Introduction to Medical Mycology

Cross Talk Between Bench side and Bedside

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ASIA FUNGAL WORKING GROUP an ISHAM working group

ISHAM INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

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Disclosures

- Has received research funds from the Ministry of Science and Technology, Taiwan; the Ministry of Health and Warfare, Taiwan; the National Health Research Institutes, Taiwan; National Taiwan University College of Medicine, Taiwan; the Industrial Technology Research Institute, Taiwan; and The University of Alabama for The University of Alabama at Birmingham, USA.
- Receive a grand for clinical trial sponsored by Taiwan Liposome Company, Ltd
- Has received honoraria for speaking or advisory board membership from Gilead, Pfizer, Merck, and Astellas,
- Has involved as a steering committee member of regional education programs from Gilead (Asia CARE) and Pfizer (ISHAM/AFWG/MMTN).

CARE: Continuing Antifungal Research & Education
ISHAM: the International Society for Human and Animal Mycology
MMTN: Medical Mycology Training Network.

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- Stop neglecting fungi
- Challenges – diagnosis
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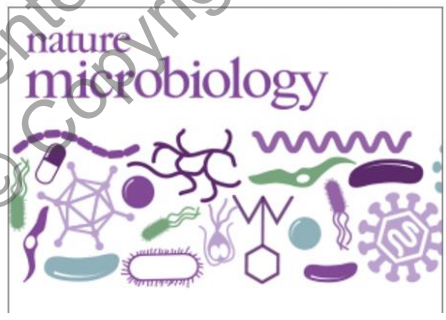
- Conclusion

PUBLISHED: 25 JULY 2017 | VOLUME: 2 | ARTICLE NUMBER: 17120

editorial

Stop neglecting fungi



Fungal pathogens are virtually ignored by the press, the public and funding bodies, despite posing a significant threat to public health, food biosecurity and biodiversity.

https://www.nature.com/articles/nmicrobiol2017120

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Stop neglecting fungi

Indeed, in comparison to the threat from drug-resistant bacterial infections or viral outbreaks, diseases caused by fungi, fungal drug resistance and the development of new antifungal therapeutics gets little coverage. Yet in this case, no news is certainly not good news, and the disparity relative to other infectious disease agents unjustified.

Has World Health Assembly (WHA) ever addressed fungal infection ?

WHO is afraid of fungus ISHAM 1 July 2018, Amstaerdam
Carmem Lúcia Pessoa-Silva, MD, PhD, WHO Antimicrobial Resistance Secretariat

WHA 1975 on mycotic diseases

WHA28.55 Mycotic diseases

The Twenty-eighth World Health Assembly,

Having examined the programme budget submitted by the Director-General for the financial years 1976 and 1977;

Noting with satisfaction the important place given in this programme budget to the control of communicable diseases in general;

Considering that superficial and deep mycotic infections are extremely widespread in both industrial and developing countries, and that they amount to an important medicosocial problem,

1. INVITES the health authorities of Member States to give mycotic infections the attention warranted by their prevalence and medicosocial importance;

2. REQUESTS the Director-General to provide assistance within the Organization's programmes to epidemiological studies on superficial and deep mycotic infections and to provide Member States with appropriate technical advice on their control; and

3. REQUESTS the Director-General to report to the Twenty-ninth World Health Assembly on the public health importance of mycotic diseases in WHO Member States.

Handb. Res., Vol. II, 1.8.3

Twelfth plenary meeting, 28 May 1975
(Committee A, first report)

World Health Assembly, 28. (1975). Mycotic diseases. World Health Organization. http://www.who.int/iris/handle/10665/92993

WHA 1976 on mycotic diseases

The Twenty-ninth World Health Assembly,

Thanking the Director-General for his report on mycotic diseases submitted in pursuance of resolution WHA28.55;

Noting with appreciation the contribution of governments in reporting on mycotic diseases in their respective countries;

Realizing the important place these diseases have in human pathology, in spite of the scarcity of data regarding their prevalence and incidence;

Stressing the fact that the control of some mycotic infections is feasible with the tools now available,

1. RECOMMENDS that Member States build up specialized expertise within their health services to enable an adequate assessment to be made of the prevalence and incidence of mycotic diseases and, subsequently, of their public health importance;

2. REQUESTS the Director-General:

(1) to assist Member States in training technical personnel for the application of available diagnostic and treatment procedures;

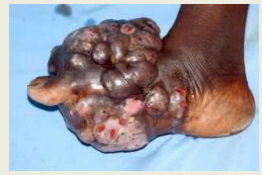
(2) to promote the establishment of an up-to-date nomenclature of mycotic disorders;

(3) to stimulate research on mycotic infections, with particular emphasis on simple diagnostic techniques and chemotherapy.

A29/B/SR/13 – 15 May 1976

WHO is afraid of fungus ISHAM 1 July 2018, Amsterdam
Carmem Lúcia Pessoa-Silva, MD, PhD, WHO Antimicrobial Resistance Secretariat

WHA 2016: resolution on mycetoma



SIXTY-NINTH WORLD HEALTH ASSEMBLY — WHA69.21

Agenda item 15.3 — 28 May 2016

Addressing the burden of mycetoma

The Sixty-ninth World Health Assembly,

Having considered the report on mycetoma,[1]

Deeply concerned about the impact of mycetoma, especially among children and young adults of working age, and the public health and socioeconomic burdens that the disease places on poor, rural communities;

Report of the Tenth Meeting of the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases

29–30 March 2017 WHO, Geneva

Recommendation:

Chromoblastomycosis to be added to the Neglected Tropical Diseases portfolio in category B together with mycetoma and other deep mycoses.

World Health Organization

WHO is afraid of fungus ISHAM 1 July 2018, Amstaerdam
Carmem Lúcia Pessoa-Silva, MD, PhD, WHO Antimicrobial Resistance Secretariat

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Global Surveillance of Antimicrobial Resistance Invasive *Candida* Infections

- On 24 April 2018, WHO organised a meeting on global surveillance of antimicrobial resistance invasive *Candida* infections.
- The Global Antimicrobial Resistance Surveillance System (GLASS) was launched in 2016 to support the efforts on implementation of the Global Action Plan on AMR. Although the GLASS early implementation phase focuses on bacterial infections in humans, it is recognized that the information gap in other types of AMR such as in invasive fungal infections must also be addressed.

World Health Organization

http://www.who.int/glass/events/AMR-in-invasive-candida-infections-meeting/en/

Few realize that over ?? people suffer from serious fungal-related diseases, or that fungi collectively kill over ?? people annually, which is ?? than malaria and ?? to the tuberculosis death toll.

The Burden of Fungal Disease (LIFE, 2017); http://go.nature.com/2sMKpuN

Few realize that over 300 million people suffer from serious fungal-related diseases, or that fungi collectively kill over 1.6 million people annually, which is more than malaria and similar to the tuberculosis death toll.

The Burden of Fungal Disease (LIFE, 2017); http://go.nature.com/2sMKpuN

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Hidden Killers: Human Fungal Infections

There are an estimated 1.5 million fungal species, of which 300 are known to be pathogenic to human.
Candida, *Aspergillus*, *Pneumocystis* and *Cryptococcus* spp. are the most common cause of serious disease in humans,

Infections primarily occur in immunocompromised patients, such as those undergoing chemotherapy or infected with HIV, and many are acquired in hospitals.
However, infections of otherwise healthy people are on the rise.
Global warming is inducing rapid poleward movement of crop fungal pathogens, and may also increase the prevalence of fungal disease in humans as fungi adapt to survival in warmer temperatures.

Hawksworth DL. Mycol Res 2001;105:1422
Garcia-Solache MA & Casadevall A. mBio 2010;1(1):e00061

Ten most significant invasive fungal infections

	Disease (most common species)	Location	Estimated life-threatening infections/ year at that location*	Mortality rates (% in infected populations)*
	Opportunistic invasive mycoses			
	Aspergillosis (*Aspergillus fumigatus*)	Worldwide	>200,000	30–95
	Candidiasis (*Candida albicans*)	Worldwide	>400,000	46–75
	Cryptococcosis (*Cryptococcus neoformans*)	Worldwide	>1,000,000	20–70
	Mucormycosis (*Rhizopus oryzae*)	Worldwide	>10,000	30–90
	Pneumocystis (*Pneumocystis jirovecii*)	Worldwide	>400,000	20–80
	Endemic dimorphic mycoses*†			
*	Blastomycosis (*Blastomyces dermatitidis*)	Midwestern and Atlantic United States	~3,000	<2–68
*	Coccidioidomycosis (*Coccidioides immitis*)	Southwestern United States	~25,000	<1–70
*	Histoplasmosis (*Histoplasma capsulatum*)	Midwestern United States	~25,000	28–50
	Paracoccidioidomycosis (*Paracoccidioides brasiliensis*)	Brazil	~4,000	5–27
	Penicilliosis (*Penicillium marneffei*)	Southeast Asia	>8,000	2–75

*Most of these figures are estimates based on available data, and the logic behind these estimates can be found in the text and in the Supplementary Materials. †Endemic dimorphic mycoses can occur at many locations throughout the world. However, data for most of those locations are severely limited. For these mycoses, we have estimated the infections per year and the mortality at a specific location, where the most data are available.

Impact of local epidemiology on global health:
Importation through travel, returned immigrants, global trade
International medicine, solid organ transplantation

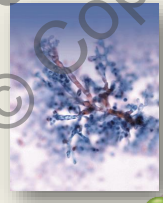
Brown GD, et al. Sci Transl Med. 2012;4;
More updated data: Bongomin F, et al. J Infect 2017;3:57

*** Biosafety level 2,3**

Challenges - diagnosis

✓**What the mind does not know, the eye does not see.**

✓**Expanded spectrum of opportunistic fungal pathogens**



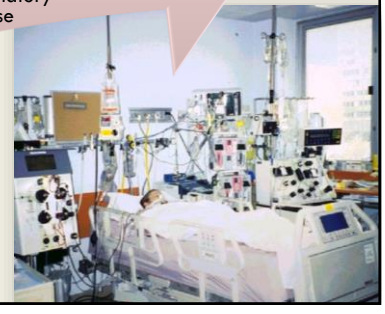
Entry

Proliferation

Tissue damage

Inflammatory response

Organ dysfunction



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Medical Mycology, 2017, 0, 1–10
doi: 10.1093/mmy/myx066
Advance Access Publication Date: 0 2017
Original Article

Original Article

Survey of laboratory practices for diagnosis of fungal infection in seven Asian countries: An Asia Fungal Working Group (AFWG) initiative

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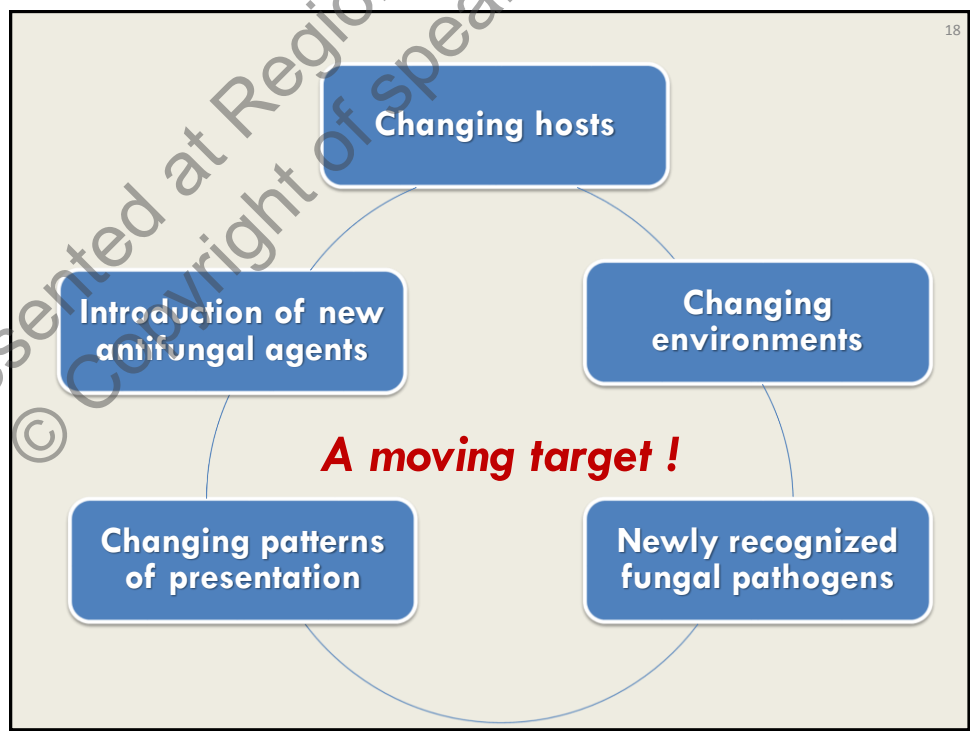

Call for Action

Clinical Infectious Diseases 2018; **66**: 140-148

VIEWPOINTS

Call for Action: Invasive Fungal Infections Associated With Ibrutinib and Other Small Molecule Kinase Inhibitors Targeting Immune Signaling Pathways

Georgios Chamilos,[1,2] Michail S. Lionakis,[3] and Dimitrios P. Kontoyiannis[4]

[1]Department of Clinical Microbiology and Microbial Pathogenesis, University of Crete, and [2]Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, Crete, Greece; [3]Fungal Pathogenesis Unit, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and [4]Department of Infectious Diseases, The University of Texas MD Anderson Cancer Center, Houston

Opportunistic infections caused by *Pneumocystis jirovecii*, *Cryptococcus neoformans*, and ubiquitous airborne filamentous fungi have been recently reported in patients with hematological cancers historically considered at low risk for invasive fungal infections (IFIs), after receipt of the Bruton tyrosine kinase inhibitor ibrutinib. The spectrum and severity of IFIs often observed in these patients implies the presence of a complex immunodeficiency that may not be solely attributed to mere inhibition of Bruton tyrosine kinase. In view of the surge in development of small molecule kinase inhibitors for treatment of malignant and autoimmune diseases, it is possible that there would be an emergence of IFIs associated with the effects of these molecules on the immune system. Preclinical assessment of the immunosuppressive effects of kinase inhibitors and human studies aimed at improving patient risk stratification for development of IFIs could lead to prevention, earlier diagnosis, and better outcomes in affected patients.

Importance of medical mycology

Purpose/benefit of better diagnoses

Individual level

- **Guide appropriate therapy**
  - This event: antimicrobial and surgical intervention,
  - For plan, time and regimen of underlying diseases
  - For secondary prophylaxis during the subsequent immunosuppressive status
- **To avoid unnecessary adverse effects**
  - Drug related toxicity
  - Delay in accurate diagnosis

Population level

- Epidemiology to improve knowledge of a specific disease
- Diagnosis and management guidelines
- Antimicrobial stewardship to combating drug resistance
- Healthcare policy including health insurance coverage
- Public awareness and resource allocation
- Outbreak investigation

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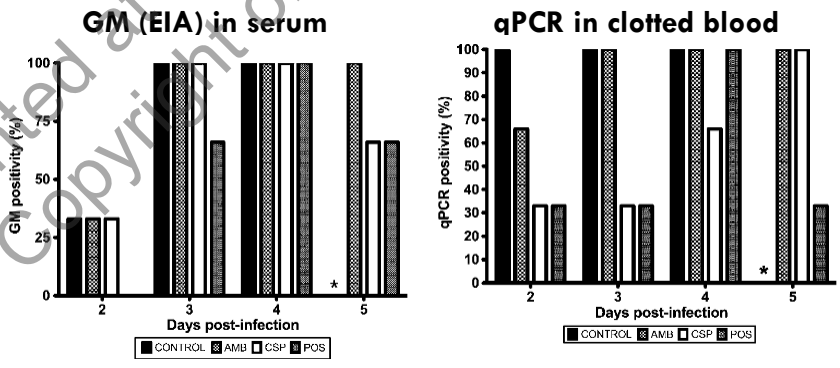
Aggressive and timely diagnostic approaches are important

- Every effort should be made to determine whether invasive fungal diseases exists before empirical antifungal therapy is started
  - Biopsy of lesions, radiographs of chest and sinuses, nasal endoscopy if indicated, cultures and CT of the abdomen and chest
- The empirical decision to start use of the drug is not as difficult as the decision to discontinue use of the drug.
- Much of the evaluation at this time is to aid in a decision about how to modify (or deescalate) antimicrobial agents, when to stop antifungal treatment later, or secondary prophylaxis in the future.

Modified from Hughes et al. Clin Infect Dis 2002;34:730

Effect of anti-mold treatment on biomarkers



- Regardless of how well optimized a diagnostic test the appropriateness of the clinical samples taken and the stage of infection is key to meaningful diagnostic results.

Rat models. McCulloch E et al. Clin Pathol 2012;65
GM, galatomanna; AMB, amphotericin B; CSP, caspofungin; POS, posaconazole

Key for better yield

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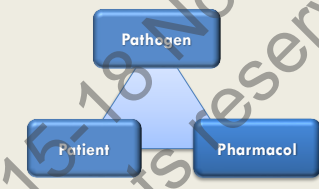
Diagnostic Approaches

1. **Localize its presence and significance**
    1. Image
    2. Histopathology: invasiveness, colonization or contamination
2. **Detect and identify to species complex level**
3. **Pharmacokinetic & -dynamic issues**
    1. In vitro susceptibility testing
    2. Therapeutic drug monitoring
    3. Serum fungicidal activity
4. **Host response and prognosis**
5. **Monitor response**



YC Chen's wish list

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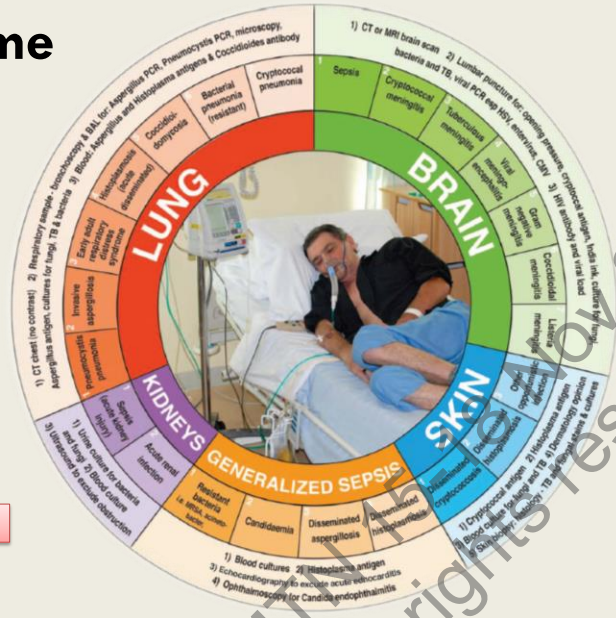
Laboratory Diagnostic Methods for invasive fungal diseases

- **Conventional microbiologic methods**
- **Histopathologic methods**
- **Immunologic and biochemical methods**
- **Molecular methods**
- **Others**

Clin Microbiol Rev 2014;27:490; Lancet Infect Dis 2005;5: 609; Clin Infect Dis. 2006;43(Suppl1):S15; Posch W et al. Invasive candidiasis: future directions in non-culture based diagnosis. Expert Rev Anti Infect Ther 2017 Sep;15(9):829-838; Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clinical Microbiology and Infection 2018;24(Supplement 1):e1-e38

Sampling strategies based on syndrome



Key for better yield

Sci Transl Med 2012;4

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Sampling strategies based on pathogenesis of invasive pulmonary aspergillosis

Pathogenesis

- Inhalation
  Respiratory tract
- Tissue invasion and damage
  Sinus and lung
- Blood
  Dissemination to non-contiguous sites (liver, spleen, kidney, CNS…….)

Sampling strategies

- Sputum
  Bronchoalveolar lavage
- Fine needle aspiration
  Open biopsy
- Blood (culture, antigen, PCR)

Hope et al. Lancet Infect Dis 2005; 5: 609–22

Key for better yield

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Several molds have hyphal forms in tissue indistinguishable from those of *Aspergillus* spp

- The microscopic appearance of the hyphae of hyaline hyphomycetes in tissue are very similar
  - e.g., *Aspergillus, Scedosporium* spp, *Fusarium* spp, *Paecilomyces* spp, *Geotrichum candidum*, *Acremonium* spp, *Scopulariopsis* spp, *Penicillium* spp, *Schizophyllum commune*
- Knowing which specific pathogen is present is important because fungi vary in their antifungal susceptibility profiles
  - *Aspergillus terreus, Scedosporium apiospermum* (*Pseudallescheria boydii*), and *Scopulariopsis* spp resistant to amphotericin B

Denning DW et al. Lancet InfectiDis 2003;3:230-40.

Appearances may differ slightly after antifungal treatment

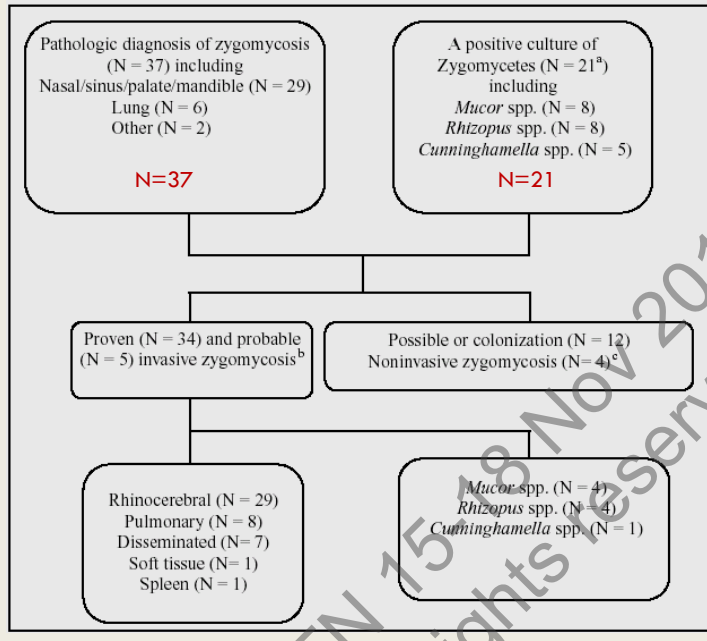
- Bulbous ends are typical of *Scedosporium apiospermum* (which is resistant to amphotericin B) and should be described if seen
- Treatment with echinocandins may yield such structures in *Aspergillus* spp.

Denning DW et al. Lancet Infecti Dis 2003;3:230-40.

Rhizopus spp.

Mucor spp.

Cunninghamella spp.



Wang JL et al. Diagnostic challenge of zygomycosis in compromised hosts. Med Mycol 2006;44;19

Low yield rate of mucormycosis isolation

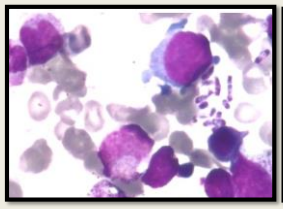
- Mucorales are particularly susceptible to chilling in the refrigerator, and the potential yield may fall with temporary storage of the sample.
- They can also be damaged by tissue homogenisation and fail to grow.
- Thus the only means of establishing a causal diagnosis (aside from biopsy or autopsy) is microscopy.

Key for better yield

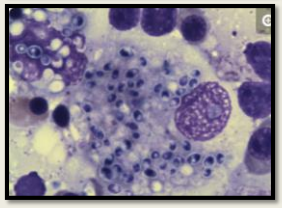
Denning DW et al. Lancet InfectiDis 2003;3:230-40.

Fungemia = candidemia ??

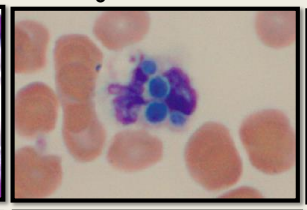
HIV
Bone marrow aspirate
Penicillium marneffei [1]



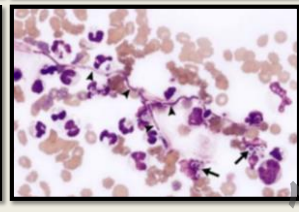
Histoplasma capsulatum [2]
HIV



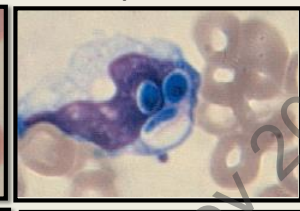
Short bowel syndrome
Peripheral blood smear
Candida glabrata [3]

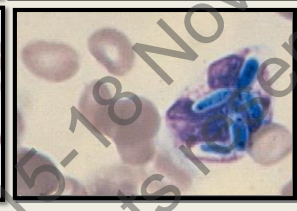


Candida albicans [4]
Premature NB



AML, neutropenic
Intracellular
Candida tropicalis [5]





[1] Blood. 2014;124:1689; [2] 2014;123:957; [3] 2012;119:1105; [4] N Engl J Med. 2005;353:e9; [5] 感謝和信醫院 施長慶主任提供

ORIGINAL ARTICLE

WILEY mycoses

The epidemiology of non-*Candida* yeast isolated from blood: The Asia Surveillance Study

Shang-Yi Lin[1,2,3,4] | Po-Liang Lu[1,2,3] | Ban Hock Tan[5] | Arunaloke Chakrabarti[6] | Un-In Wu[7] | Jui-Hsuan Yang[7] | Atul K. Patel[8] | Ruo Yu Li[9] | Siriorn P. Watcharananan[10] | Zhengyin Liu[11] | Ariya Chindamporn[12] | Ai Ling Tan[13] | Pei-Lun Sun[14,15] | Li-Yin Hsu[7,16] | Yee-Chun Chen[7,17] | on behalf of the Asia Fungal Working Group (AFWG)*

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Shang-Yi Lin, et al. Mycoses 2018 Sep 19. doi: 10.1111/myc.12852

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The epidemiology of non-*Candida* yeasts isolated from blood

- Current guidelines recommend echinocandins as first-line therapy for candidemia. However, several non-*Candida* yeasts are non-susceptible to echinocandins (echinocandin non-susceptible yeast, ENSY), including *Cryptococcus, Geotrichum, Malassezia, Pseudozyma, Rhodotorula, Saprochaete, Sporobolomyces,* and *Trichosporon*.
- In laboratories that are not equipped with rapid diagnostic tools, it often takes several days to identify yeasts, and this may lead to inappropriate presumptive use of echinocandins in patients with ENSY fungemia.

Shang-Yi Lin, et al. Mycoses 2018 Sep 19. doi: 10.1111/myc.12852

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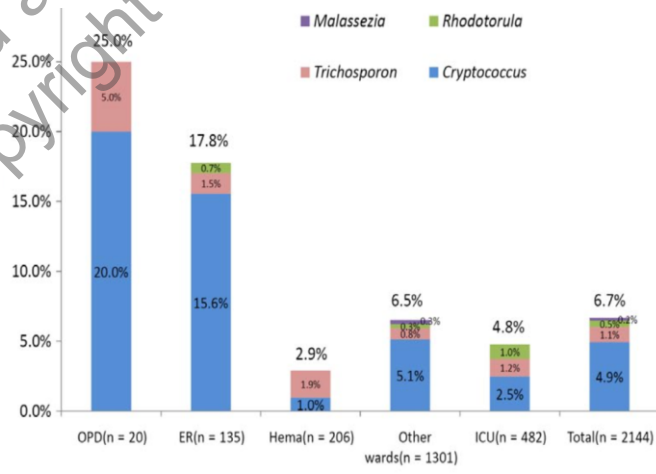
Yeasts isolated from blood and bone marrow specimens that were intrinsically resistant or had a high probability of non-susceptibility to echinocandins by hospital services



Shang-Yi Lin, et al. Mycoses 2018 Sep 19. doi: 10.1111/myc.12852

Changing Patterns of Cryptococcosis, NTUH

	1982-1997[a] (N=59)		1957-1972[b] (N=51)	
Sources of positive cultures	87		59	
CSF	36	41.4%	37	62.7%
Blood or bone marrow	29	33.3%	8	13.6%
Sputum, pleural effusion, lung tissues	9	10.3%	5	8.5%
Underlying diseases/intervention				
T cell dysfunction	33	55.9%	3	5.9%
Immunocompetent hosts	26	44.1%	48	94.1%

a. Chen et al. Diagn Microbiol Infect Dis 2000; b. Fan et al., J Formos Med Assoc 1974

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One Size not Fit All - Usual susceptibility patterns for fungal pathogens

Species	Amphotericin B	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Echinocandins
C. albicans	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S[b]
C. glabrata	S, R	SDD, R[c]	SDD, R[d]	S[b]	S[b]	S
C. krusei	S, R	R	SDD, R[d]	S[b]	S[b]	S
C. lusitaniae	S, R[e]	S	S	S	S	S
C. guilliermondii	S, R	S, SDD	S	S		R
C. dubliniensis	S, R[b]	S, SDD, R	S	S		S
Trichosporon spp.	S, R	S, SDD, R	S, SDD	S		R
Blastoschizomyces	S, R	S, SDD, R	S, SDD	S		R
Malassezia spp.	S, R	S	S	S		ND
Rhodotorula spp.	S	S, SDD	S, SDD	S, SDD		R
Cryptococcus spp.	S	S, SDD	S	S	S	R
A. fumigatus	S	R	S, R	S	S	S
A. terreus	R	R	S	S	S	S
A. niger	S	R	S	S	S	S
A. flavus	S	R	S	S	S	S
Fusarium solani	R	R	R	S	S	R
S. apiospermum	R	R	R	S	S	S
S. prolificans	R	R	R	R	R	R
Zygomycetes	S	R	R	R	S ★	R

Notes: [a]S, susceptible; I, intermediate; R, resistant; SDD, susceptibility depends on the dose; ND, no data. [b]Susceptible, but few clinical data are available. [c]10%–15% of *C. glabrata* isolates are resistant to fluconazole. [d]Resistant to itraconazole ~50% and ~30% of *C. glabrata* and *C. krusei* isolates, respectively. [e]20% of isolates are resistant to amphotericin B.

Modified from Zaragoza et al. Ther Clin Risk Manag. 2008;4:1261–80

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Review Article

Are we ready for the global emergence of multidrug-resistant *Candida auris* in Taiwan?

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Essential elements for better diagnosis

6A in an ideal scenario

1. Be aware of the risk
2. Be alert when it occurs
3. Be accessible to tests needed
4. Samples adequate for tests
5. Results available timely
6. Be affordable

*Sensitive, specific, accuracy, clinical relevant

YC Chen's personal opinion

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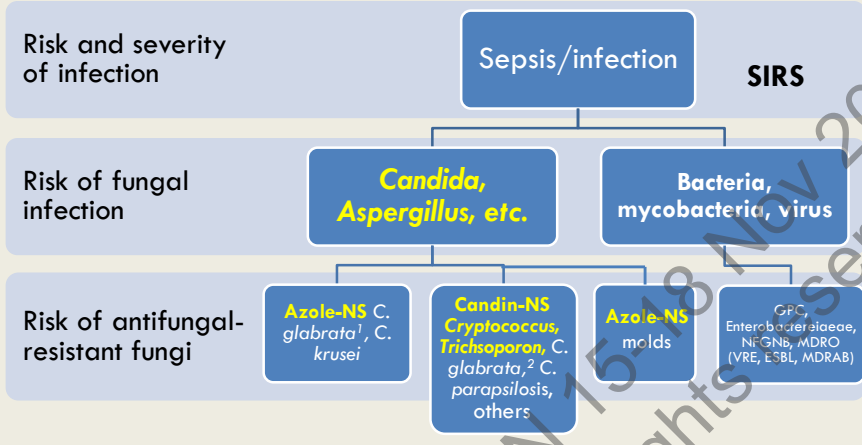
Concept Maps Related to Considerations of Antifungal Therapy for Invasive Fungal Diseases



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Practical considerations for individualized selection of antifungal agents

	Factors	Setting	Agent of choice, alternatives, and route
1	**Host-related**		
	Hemodynamic instability	Hematogenous candidiasis	Echinocandin; fluconazole and L-AMB as alternatives
	Organ dysfunction, severe		
	Gastrointestinal tract	Mucositis, nausea, vomiting, diarrhea, poor adherence, drug-food interaction	IV route
	Kidneys	Tumor lysis syndrome	Azoles, echinocandin; avoid amphotericin B products
	Liver		Echinocandin, L-AMB, ABLC; avoid azoles
4	**Drug-related**		
	Drug-drug interaction	Chemotherapy administration	Echinocandin, L-AMB, ABLC; avoid mold-active triazoles
	Drug-food interaction	Food intake	Echinocandin, L-AMB, fluconazole IV; food intake may alter absorption of azoles
	Breakthrough infection	Infection while on antifungal agent	Use different class of antifungal agents
	Cost and convenience	Outpatient setting	Oral route always preferable to IV if gut function intact Select agent with longest dosing interval
3	**Infection-related**		
	Site of infection	Urinary	Fluconazole: only agent with urinary concentrations
		Ocular	Triazoles, L-AMB; avoid echinocandins (poor distribution)
		CNS	Triazoles, L-AMB; avoid echinocandins (poor distribution)
2	**Pathogen**		
	Candida species	Disseminated, acute and chronic	Echinocandin, fluconazole, L-AMB
	C krusei	Disseminated, acute and chronic	Echinocandin, L-AMB; avoid fluconazole
	C glabrata	Disseminated, acute and chronic	Echinocandin, L-AMB, voriconazole; avoid fluconazole
	C parapsilosis	Disseminated, acute and chronic	L-AMB, voriconazole; avoid echinocandins
	Trichosporon spp	Disseminated, acute and chronic	Fluconazole, other azoles; amphotericin B not effective
	Aspergillus spp	Sinus, pulmonary, disseminated	Voriconazole, L-AMB, ABLC; no role for fluconazole
	Aspergillus flavus	Sinus, pulmonary, disseminated	Voriconazole; posaconazole alternative
	Fusarium spp	Sinus, pulmonary, cellulitis, disseminated	L-AMB, ABLC; voriconazole maintenance if susceptible
	Scedosporium apiospermum	Sinus, pulmonary, ocular, CNS, bone and soft tissues, disseminated	Voriconazole; posaconazole alternative
	Black molds	Various sites	Voriconazole; posaconazole alternative
	Agents of mucormycosis	Sinus, pulmonary, disseminated	L-AMB, ABLC; posaconazole maintenance if susceptible

M Nucci & E Anaissie. Blood 2014;124:3858

Diagnosis!!