WG, et al. J Clin Microbiol 2011;49:3139–42, 3.Chowdhary A, et al. Emerg Infect Dis 2013;19:1670–3, 4. Chowdhary A, et al. Eur J Clin Microbiol Infect Dis 2014;33:919–26, 5. Girard V, et al. Mycoses 2016;59:535–8, 6. Emara M, et al. Emerg Infect Dis 2015;21:1091–2, 7. Calvo B, et al. J Infect 2016;73:369–74

Invasive Candidiasis



Clancy and Nguyen CID 2013;56:1284–1292

Diagnostic test

Tests	Sensitivity	Specificity	Turn-around time
Blood culture	21-71	NA	24-48 hours
Beta-D glucan	65-100	31-79	24 hours
Candida mannan antigen and anti-mannan antibody	83	86	24 hours
PCR			
- In house	82-98	97-98	6-12 hours
- SeptiFast	48-72	99	3-4 hours
- T2 *Candida* panel	91	94	3-5 hours

Kullberg BJ and Arendrup MC.N Engl J Med 2015;373:1445-56

Candida Scores

Leon score[1]

- Non-neutropenic ICU patients

Total score = 1x (Multifocal *Candida* colonization)
Add Your Title
+ 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

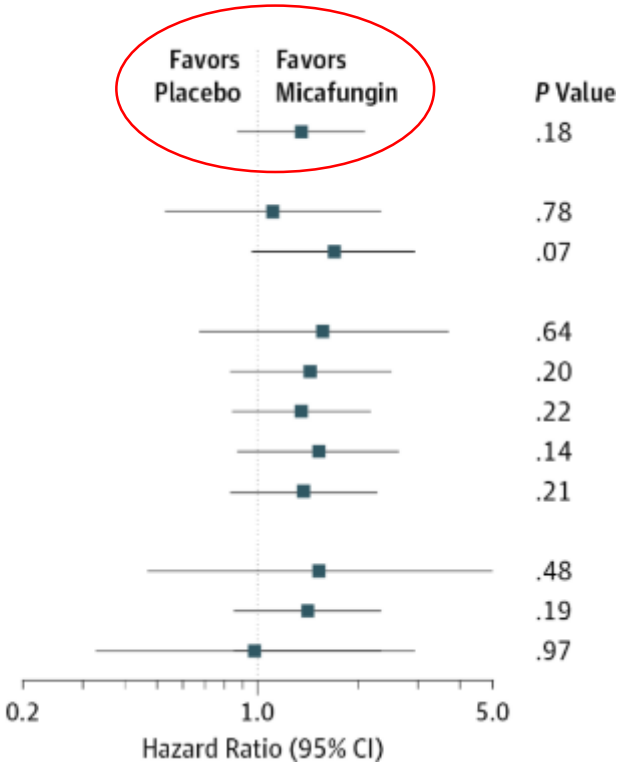
	Leon score		Ostrosky score	
	Our setting	Previous study	Our setting	Previous study
Sensitivity (%)	46.8	81.0	29.2	34.0
Specificity (%)	84.9	74.0	82.6	90.0
PPV (%)	63.8	NR	44.9	9.0
NPV (%)	73.8	NR	70.7	79.0

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

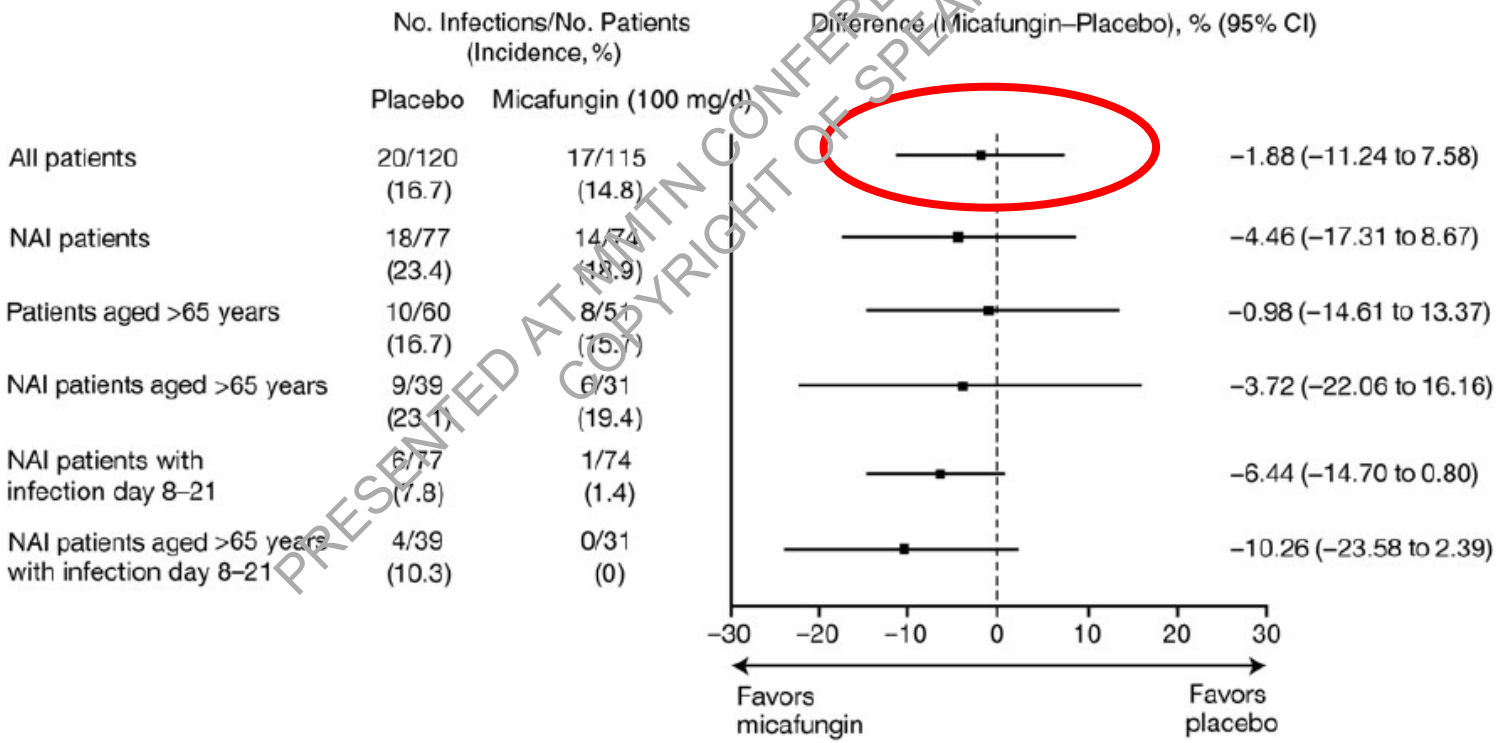
	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	87	128	74	123	1.35 (0.87-2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53-2.33)	.78
>8	36	62	22	55	1.69 (0.96-2.94)	.07
Admission category						
Surgical	22	34	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

Editorial

The EMPIRICUS trial—the final nail in the coffin of empirical antifungal therapy in the intensive care unit?

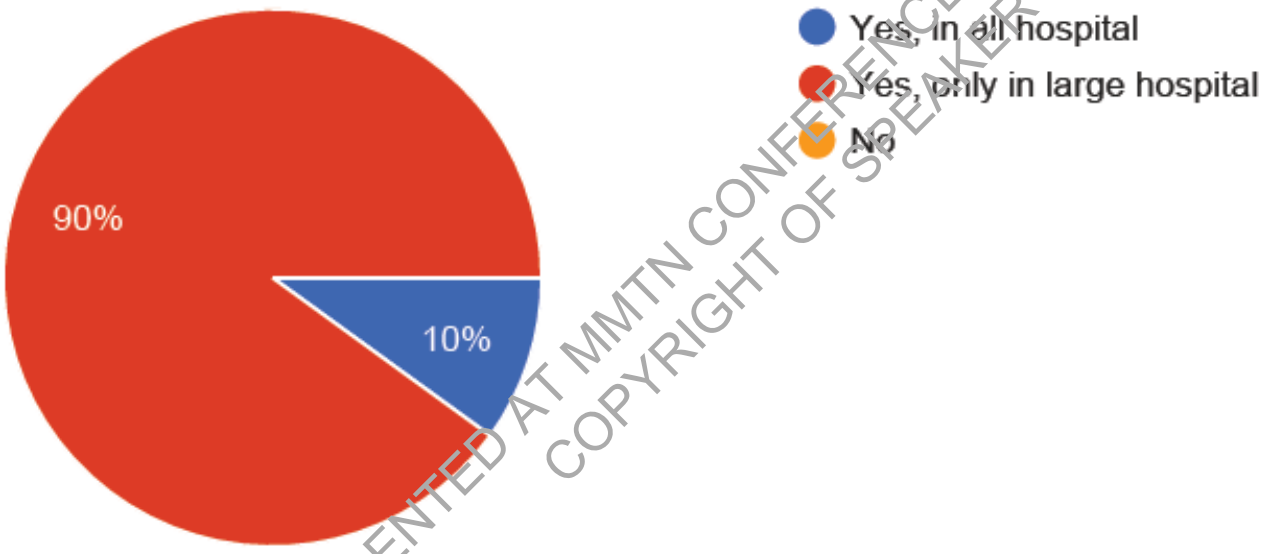
Michael Osthoff[1,2], Nina Khanna[1,2], Martin Siegemund[3]

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

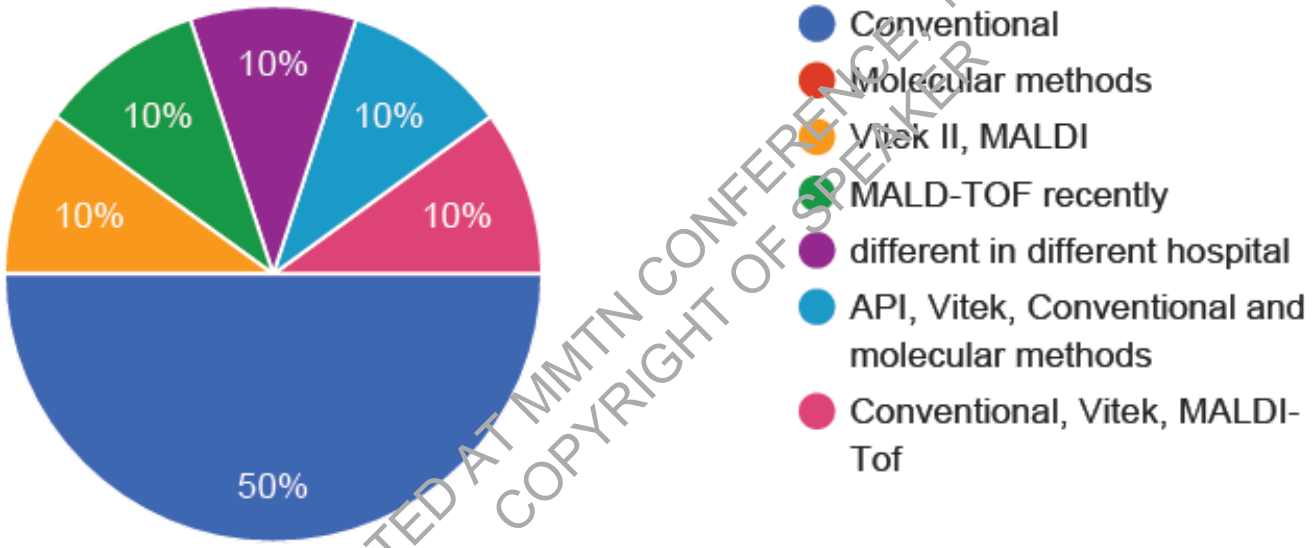
Identification of *Candida* into Species Level: Where we are?



10 responses:

India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1

Routine Techniques for Identification

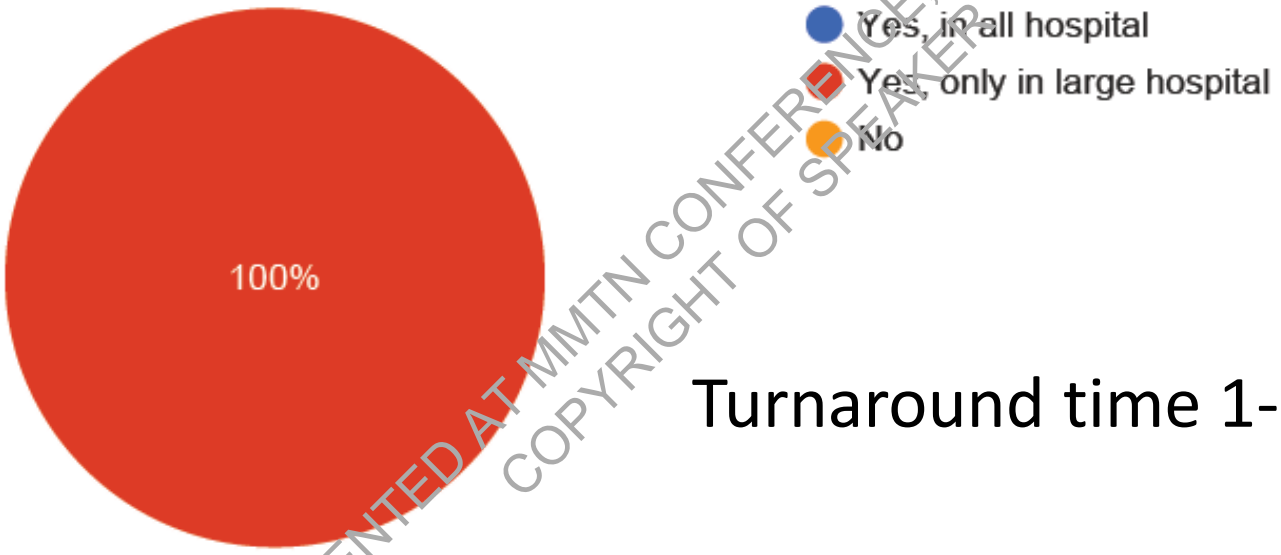


Turnaround time 1-5 days

10 responses:

India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1

Antifungal Susceptibility Test: Where we are?



Turnaround time 1-5 days

10 responses:

India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1

Our Future Direction

Need to implement and develop diagnostic tools to make it available widely with shorter turnaround time (for both identification and antifungal susceptibility)

Candidiasis Guidelines

	Non-neutropenia			
	IDSA guidelines 2016		ESCMID guidelines 2012	
	Recommendation	Evidence	SoR	QoE
Echinocandins	Strong	Moderate	A	I
Liposomal amphotericin B 3-5 mg/kg/day	Strong	Low	B	I
Fluconazole 400-800 mg/day	Strong	Moderate	C	I
Voriconazole 6/3 mg/kg/day	-	-	B	I
Amphotericin B lipid complex 5 mg/kg/day	Strong	Low	C	II
Amphotericin B deoxycholate 0.7-1 mg/kg/day	-	-	D	I

Pappas PG, et al. CID 2016;62:e1–50
Cornely OA, et al. Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37

Echinocandins

For the treatment of invasive candidiasis/candidaemia

	Micafungin[1,2]		Caspofungin[3]	Anidulafungin[4]
Number of patients receiving ≥ 1 dose study drug	531	595	239	256
Reference therapy	L-AmB[1]	Caspofungin[2]	AmB-d[3]	Fluconazole[4]
Inclusion	At least one positive *Candida* culture within the previous 3–4 days			
Important patient groups excluded	–	Patients with endocarditis, osteomyelitis or meningitis	Patients with endocarditis, osteomyelitis or meningitis; or receiving ciclosporin, ritonavir or rifampicin	Patients with endocarditis, osteomyelitis or meningitis; or with *C. krusei*
Primary endpoint: success	Clinical and mycological response at end of therapy			
Result	Non-inferiority	Non-inferiority	Non-inferiority	Superiority

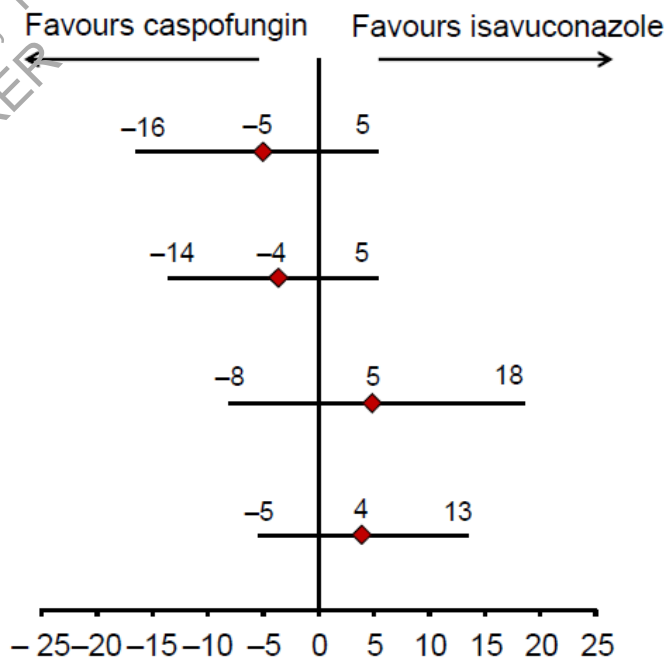
1. Kuse ER, et al. *Lancet* 2007;369:1519–27; 2. Pappas PG, et al. *Clin Infect Dis* 2007;45:883–93; 3. Mora-Duarte J, et al. *N Engl J Med* 2002;347:2020–9; 4. Reboli AC, et al. *N Engl J Med* 2007;356:2427–82.

ACTIVE Study

Isavuconazole vs. Caspofungin (non-inferiority trial)

Category, n (%)	Isavuconazole (N = 69)	Caspofungin (N = 80)
Successful overall response at EOIVT*	**58 (84.1)**	**71 (88.8)**
Successful overall response at EOT	60 (87.0)	73 (91.3)
Successful overall response at EOT + 2 weeks	57 (82.6)	62 (77.5)
All-cause mortality Day 56	5 (7.2)	9 (11.3)

*Stratified by geographical region and baseline neutropenia status.
Successful overall response required successful clinical and mycological response plus no use of alternative systemic antifungal therapy within 48 hours after the last dose of study drug.

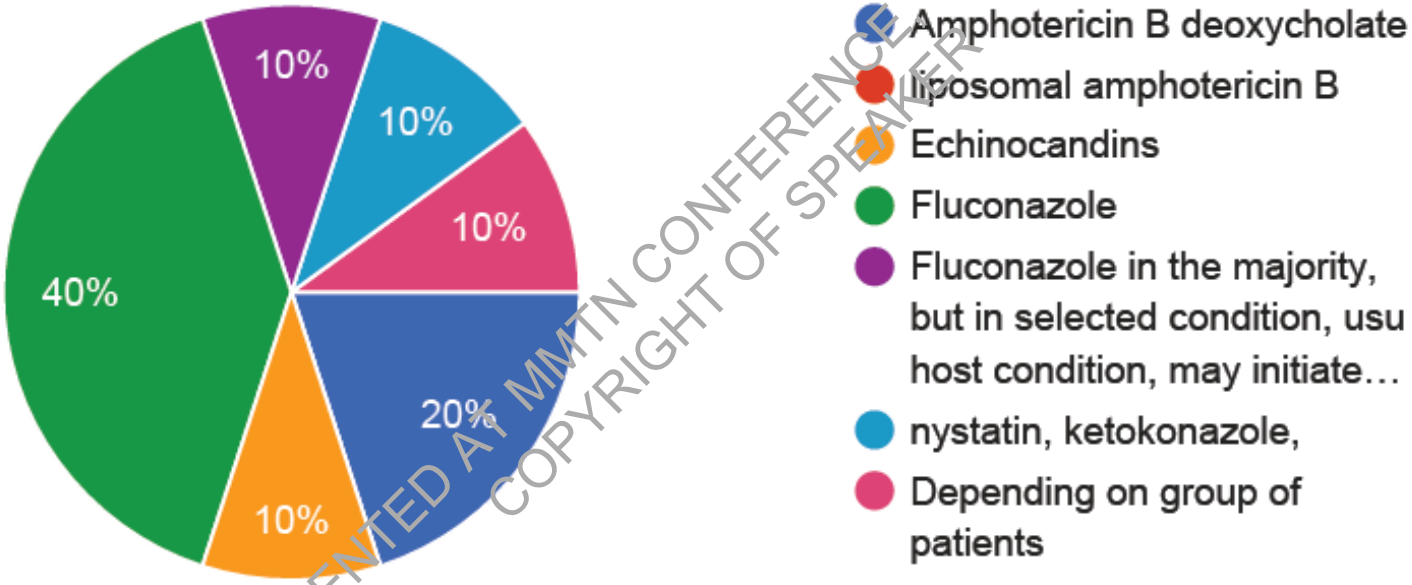


Adjusted difference (%; 95% CI) between isavuconazole versus caspofungin.

Isavuconazole did not meet non-inferiority criteria

Kullburg BJ, et al. ECCMID 2016 Abstract #023

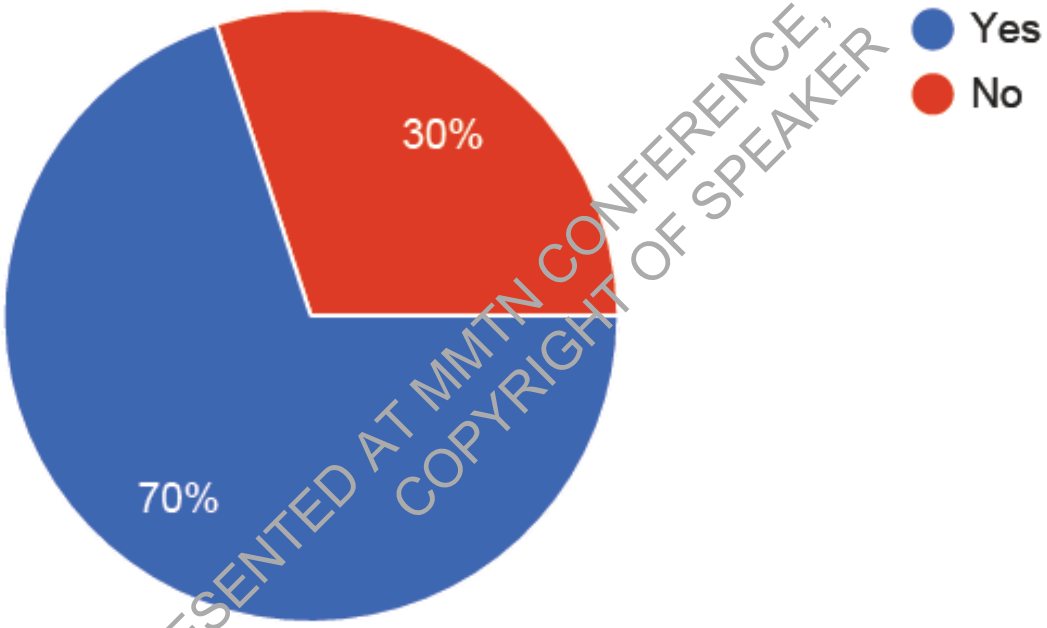
Empirical Antifungal Agents for Candidemia



10 responses:

India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1

Echinocandins in National Formulary Drug List



10 responses:

India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1

Candidemia in Asian Countries

- Similar risk factors as western countries
- Higher incidence
- Different species distribution – more *C. tropicalis* in tropical countries
- Increased antifungal resistance
- Lack of diagnostic facilities and antifungal susceptibility testing
- Limited access to antifungal agents

What Should Be Our Strategies to Improve Management in Candidemia?

- Development and improvement of mycology laboratory
- Improvement of infection control
- Local epidemiology studies
- Antifungal treatment
  - Education – appropriate drug
  - Availability of antifungal agents
  - Prophylaxis in specific cases
  - Antifungal stewardship
- Source control
  - Surgery, remove prosthesis/catheter

Thank you