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
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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 Candidemia

Antibiotics

↓

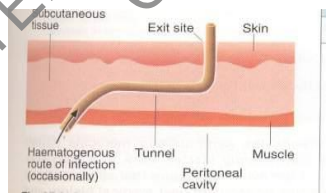
Colonization

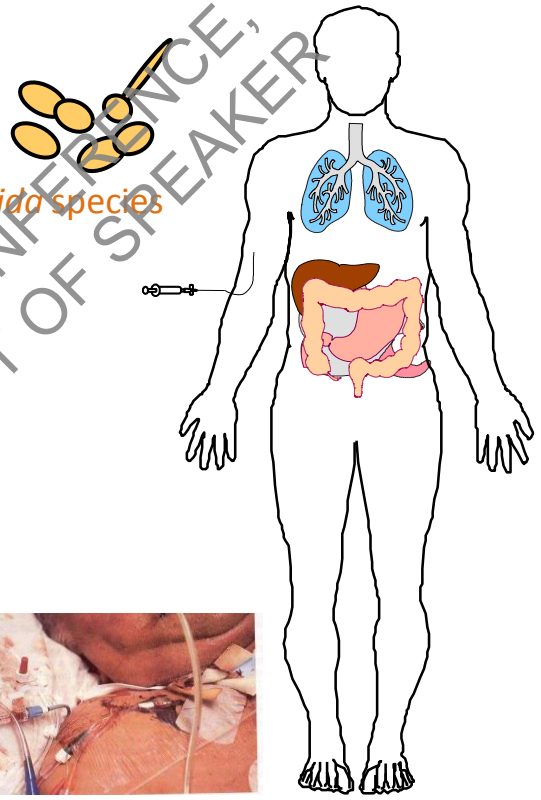
Candida species

↓

Barrier disruption

GI surgery
Vascular access
Mucosal barrier injury
Neutropenia





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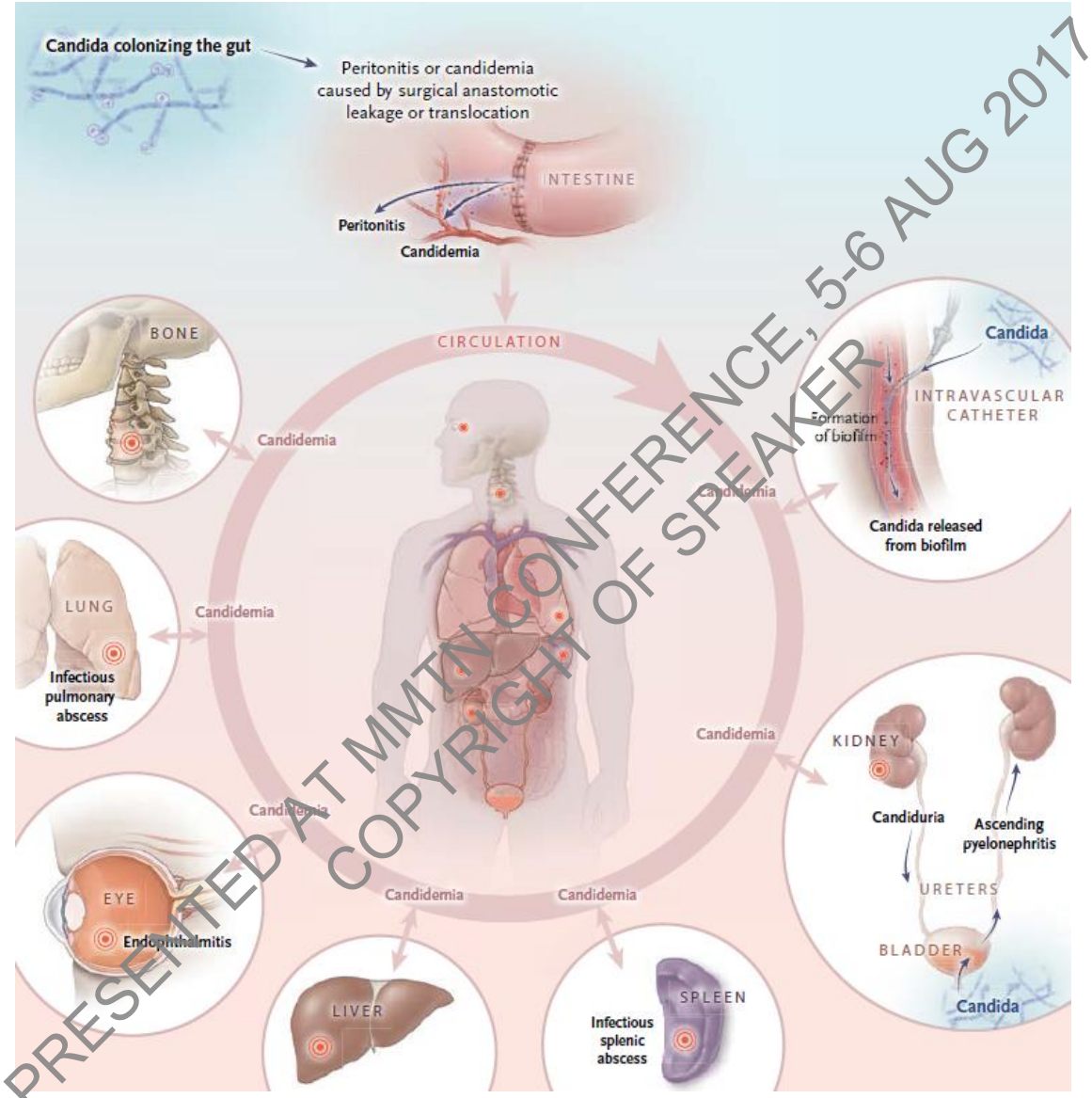
Candidemia (*candida* BSI)



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

Disseminated Candidiasis

Skin lesions

Chorioretinitis

Hepatosplenic abscess

Risk Factors for Candidemia

Healthcare-related

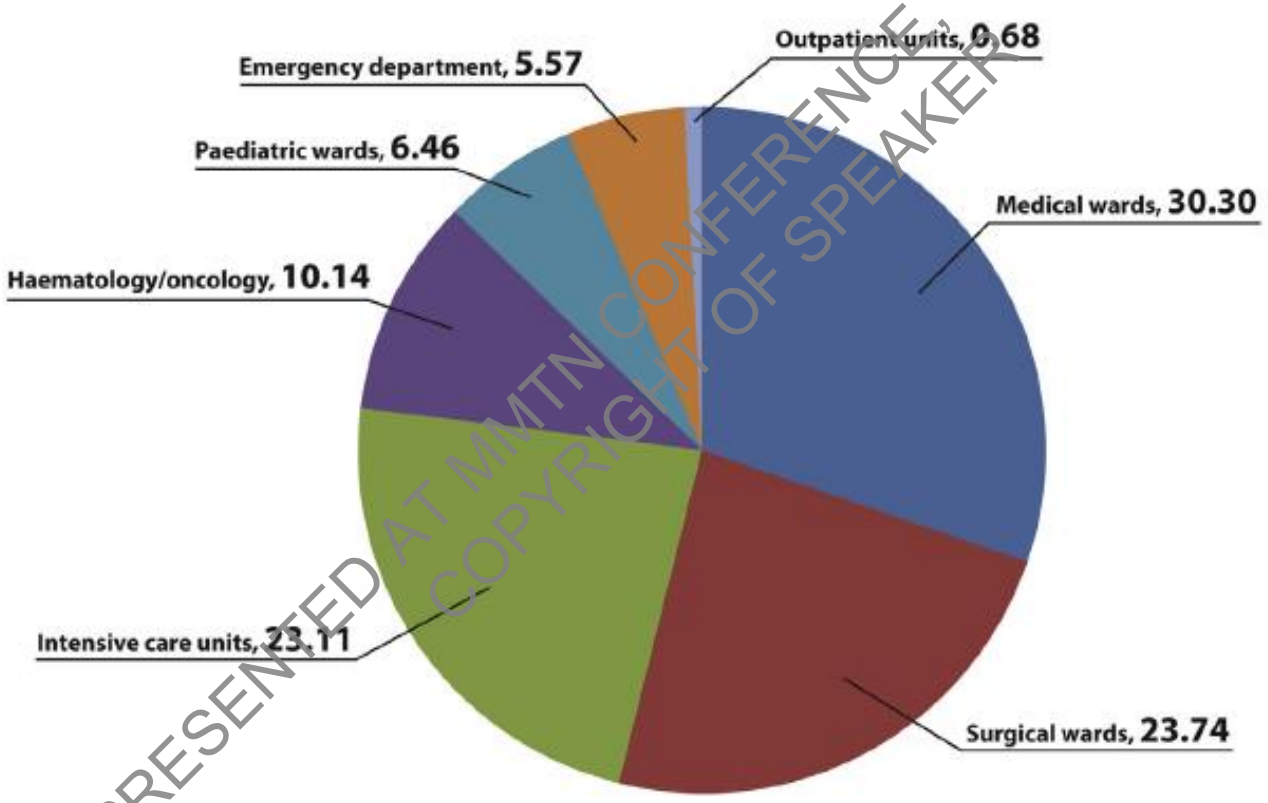
- Critical illness, especially long-term ICU stay
- Abdominal surgery, especially with anastomotic leakage
- Broad-spectrum antibiotics
- Central vascular catheter / total parenteral nutrition
- Hemodialysis
- Solid organ transplantation
- Glucocorticoid / chemotherapy

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

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

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

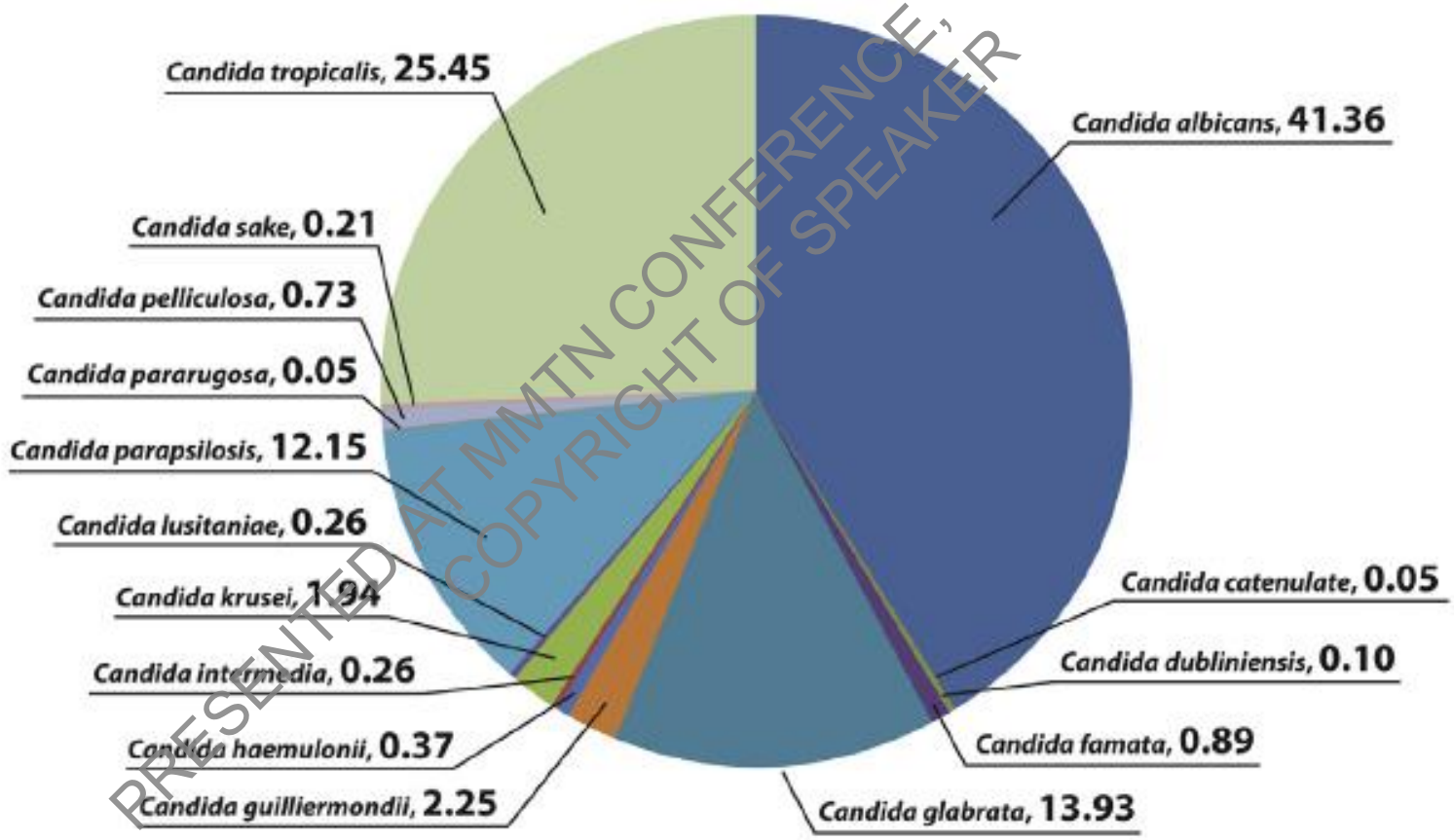
Antifungal susceptibility of invasive *Candida* bloodstream isolates from the Asia-Pacific region

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

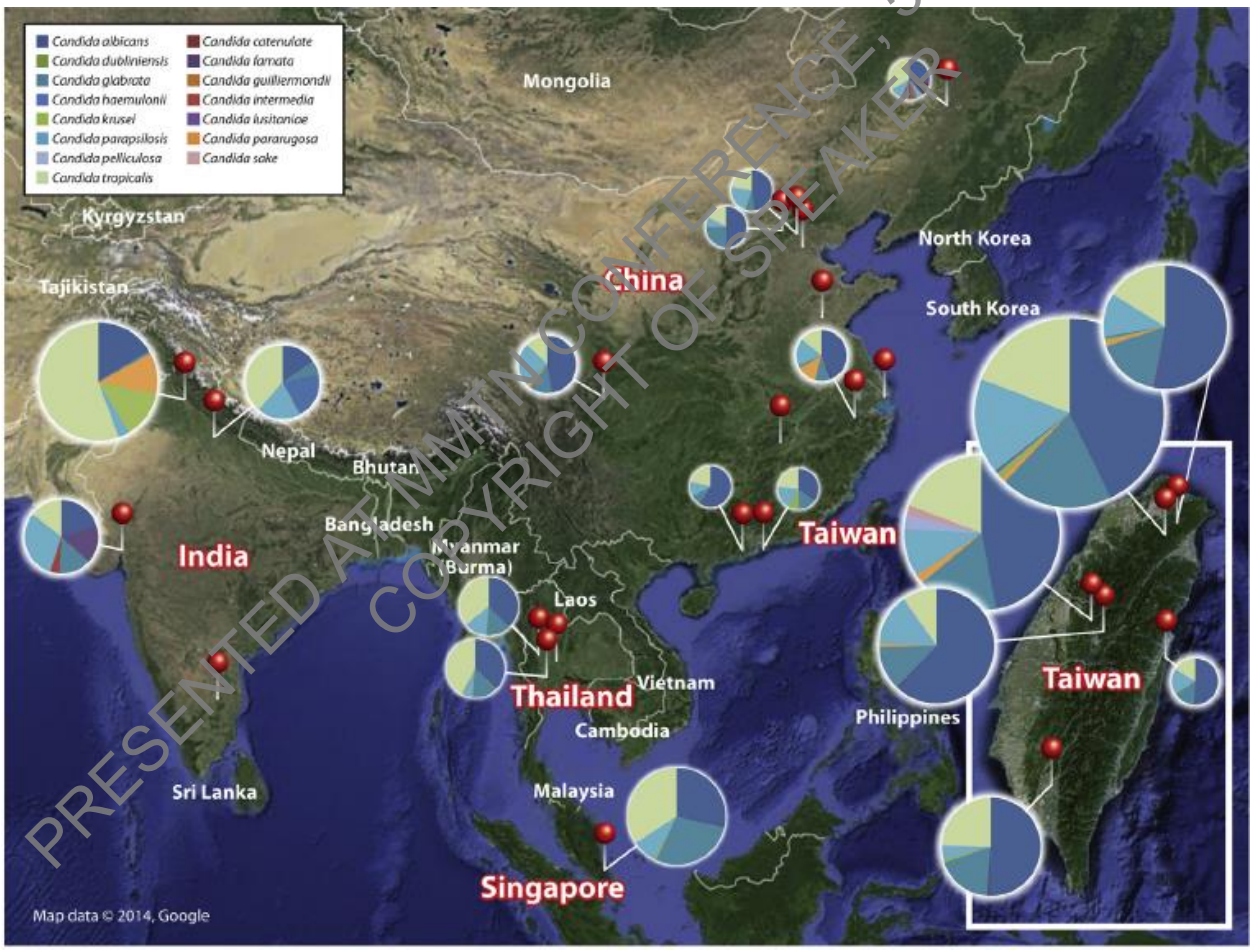
From 2013-2015
861 isolates

Species Distribution of *Candida* in Asia



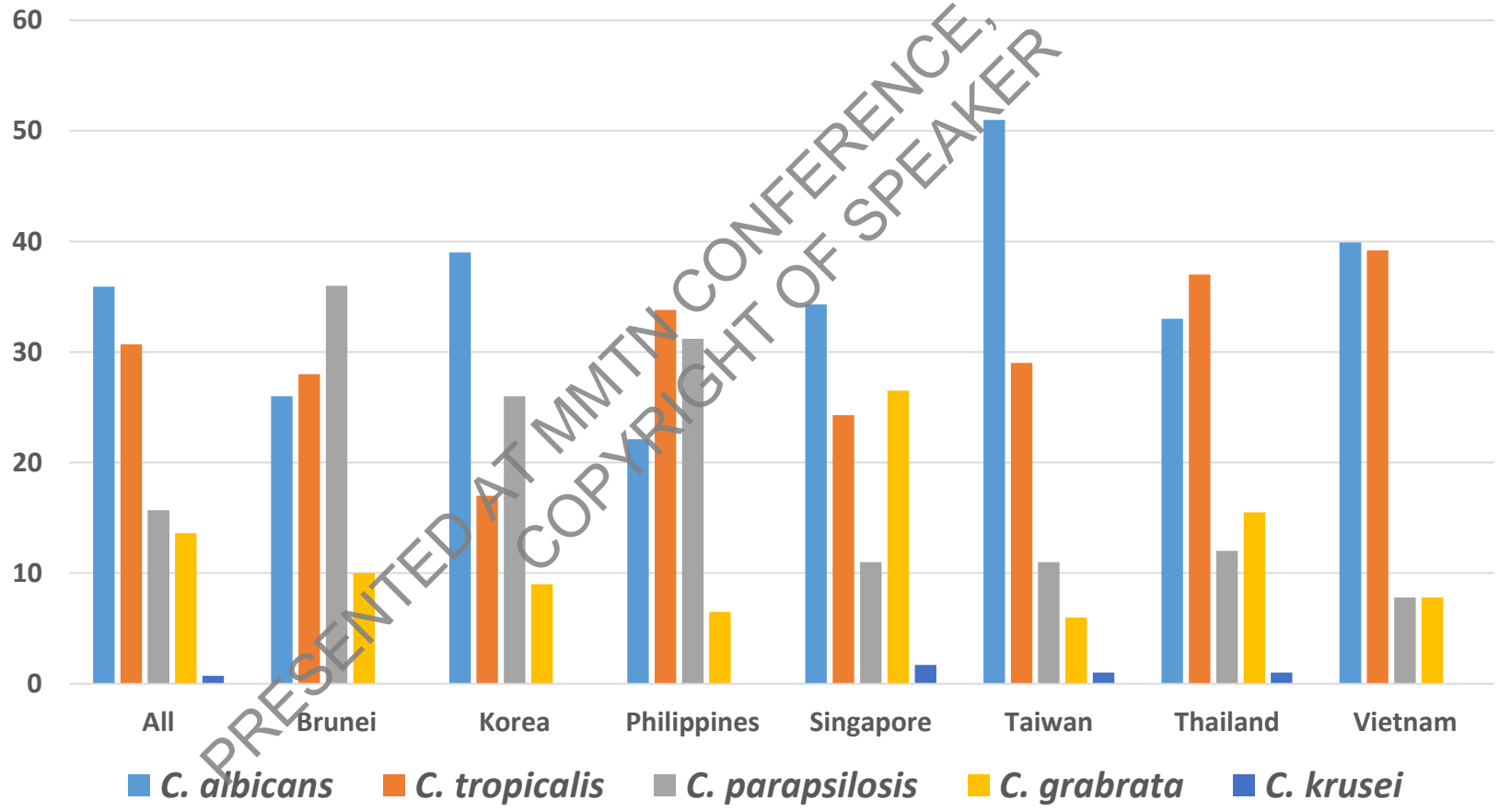
Tan BH., et al. Clin Microbiol Infect 2015; 21: 946–953

Species Distribution of *Candida* in Asia



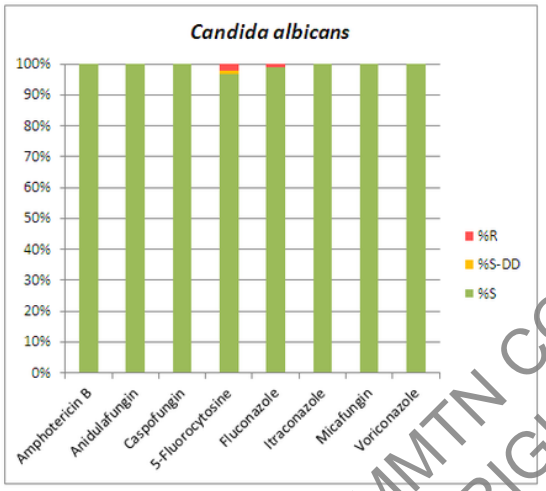
Tan BH., et al. Clin Microbiol Infect 2015; 21: 946–953

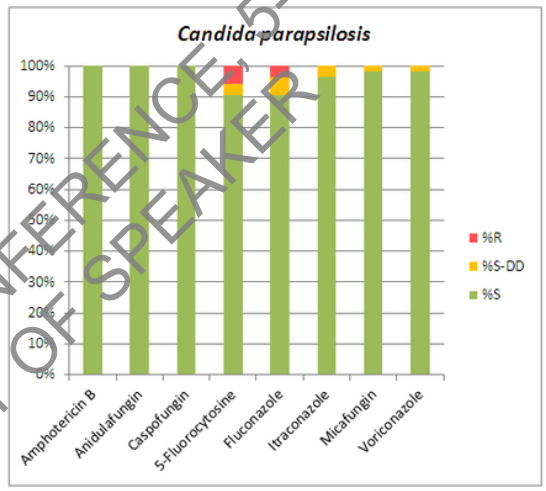
Species Distribution of *Candida* in Asia

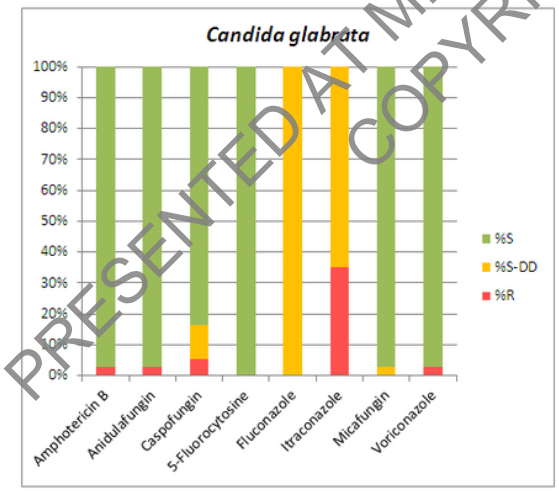


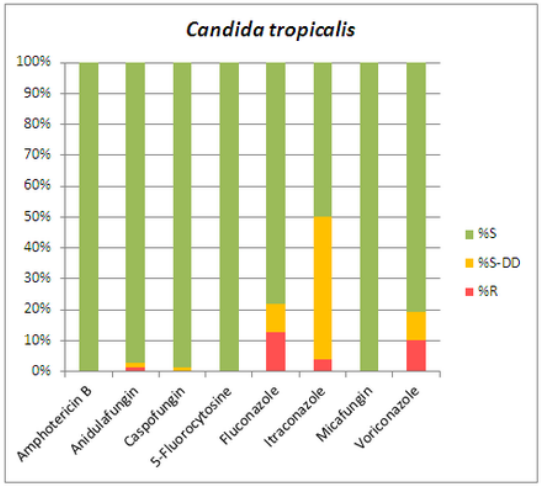
Tan TY., et al. Med Mycol 2016; 54: 417-7

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

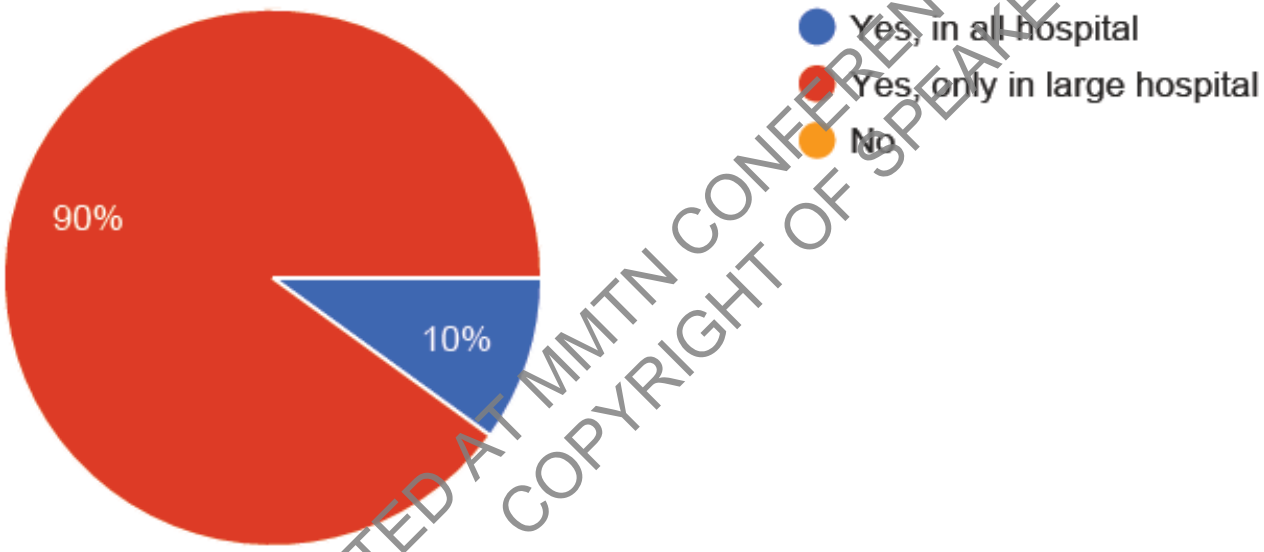
Modified from Clin Infect Dis 2009: 48:503-35

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

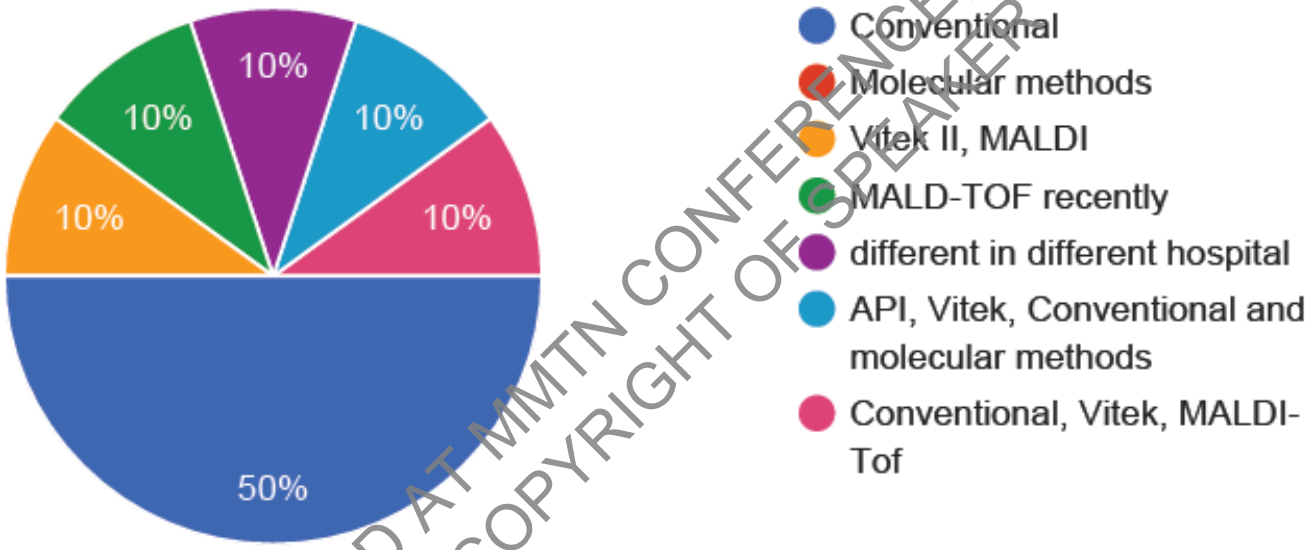
Identification of *Candida* into Species Level: Where we are?



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)

Antifungal Treatment of Invasive Candidiasis

IDSA 2016

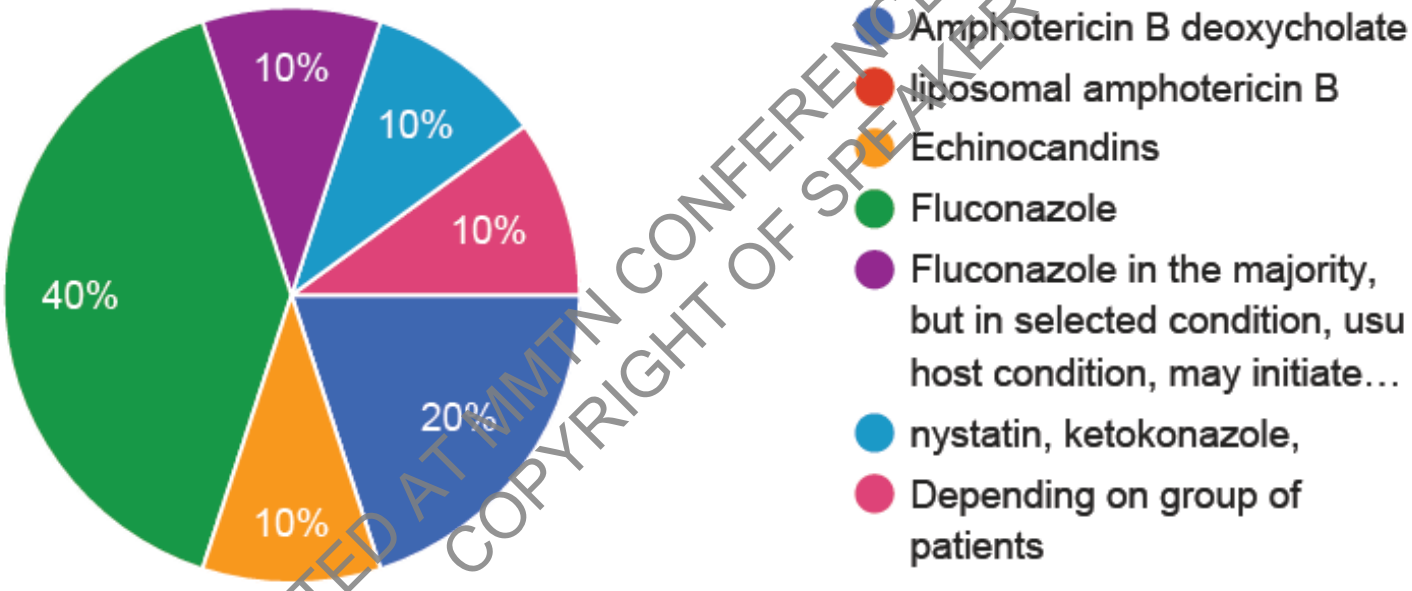
- **Echinocandins** - strong recommendation; high-quality evidence
- **Fluconazole** - strong recommendation; high-quality evidence in selected patients
  - Not critically ill
  - Unlikely fluconazole-resistant
- **Lipid amphotericin B** – strong recommendation; high-quality evidence for alternative
- **Voriconazole** - strong recommendation; moderate-quality evidence

ESCMID 2012

- **Echinocandins** – AI
- **Liposomal AM**B – BI
- **Voriconazole** – BI
- **Fluconazole** – CI

1. Pappas PG., et al. Clin Infect Dis 2016:15;62(4):e1-50
2. Cuenca-Estrella M. Clin Microbiol Infect 2012; 18(suppl7):9-18

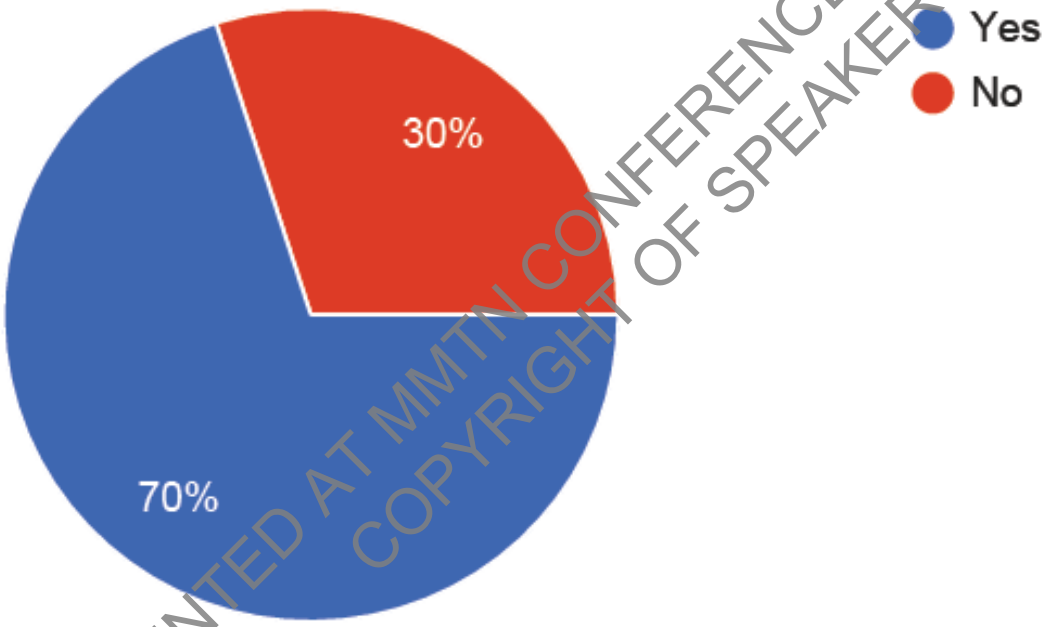
Empirical Antifungal Agents for Candidemia



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