

MMTN

Best Practices in Antifungal Management

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

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

Best Practices in Antifungal Management

- Improve outcomes
- Decrease costs (and/or drug related toxicity)
- Curb increases in antifungal resistance

Faster, simpler, more efficient

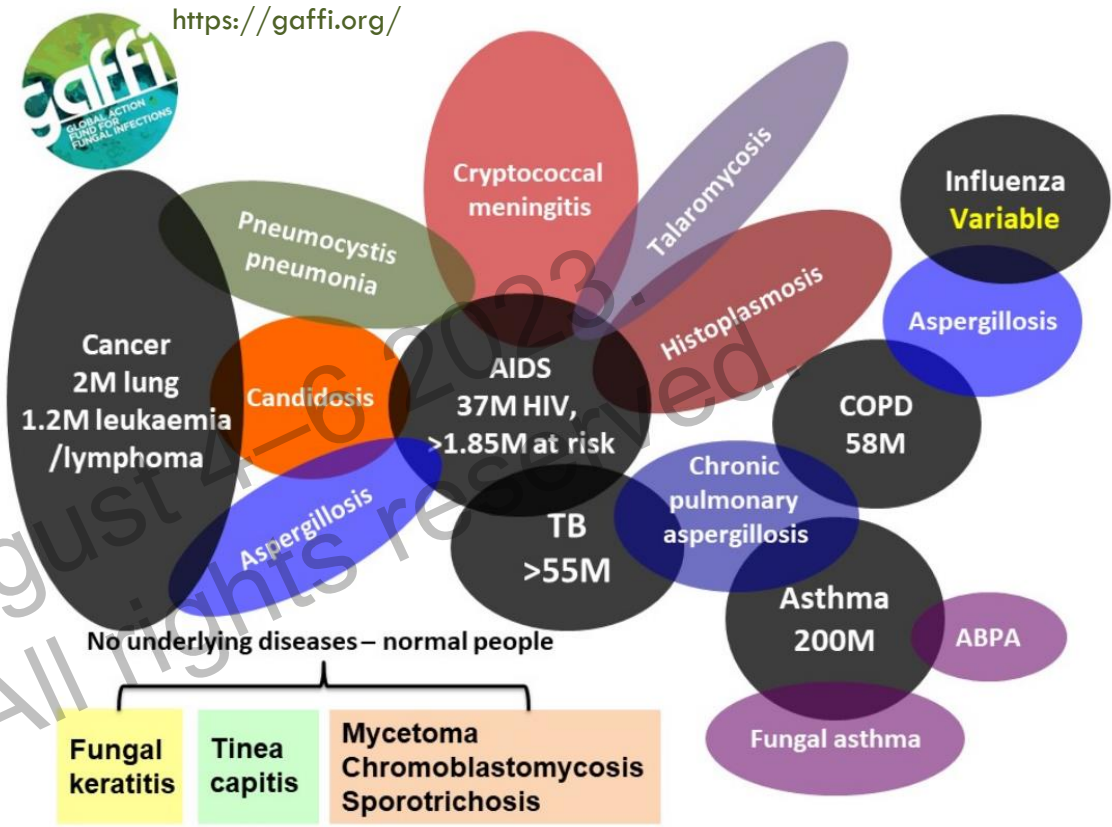
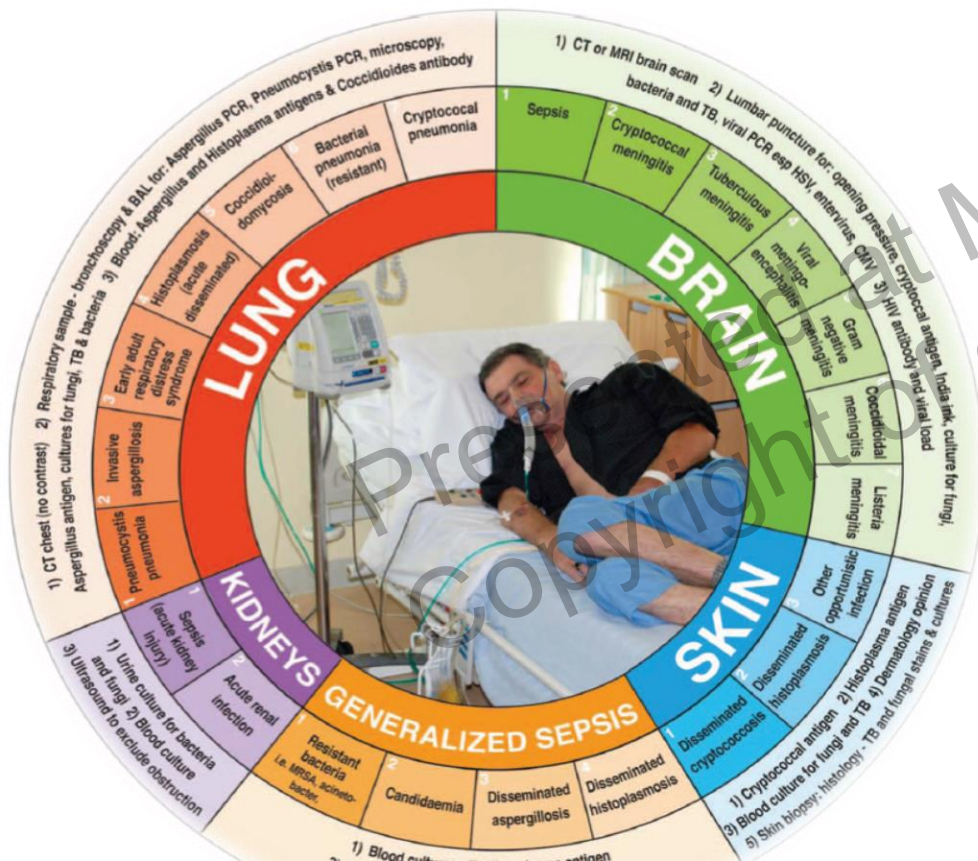


The Hidden Killers

Over 300 million people suffer from serious fungal-related diseases.

Fungi kill over 1.6 million people annually, which is more than malaria and similar to the tuberculosis death toll.

150 people die every hour.....



Expanded spectrum of population at risk
 Various presentation
 The diagnostic dilemma
 Expanded spectrum of fungal pathogens

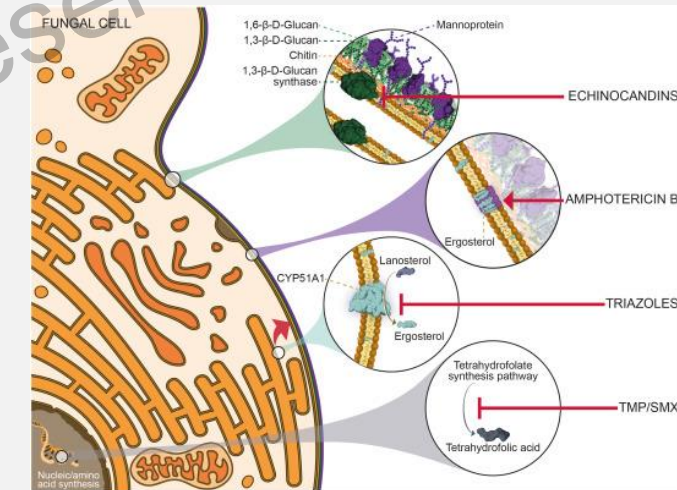
Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; CPA, chronic pulmonary aspergillosis; Crypto, cryptococcosis; Histo, histoplasmosis; IA, invasive aspergillosis; IC, invasive candidiasis; PCP, Pneumocystis pneumonia; SAFS, severe asthma with fungal sensitization; TB, tuberculosis. <https://gaffi.org/why/fungal-disease-frequency>; The Burden of Fungal Disease (LIFE, 2017); <http://go.nature.com/2sMKpuN>; Brown GD, et al. Sci Transl Med. 2012;4:165rv13; Bongomin F, et al. J Fungi (Basel). 2017;3:57; Lancet Infect Dis 2018; 18: 1150

Unmet Medical Needs

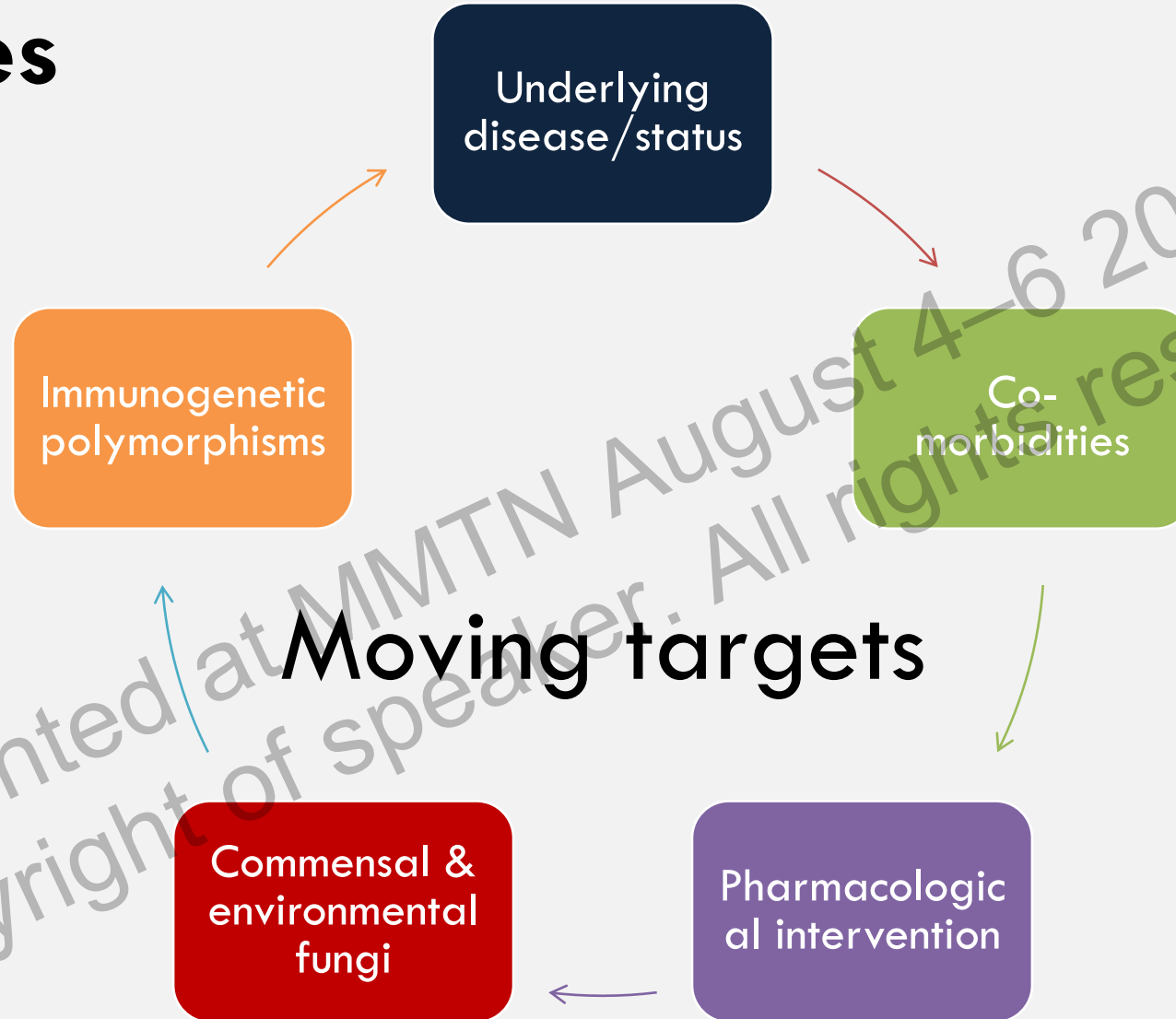
- Substantial or increased burdens (incidence/mortality/morbidity) of invasive fungal diseases due to the growing pool and higher survival of susceptible populations, etc.
- Existing treatment options are limited and emergence of antifungal resistance
 - Few antifungal families/targets of action, cross resistance
 - Efficacies vary depending on the infecting species
 - Drug-drug interaction, tissue penetration, and other pharmacokinetic and –dynamic considerations
- Gap exists in real world daily practice
 - Chindamporn A, et al. Survey of laboratory practices for diagnosis of fungal infection in seven Asian countries – an Asia Fungal Working Group (AFWG) initiative. *Med Mycol* 2018;
 - Tan BH, et al. Clinicians' challenges in managing patients with invasive fungal diseases in seven Asian countries: An Asia Fungal Working Group (AFWG) Survey. *Int J Infect Dis.* 2020;



Webinar, May 26, 2023 <https://msgerc.org/>



Challenges



Presented at MMTN August 4-6 2023.
Copyright of speaker. All rights reserved.

Principles of precision medicine

Diseases
對症下藥

Personalized
因人而異



Etiology
究因解決

Time matter
因時制宜

The continuum of invasive fungal disease

From colonization, infection, to invasive disease

At risk

Symptoms & Signs

Full-blown disease

Sequelae

Prevention

**Modify
risk factors**

Detection

Identify risk factors

Diagnostic approach (strategy, detection, identification)

Interpretation and decision making

Intervention (antifungal strategy/regimen)

Determine antifungal strategy

Selection of antifungal agent

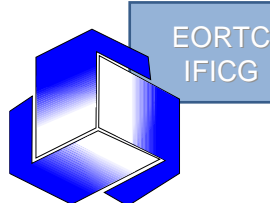
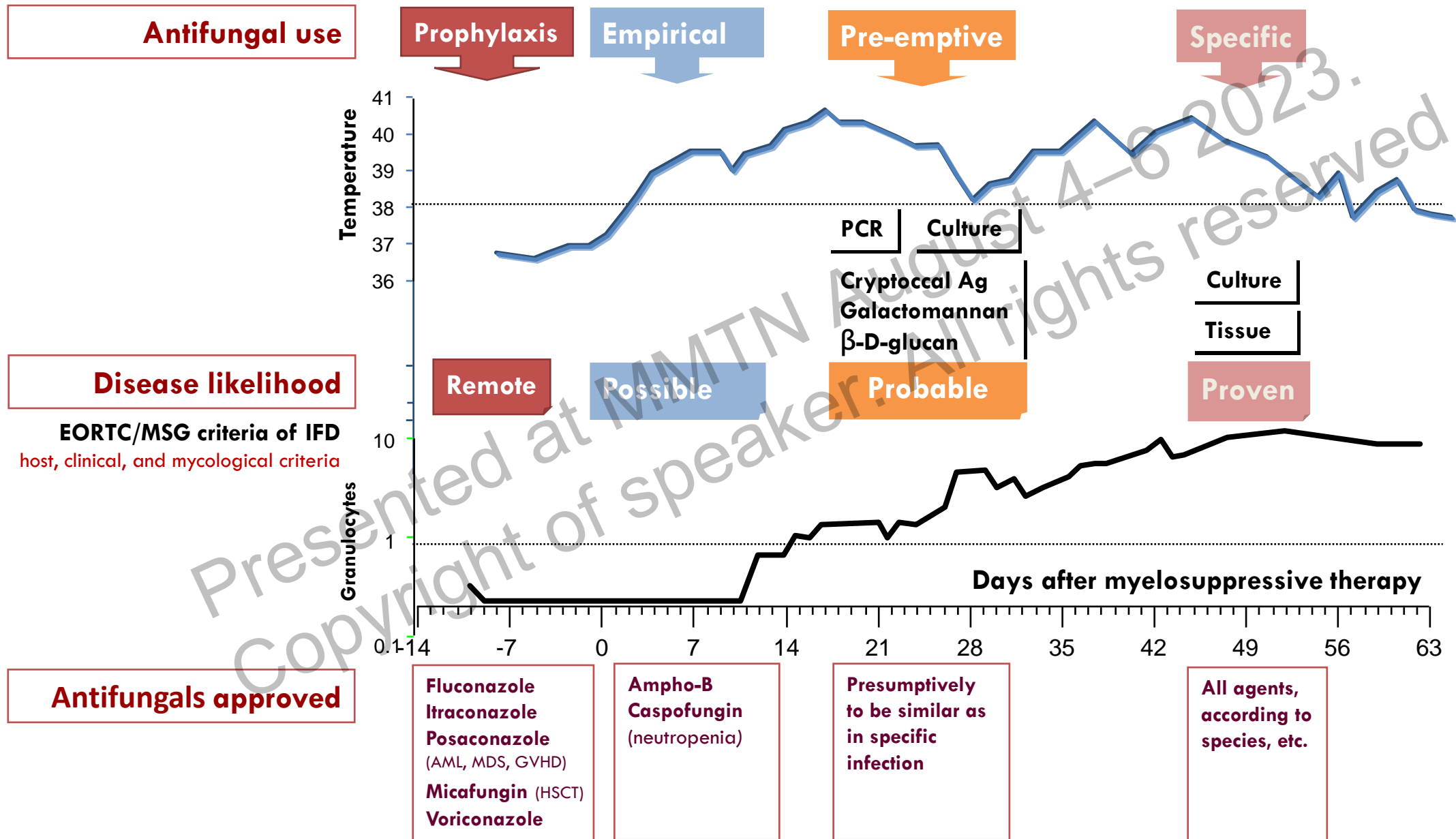
Re-assess and modify (discontinue, step-down, transit agent)

Determine duration of therapy

Evidence-based practice

- J Peter Donnelly et al. Revision and Update of the Consensus **Definitions** of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis* 2020
 - Bassetti M, et al. EORTC/MSGERC Definitions of Invasive Fungal Diseases: Summary of Activities of the Intensive Care Unit Working Group. *Clin Infect Dis*. 2021
 - Alexander BD, et al. Guidance on Imaging for Invasive Pulmonary Aspergillosis and Mucormycosis: From the Imaging Working Group for the Revision and Update of the Consensus Definitions of Fungal Disease from the EORTC/MSGERC. *Clin Infect Dis*. 2021
- Pappas PG, et al. Clinical Practice Guideline for the Management of **Candidiasis**: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016
- Patterson TF , et al. Practice Guidelines for the Diagnosis and Management of **Aspergillosis**: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016;63
- Chen SC, et al. Global guideline for the diagnosis and management of rare **yeast** infections: an initiative of the ECMM in cooperation with ISHAM and ASM. *Lancet Infect Dis*. 2021
- Hoenigl M , et al. Global guideline for the diagnosis and management of rare **mould** infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and the American Society for Microbiology. *Lancet Infect Dis*. 2021
- Thompson GR 3rd, et al. Global guideline for the diagnosis and management of the **endemic** mycoses: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology. *Lancet Infect Dis*. 2021
-
-

Integrated diagnostic and antifungal strategy



J Peter Donnelly et al
Clin Infect Dis
2020;71:1367

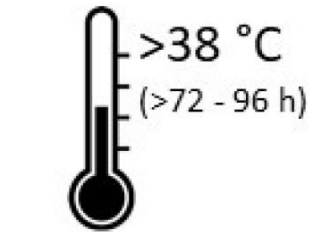
Antifungal strategies and number-needed-to-treat

Prophylaxis

No signs and symptoms of IFD



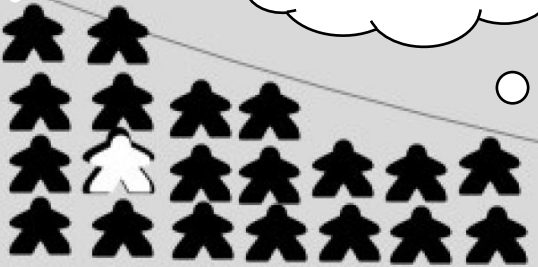
Empirical Therapy



Neutropenia

not infected

infected



Pre-emptive Therapy



Neutropenia

+

Suggestive imaging



and/or galactomannan



Documented Infection

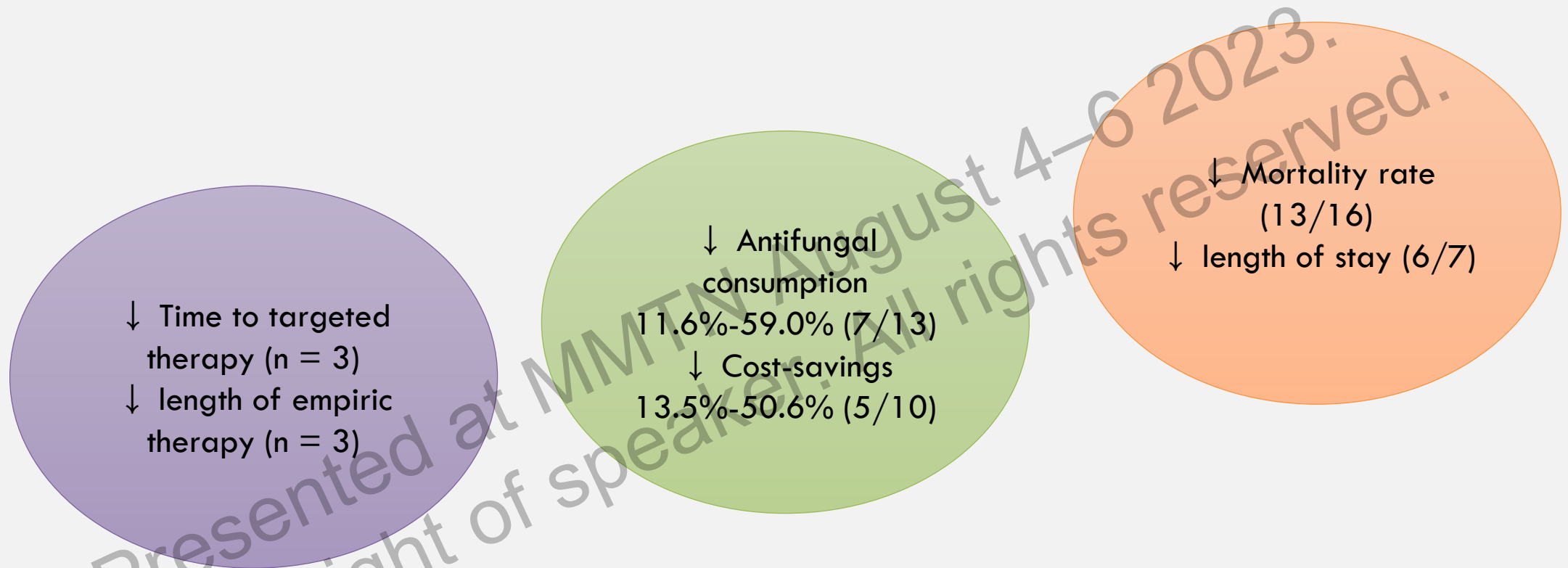


Histology

J. Fungi 2023, 9, 387.



Diagnostics-Driven Antifungal Stewardship



- Most eligible studies were from Europe and the United States (n = 12/17).
- Diagnostic approaches included serum β -1-3-D-glucan test (n/N studies, 7/17), galactomannan test (4/17), computed tomography scan (3/17), magnetic resonance (2/17), matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS; 2/17), polymerase chain reaction (1/17), peptide nucleic acid fluorescent in situ hybridization (PNA-FISH) assay (1/17), and other routine methods (9/17).

Chakrabarti A, et al. Open Forum Infect Dis. 2022;9:ofac234.

Unmet needs and practical solutions in the management of invasive mould infections in Asia

Yee-Chun Chen¹, Methee Chayakulkeeree², Arunaloke Chakrabarti^{3,4*}, Gin Gin Gan⁵, Yok Lam Kwong⁶, Wei-Lun Liu^{7,8}, Ban Hock Tan⁹ and Subhash Todi¹⁰

¹Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; ²Division of Infectious Diseases and Tropical Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; ³Department of Medical Microbiology, Postgraduate Institute of Medical Education & Research, Chandigarh, India; ⁴Doodhadhari Burfani Hospital and Research Institute, Haridwar, India; ⁵Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; ⁶Division of Haematology, Oncology and Bone Marrow Transplantation, University of Hong Kong, Pokfulam, Hong Kong; ⁷School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei, Taiwan; ⁸Division of Critical Care Medicine, Department of Emergency and Critical Care Medicine, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei, Taiwan; ⁹Department of Infectious Diseases, Singapore General Hospital Singapore 169608, Singapore; ¹⁰Critical Care and Emergency Medicine, AMRI Hospitals, Kolkata, India



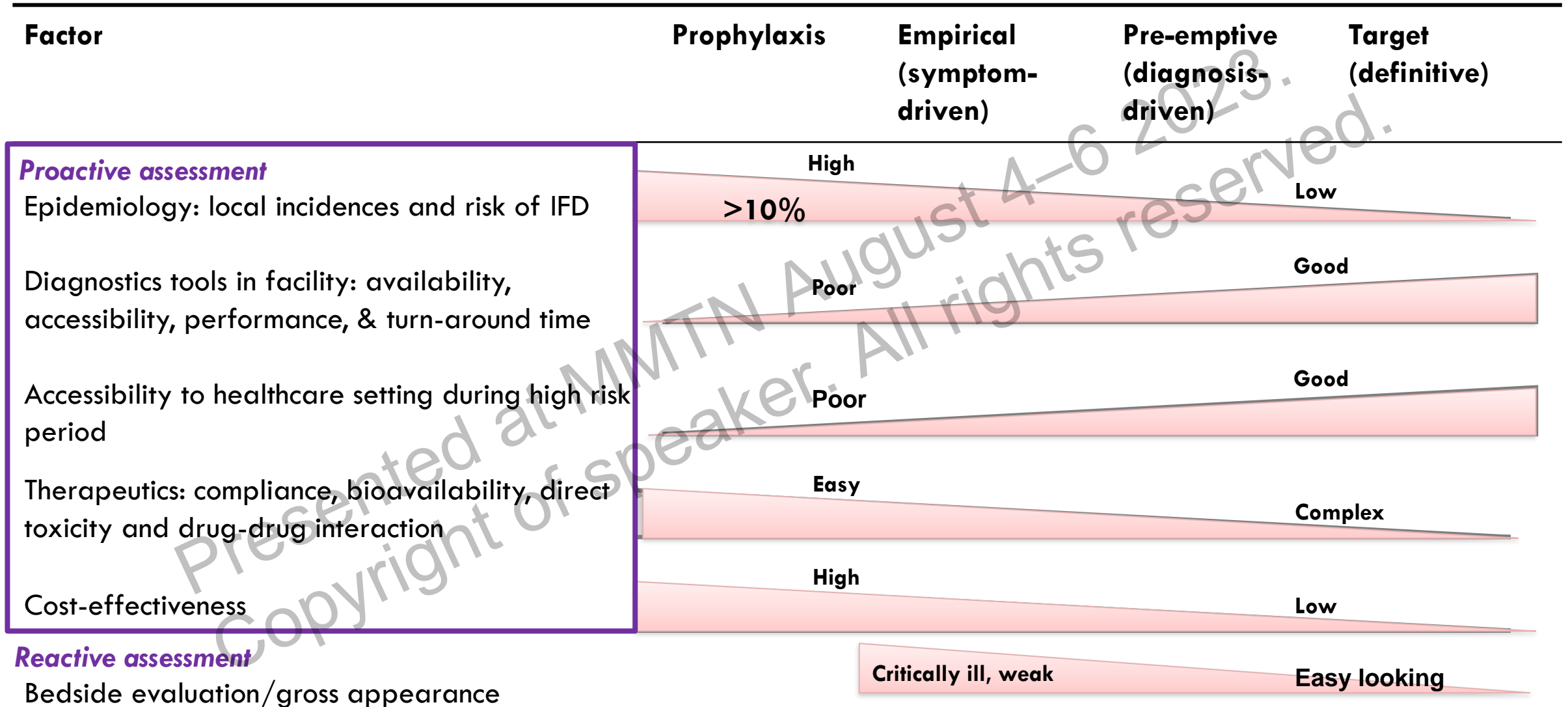
Pros and cons of selected diagnostic tools for invasive mold diseases

Diagnostic method	Pros	Cons
Galactomannan	<ul style="list-style-type: none"> Allows early diagnosis of IA Rapid Specific to <i>Aspergillus</i> Can be tested on blood, BALF and other fluids 	<ul style="list-style-type: none"> Lack of sensitivity Variable clinical performance
β -D-glucan	<ul style="list-style-type: none"> Rapid Can be tested on blood, BALF and other fluids 	<ul style="list-style-type: none"> Lack of sensitivity Lack of specificity
Lateral flow assay	<ul style="list-style-type: none"> Rapid Economical Simple to use at POC Can be tested on blood, BALF and other fluids Can detect antigens or antibodies 	<ul style="list-style-type: none"> Confirm with other diagnostics More data needed Limited commercial availability
PCR	<ul style="list-style-type: none"> Specific Rapid Range of genetic targets (mitochondrial DNA, ribosomal DNA and RNA) Identifies pathogenic species 	<ul style="list-style-type: none"> False negatives due to suboptimal extraction of fungal DNA from clinical samples False positives due to contamination
Bronchoscopy	Sensitive	Invasive
Lung biopsy		Risk to patient
Bronchoalveolar lavage	Sensitive	Invasive
		Risk to patient
Direct microscopy and histopathology	<ul style="list-style-type: none"> Inexpensive Proven diagnosis Phenotypic species identification 	<ul style="list-style-type: none"> Low sensitivity Slow turnaround time Invasive patient specimens Dependent on laboratory expertise
Fungal blood cultures	<ul style="list-style-type: none"> Non-invasive Specific 'Gold standard' for proven diagnosis 	<ul style="list-style-type: none"> Prolonged incubation and turnaround time Lack of sensitivity, especially in early phases Positive blood cultures are rare for patients with angioinvasive fungal infections
MALDI-TOF MS	<ul style="list-style-type: none"> Rapid Specific Inexpensive Easy to perform Identifies pathogenic species 	<ul style="list-style-type: none"> Large capital investment in equipment and databases Technology needs optimizing

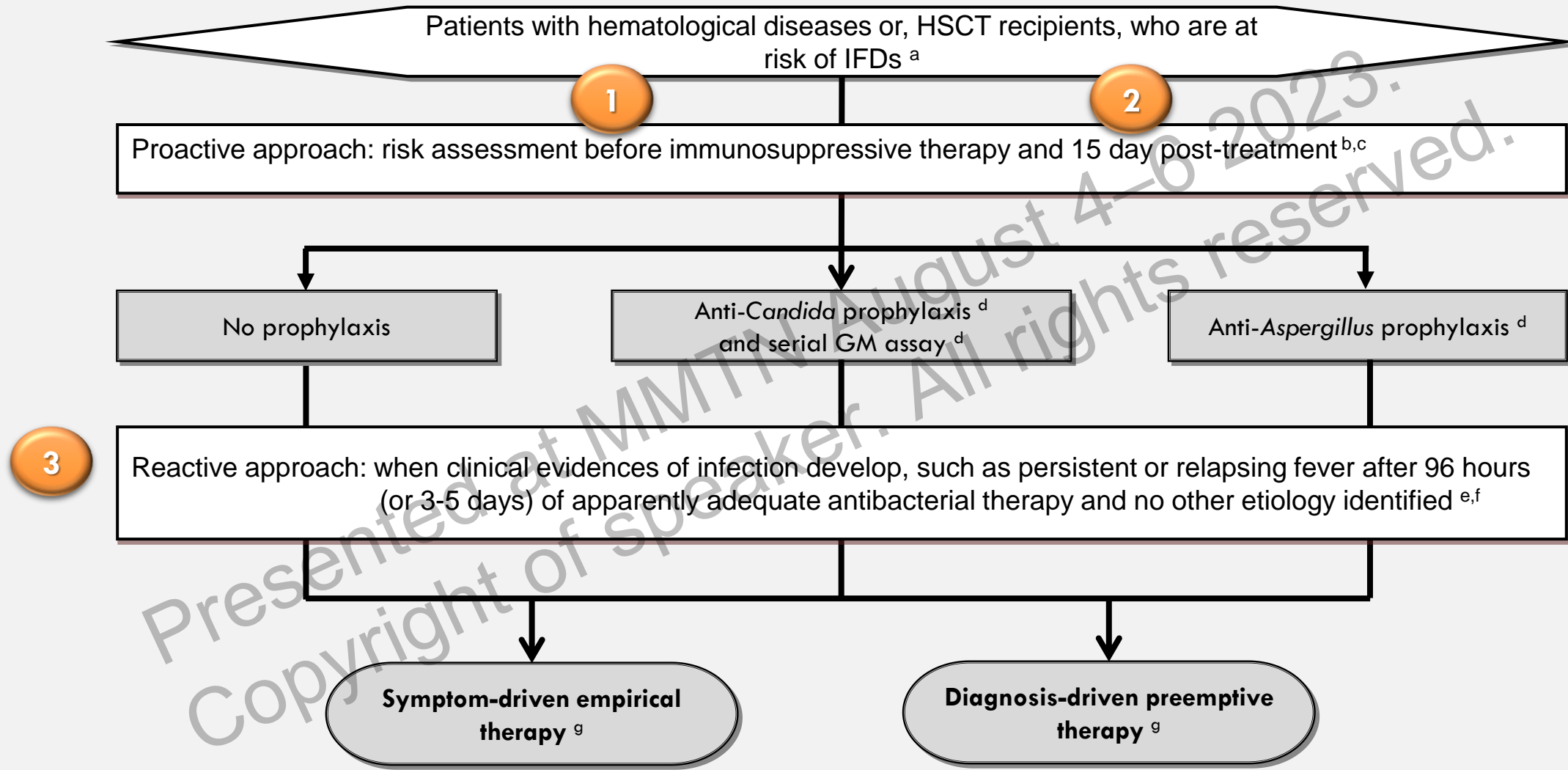
Chen YC, et al. Unmet needs and practical solutions in the management of invasive mould infections in Asia. *J Antimicrob Chemother.* 2022;77:2579

BALF, bronchoalveolar lavage fluid; POC, point-of-care.

Selection of antifungal strategy



A risk-adapted and dynamic antifungal strategy



Pretreatment risks assessment for IFDs

Immunogenetic status

Toll-like receptors polymorphism
C-type lectin receptor polymorphism
Mannose binding lectin polymorphism
Plasminogen polymorphism
Pentraxin-3 gene polymorphism
Others

Underlying conditions & pharmacological intervention

Neutropenia
Progressive cancer
GvHD
Anticancer chemotherapy
Steroids
T-cell suppressors

Primary diseases

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

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

Environmental factors

Co-morbidities & other factors

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

Environmental risk factors for mould-related diseases in immunocompromised patients

- ✓ Risk assessment
- ✓ Patient education

Seasonal incidence

Weather variation

temperature

rainfall

humidity

wind speed

Personal habits

smoking

living in countryside

fungus exposure

type of work (e.g. farmer, agriculture)

Exposure outside

pets

dusty household

construction work

Exposure inside

potted plants

absence of HEPA-filtered rooms

water

HEPA, high-efficiency particulate air.

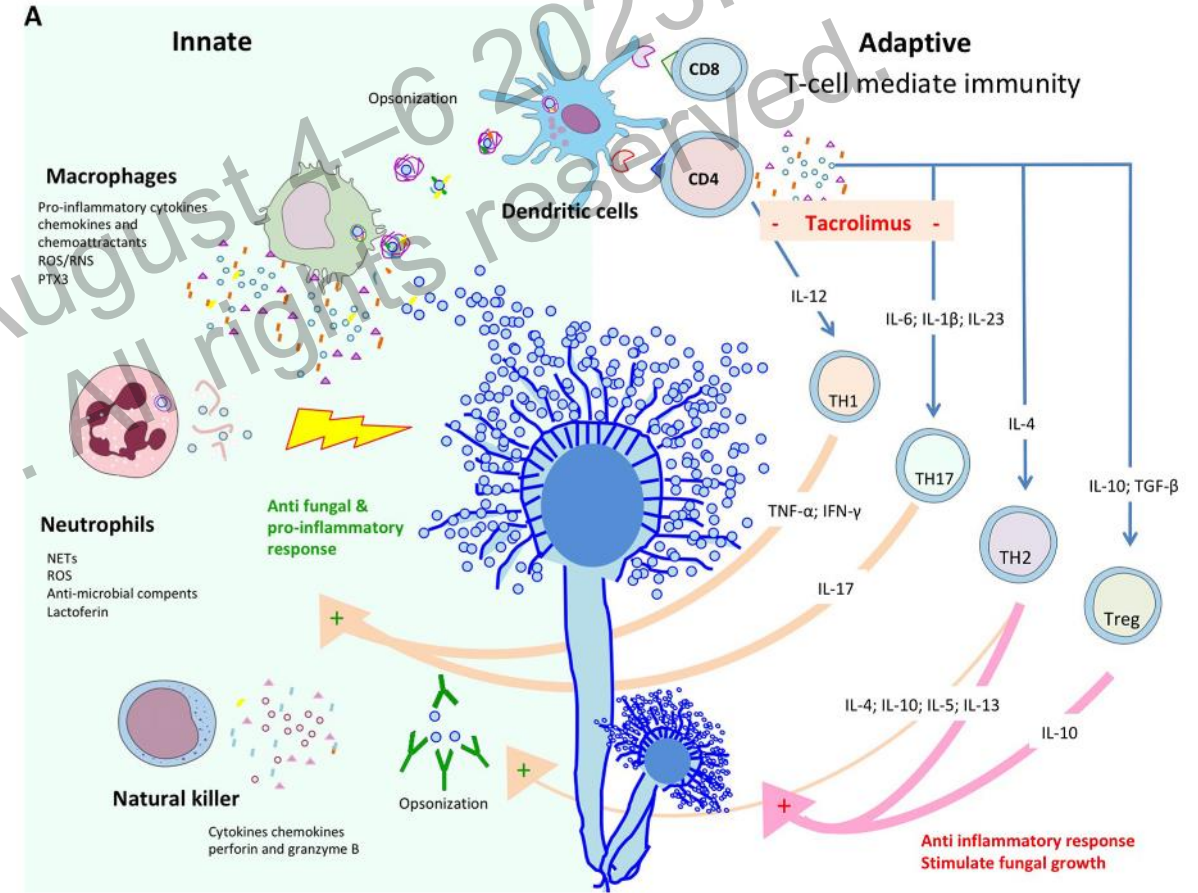
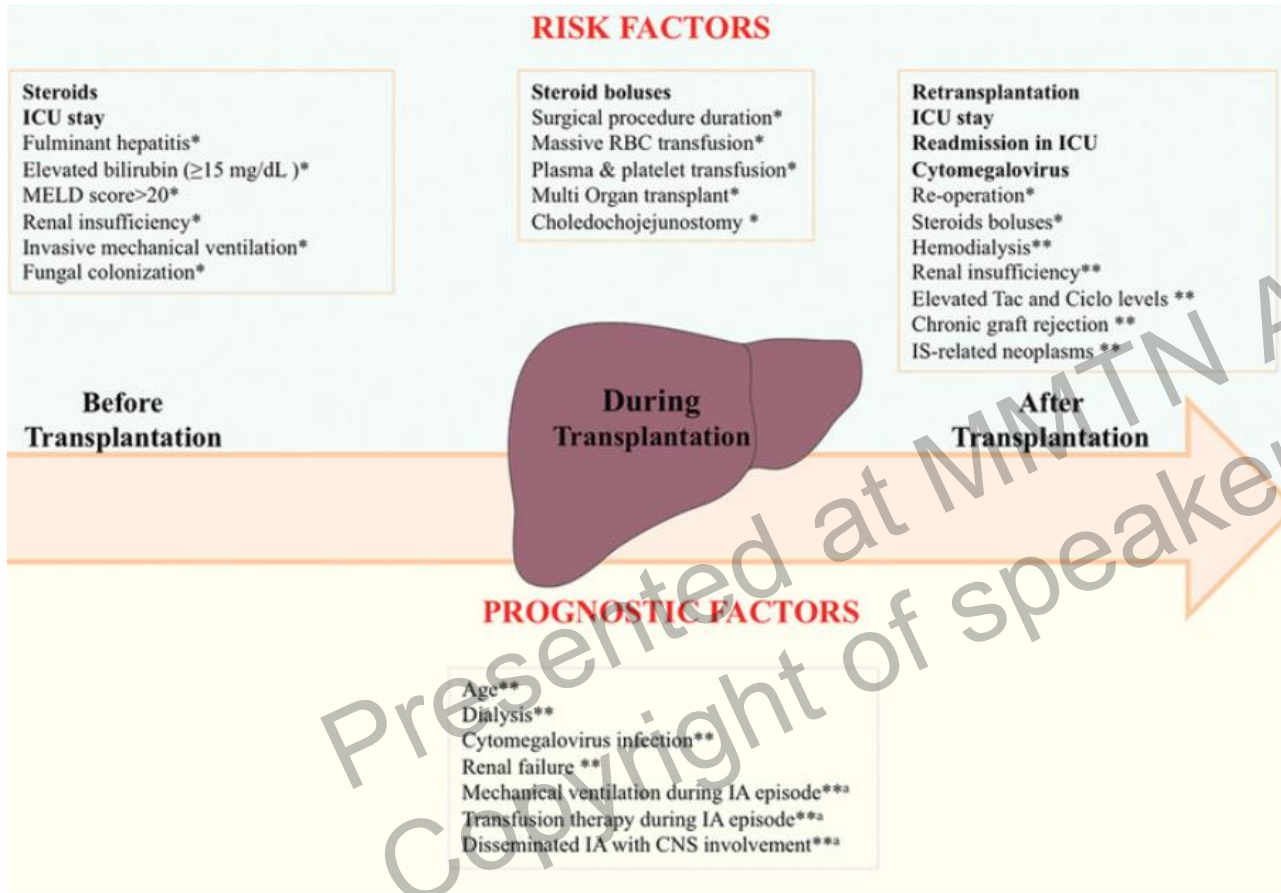


Recommendations for non-pharmaceutical interventions to prevent invasive fungal infections

Intention	Intervention	SoR	QoE
To prevent IFD	Neutropenic diet	D	llr,u
To prevent invasive aspergillosis	Wearing well-fitting masks	C	llf
To prevent IFD	HEPA filters	A	llu
	LAF systems	B	llu
To prevent CVC-related fungal bloodstream infections	Chlorhexidine-coated CVC dressings	C	I
To prevent IFD	romyelocel-L*	B	I
	granulocyte transfusions	B	llr
	G-CSF	B	llu
To prevent IFD	Quit smoking	A	llu

SoR, strength of recommendation; QoE, quality of evidence; CVC, central venous catheter; FFP2, filtering face piece 2; G-CSF, granulocyte-colony-stimulating factor; HEPA, high efficiency particulate air; IFD, invasive fungal disease; LAF, laminar air flow. *Cryopreserved human allogeneic myeloid progenitor cells.

Invasive aspergillosis in liver transplant recipients

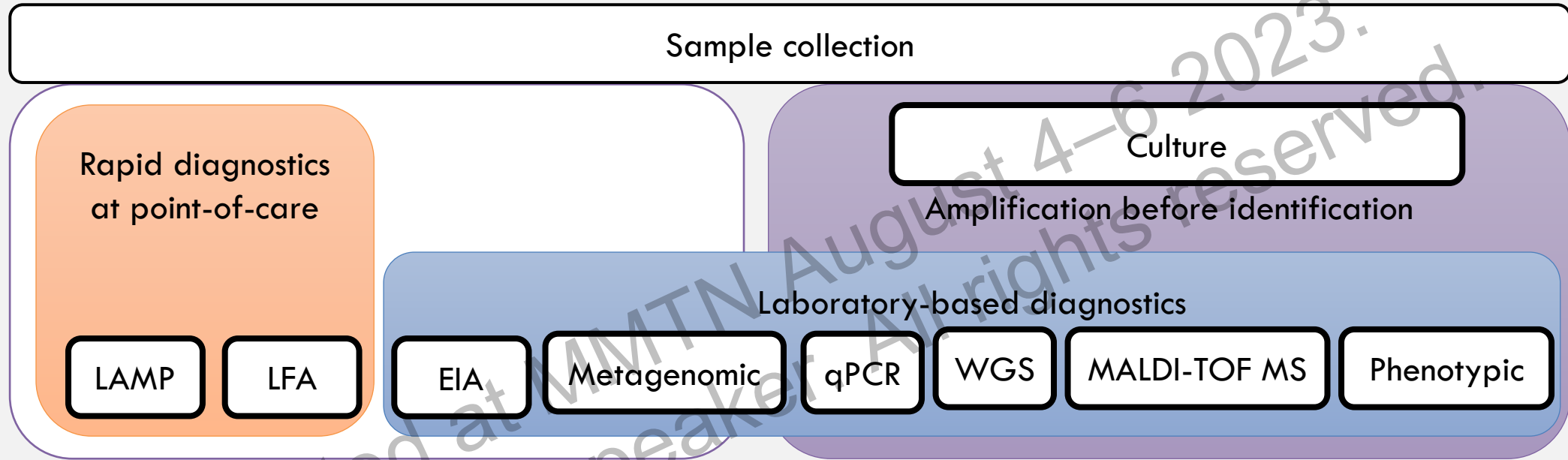


Melenotte C, et al. Transpl Infect Dis. 2023;25:e14049

Essential elements for better diagnosis

Elements	Challenges or obstacles
Be AWARE of the risk	Low awareness of invasive mold diseases, gaps in local epidemiological data, non-traditional host factors
Be ALERT when the risk occurs	
Be ACCESSIBLE to tests needed	Only available during working hours and in selected hospitals
Samples ADEQUATE for tests	Usually require invasive procedure, multiple tests from a single specimen of limited volume, large volume for higher yield rate
Results AVAILABLE in timely manner	Time to test, and turnaround time of the test
Be AFFORDABLE for repeated diagnostics	Cost, risk of invasive procedures

Detection & species identification of fungi



- **Conventional microbiologic methods:** Direct microscopy (Gram, Giemsa; Wet mount, KOH/calcofluor stains), culture , Identification, susceptibility testing
- **Histopathologic methods:** Conventional microscopy, direct immunofluorescence, in situ hybridization

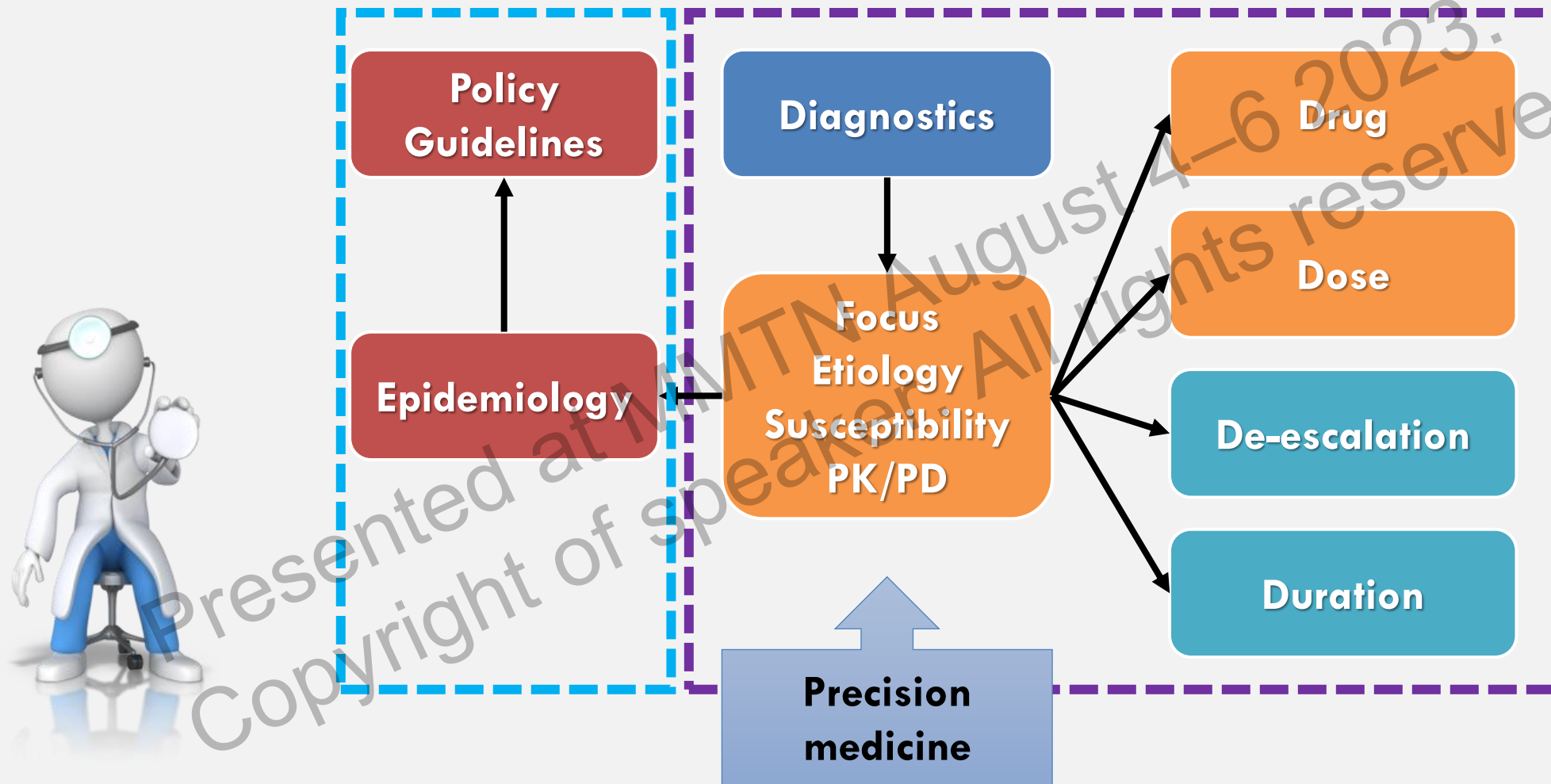
Risk stratification

Prognosis prediction

Response evaluation

Note. Direct detection versus through culture amplification; Pathogen-specific versus panfungal or syndromic testing; **Abbreviations:** LAMP, loop mediated isothermal amplification; LFA, lateral flow assay; qPCR, quantitative polymerase chain reaction; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

Anti-Fungal Stewardship



PK, pharmacokinetics; PD, pharmacodynamics

YC Chen, et al. Taiwan Antimicrobial Stewardship Program, 2013-2015; YC CHEN, M CHAYAKULKEEREE, A CHAKRABARTI, GG GAN, YL KWONG, WL LIU, BH TAN, S TODI. Unmet needs and practical solutions in the management of invasive mould infections in Asia. J Antimicrob Chemother (accepted)

Practical considerations for individualized selection of antifungal agents

	Factors	Setting	Agent of choice, alternatives, and route
Host	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
Drug	Liver		Echinocandin, L-AMB, ABLC; avoid azoles
	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
Infection	Cost and convenience	Outpatient setting	Oral route always preferable to IV if gut function intact Select agent with longest dosing interval
	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)
Pathogen	Pathogen		
	<i>Candida</i> species	Disseminated, acute and chronic	Echinocandin, fluconazole, L-AMB
	<i>C. krusei</i>	Disseminated, acute and chronic	Echinocandin, L-AMB; avoid fluconazole
	<i>C. glabrata</i>	Disseminated, acute and chronic	Echinocandin, L-AMB, voriconazole; avoid fluconazole
	<i>C. parapsilosis</i>	Disseminated, acute and chronic	L-AMB, voriconazole; avoid echinocandins
	<i>Trichosporon</i> spp	Disseminated, acute and chronic	Fluconazole, other azoles; amphotericin B not effective
	<i>Aspergillus</i> spp	Sinus, pulmonary, disseminated	Voriconazole, L-AMB, ABLC; no role for fluconazole
	<i>Aspergillus flavus</i>	Sinus, pulmonary, disseminated	Voriconazole; posaconazole alternative
	<i>Fusarium</i> spp	Sinus, pulmonary, cellulitis, disseminated	L-AMB, ABLC; voriconazole maintenance if susceptible
	<i>Scedosporium apiospermum</i>	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	

Primary versus alternative agents

Diagnosis or status of the hosts	Primary	Alternative ^a	Comments

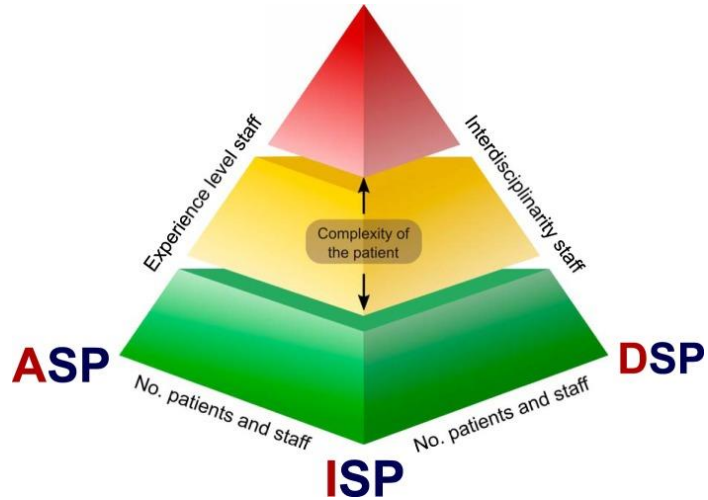
^a Alternative agent is considered in the following conditions:

1. local resistance profiles (before patient data are available)
2. allergy
3. Drug-drug interaction & other pharmacokinetics/pharmacodynamics
4. refractory to or intolerant of primary regimen
5. breakthrough infection during or prior use of primary regimen

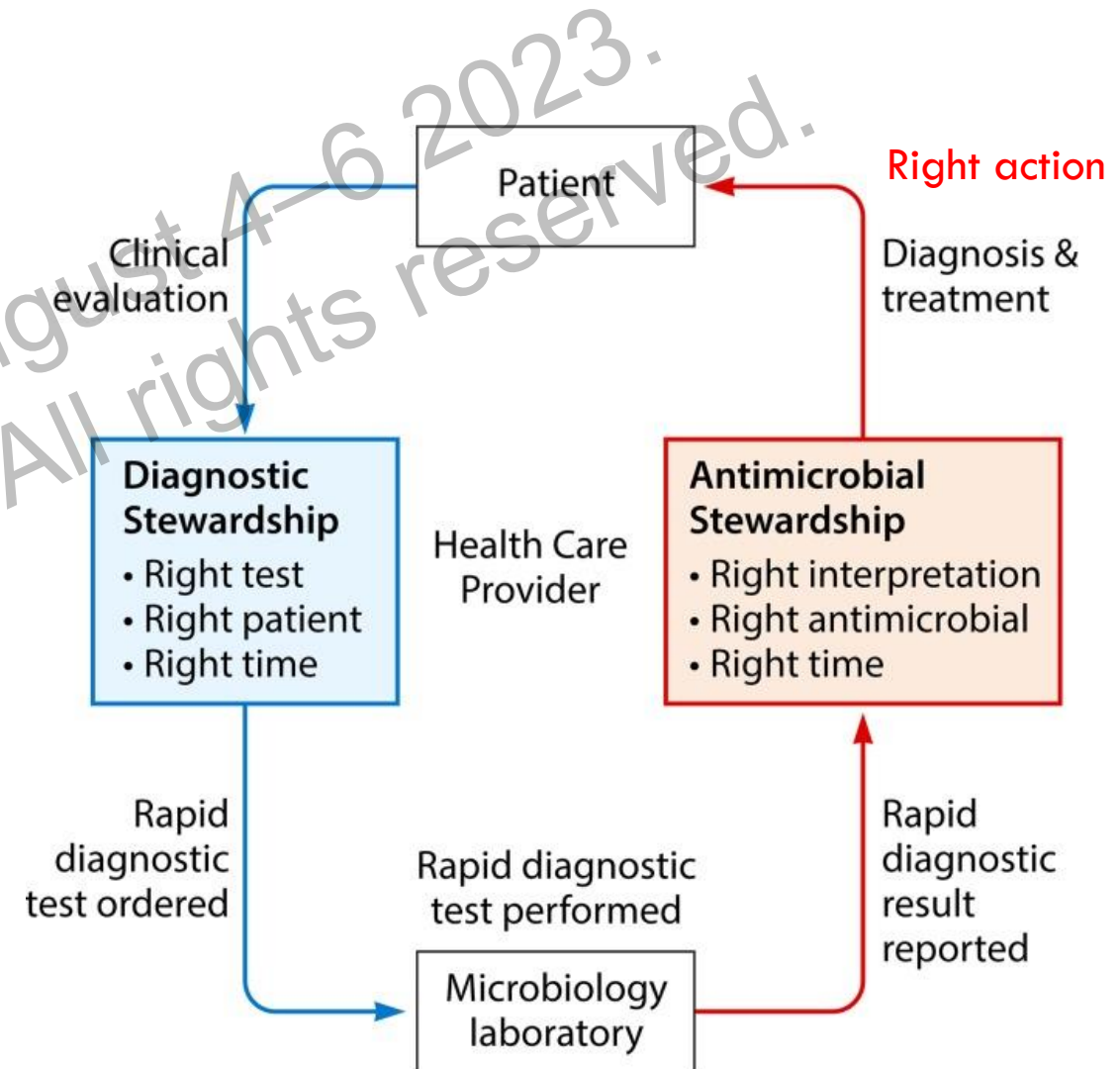
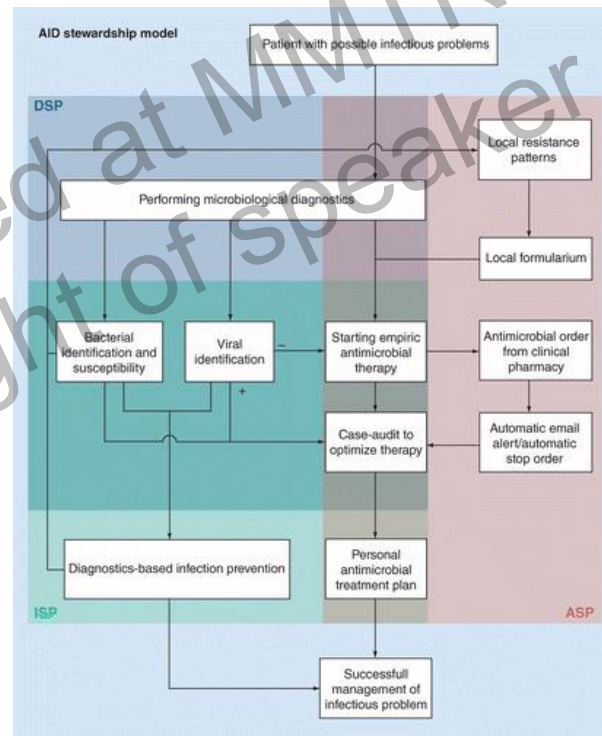
Proactive

Reactive

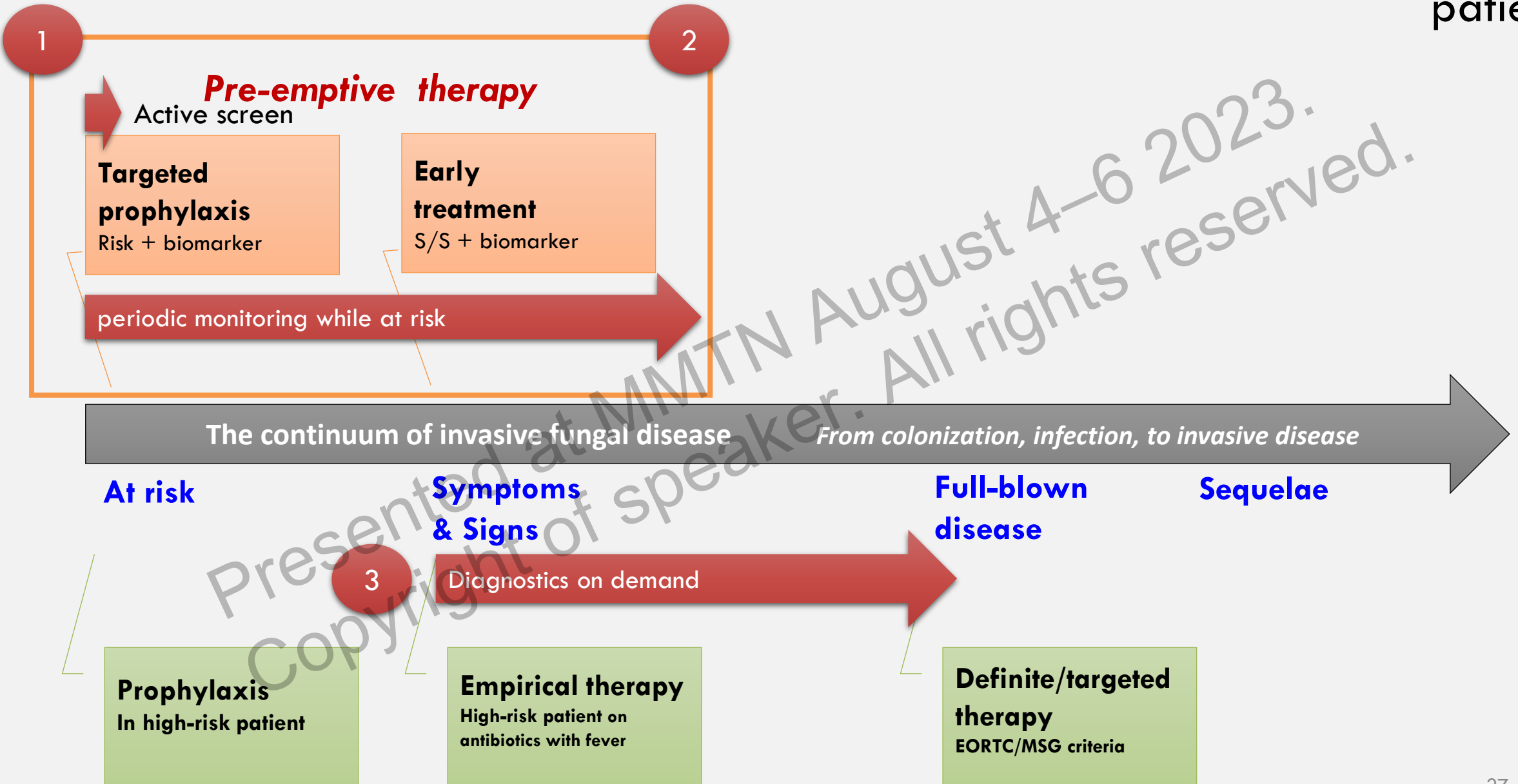
AID Model combating antimicrobial resistance: Integrating Antimicrobial, Infection prevention and Diagnostic stewardship



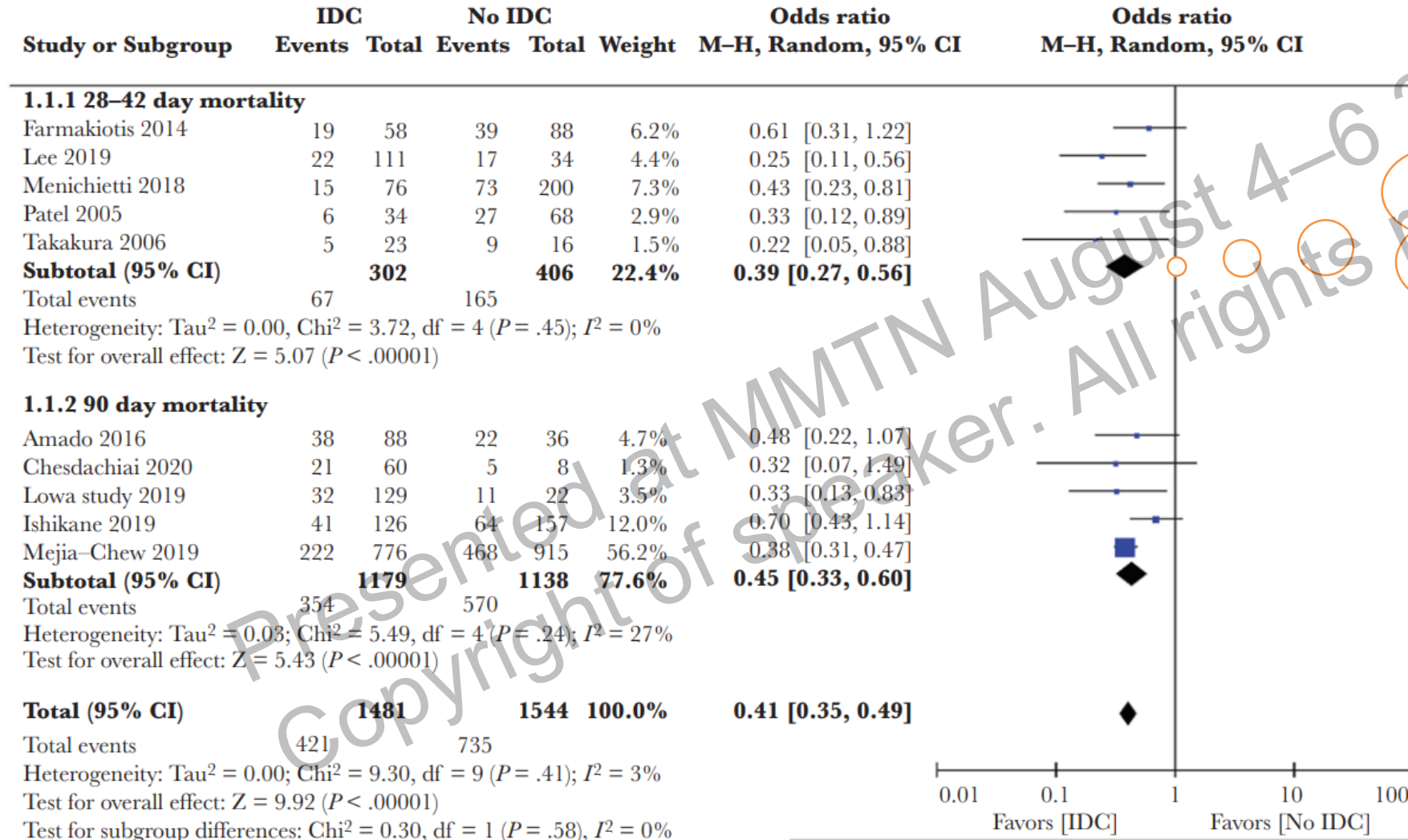
ASP: Antimicrobial Stewardship Program; DSP: Diagnostic Stewardship Program; ISP: Infection Prevention Stewardship Program
 Dik JW, et al. Future Microbiol. 2016;11:93;
 Messacar K, et al. J Clin Microbiol. 2017;55:715



Integrated antifungal and diagnostic stewardship in high-risk and/or critically ill patients

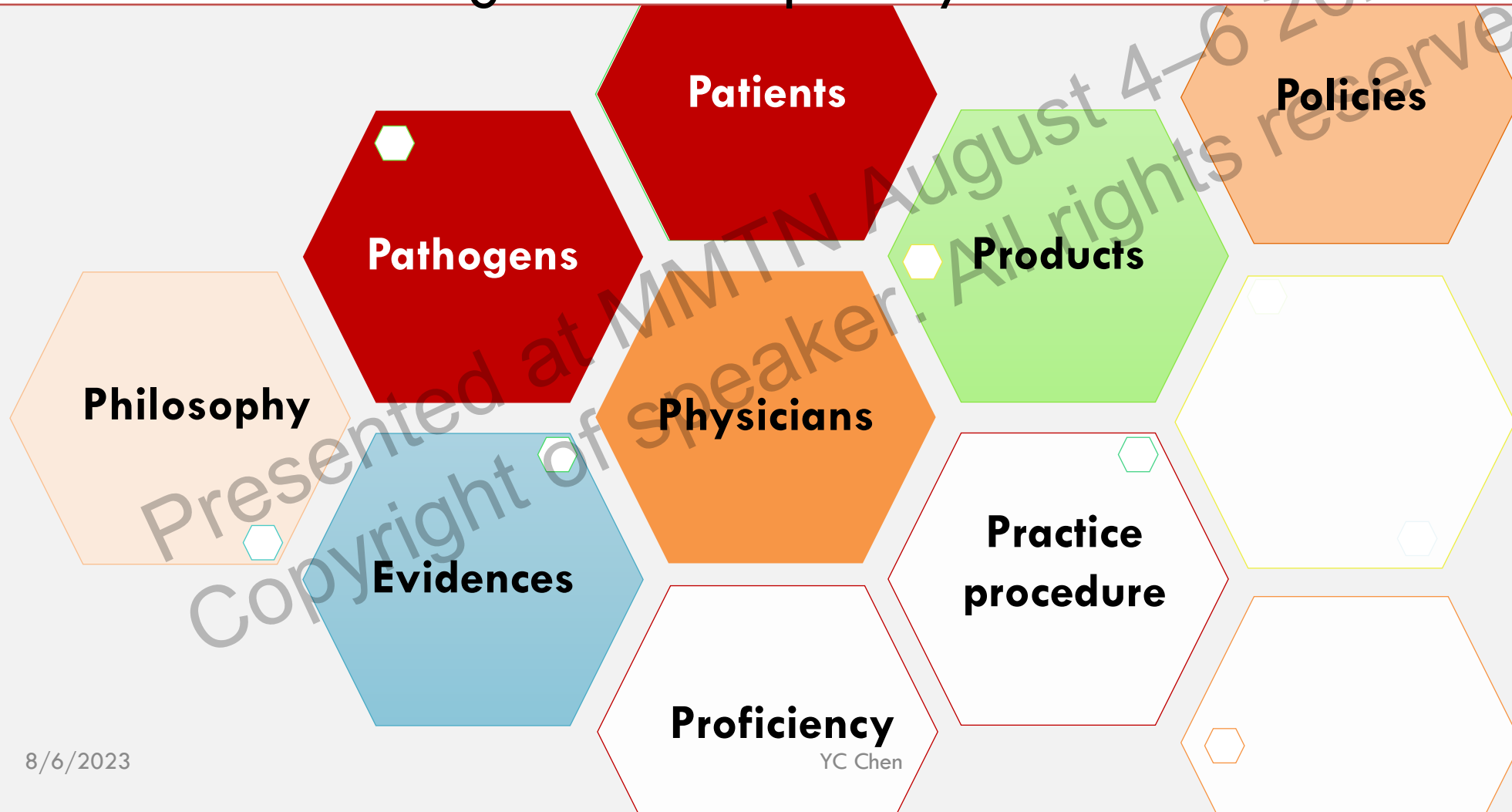


Impact of infectious diseases consultation as a part of an antifungal stewardship program



Favor infectious disease consult (IDC)

The best practices in antifungal management = Smart use of right weapons (integrated diagnostics & therapeutics) for the right patients at the right time through timely adjusted risk assessment & risk reduction through multidisciplinary collaboration



Thank you!

August 4-6 2023.
All rights reserved.

