ASIA FUNGAL WORKING GROUP
an ISHAM working group

Invasive fungal disease due to *Fusarium*

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- Three cases
- Diagnostic stewardship
- Therapeutic challenges
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- A 21-year-old man developed fever, myalgia and generalized erythematous papules on day 8 after undergoing allogeneic hematopoietic stem cell transplantation for severe aplastic anemia.
- Histopathology of the skin lesion revealed mycotic emboli.
- Cultures of both blood and tissue from skin biopsy grew *Fusarium solani*.
- Despite amphotericin B therapy, fever persisted and graft failure developed.
- A second transplantation, using mobilized peripheral blood stem cells from the same donor, was tried but the patient died of progressive multiple organ failure before any evidence of engraftment.

Fang CT, et al. J Formosan Med Assoc 1997;96:129

2

A 27-year-old man received alemtuzumab, an anti-CD52 monoclonal antibody, as salvage therapy for refractory cutaneous T cell lymphoma with leukemia transformation.

Liu JY, et al. Combination Antifungal Therapy for Disseminated Fusariosis in Immunocompromised Patients: A Case Report and Literature Review. Med Mycol. 2011;49:872

3 A 37 y/o man with mixed phenotypic acute leukemia, relapsed and refractory

2020/08/27

I3A7 induction
- Posaconazole primary prophylaxis

02/16 BM: MRD 0.16%
04/26 PB blast 14%

2021/02/02

TBI, haplo-sibling BM+PBSCT
- GVHD prophylaxis: rATG 6.0 mg/kg + CsA + MMF
- Letermovir and micafungin primary prophylaxis

2021/04/30

Venetoclax & azacitidine

Poor response, prolonged neutropenia

2021/05/01

2021/05/05

Nasal congestion & cough
Serum GM negative
Voriconazole, May 1 to Sept 10

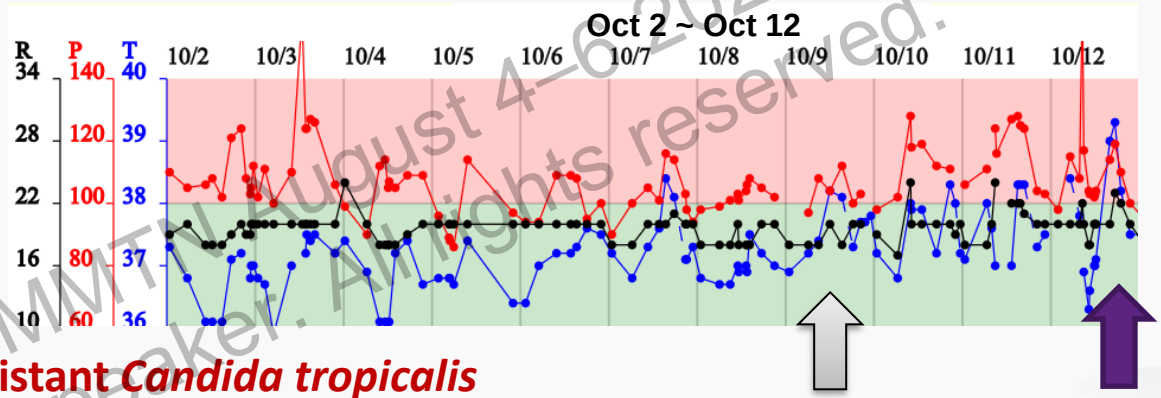
TBI, total body irradiation; BM, bone morrow; PBSCT, peripheral blood stem cell transplantation; GVHD, graft-versus-host disease; rATG, rabbit anti-thyroglobin; MRD, minimal residual disease

Courtesy of, Dr. Pao-Yu Chen (ID physician), Dr. Cheng-Hong Tsai (hematologist), Dr. Chih-Feng Lin (otolaryngologist) and Dr. Yu-Tsung Huang (microbiologist), NTUH, Taiwan

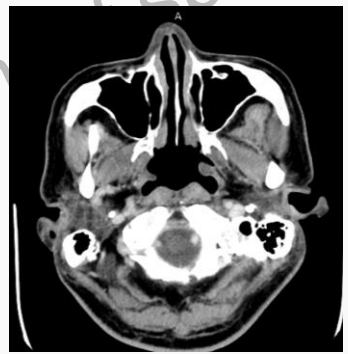
Fever developed in the absence of respiratory symptoms under antibacterials, micafungin and flucytosine

May ~ Oct 2021
EFLAG, Nivolumab, CLAG-M, DLI, Vidaza, Selinexor (Oct 05 ~ Oct 14)
Chronic GVHD

WBC 4K~5K, Seg+Band 5%
Blast + immature mono 80%~90%
Ferritin 6958, iron saturation 100%
IgG 645



Sept 9, blood culture: azole-resistant *Candida tropicalis*



Pre-HSCT evaluation
Oct 9
- Paranasal sinus: Clear
- Nasal swab

Mold isolated 3 days later

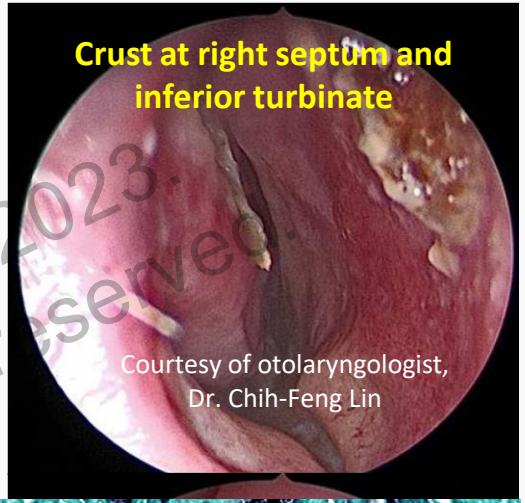
Next step?

A challenging invasive mould disease!

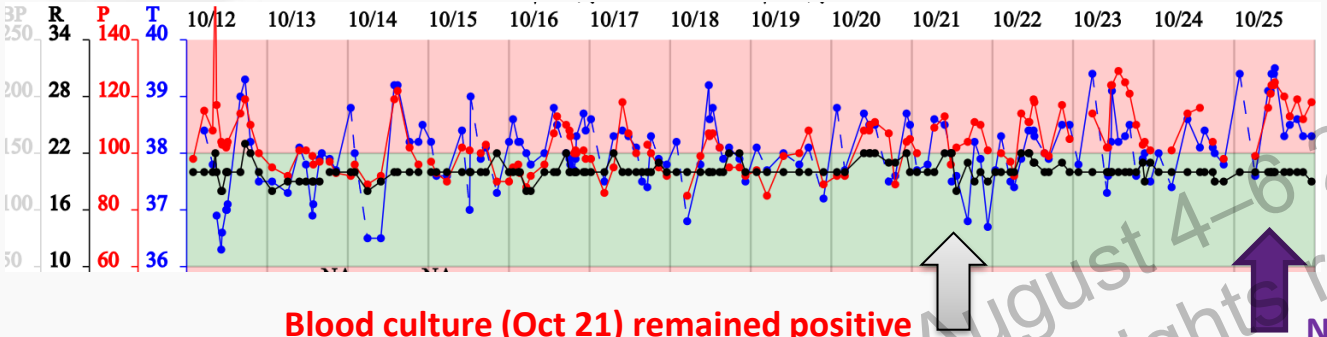
2021/10/13

Consult otolaryngologist
Functional endoscopic sinus surgery (FESS)
Initiate **voriconazole and liposomal amphotericin B 5mg/kg/d**

Nasal swab (Oct 9) grew mold
Blood culture (Oct 12) grew mold
FESS culture (Oct 13) grew mold
Serum galactomannan antigen assay: negative



Fever persisted 7-day after antifungal combination therapy

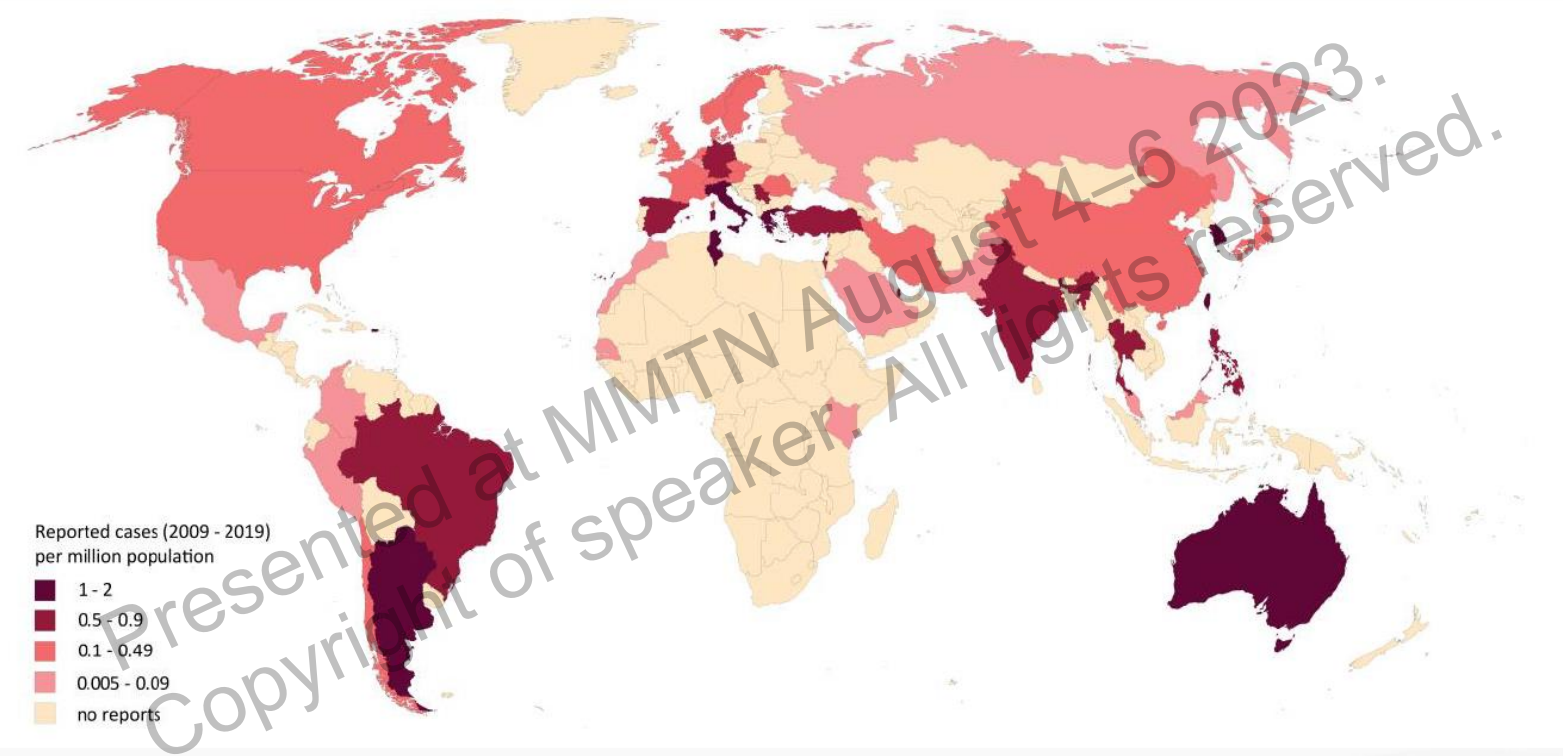


WBC	480
Neutrophil	0
Monocyte	5
Lymphocyte	5
Platelet	17k/uL
CRP	12.41 mg/dL

1. Escalate liposomal amphotericin B to 10mg/kg/day, continue voriconazole, and add caspofungin
2. Surgical debridement
3. Granulocyte infusions

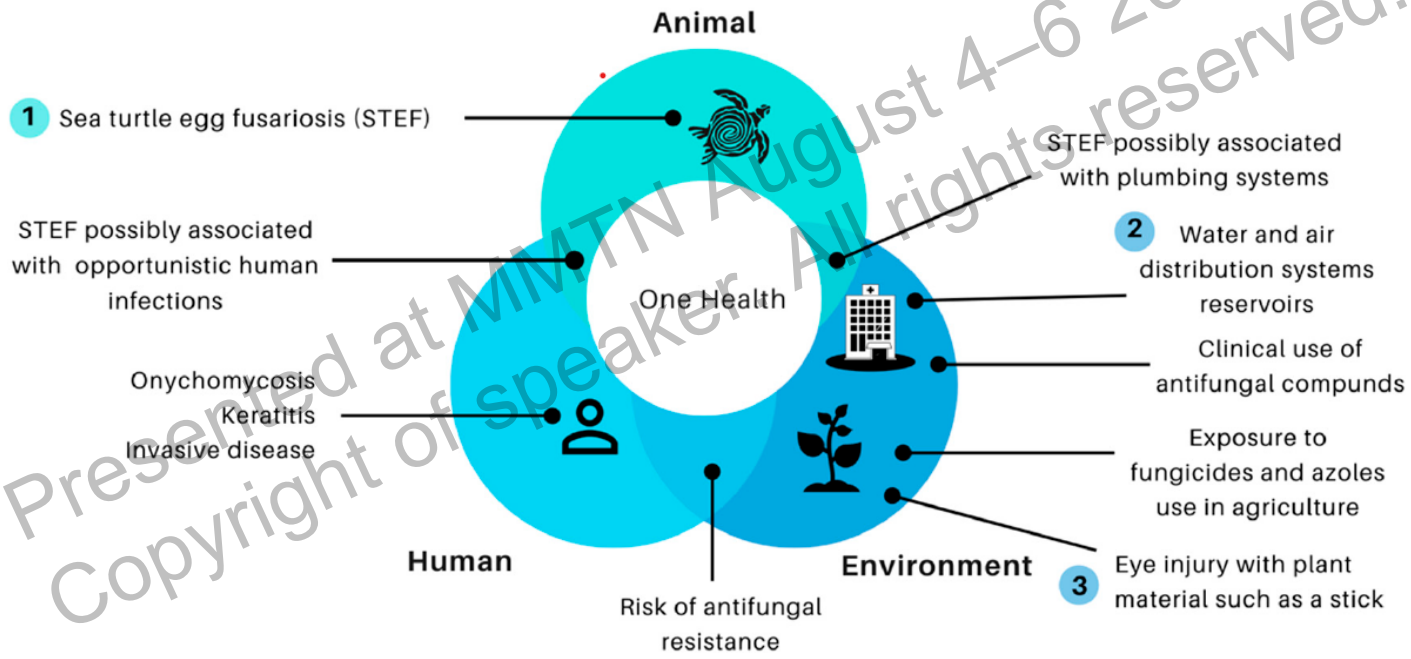
His condition improved and neutropenia resolved.
However, the patient died of refractory leukemia with CNS involvement 13 weeks later.

Worldwide distribution of fusariosis



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;21:e246

Animal, environment, and human interaction: a One Health perspective



Sáenz V, et al. A One Health Perspective to Recognize *Fusarium* as Important in Clinical Practice. J Fungi (Basel). 2020;6:235

Breakthrough invasive fungal infection (BtIFI) among patients with hematologic malignancies: a national, prospective, and multicentre study

SETTING

13 Spanish hospitals

Prospective 2017-2020

Hematologic malignancies

≥7 days of prior antifungals

BtIFI based on EORTC/ MSG definitions

121 BtIFI episodes: 41 proven, 53 probable, 27 possible

Proven and probable BtIFI

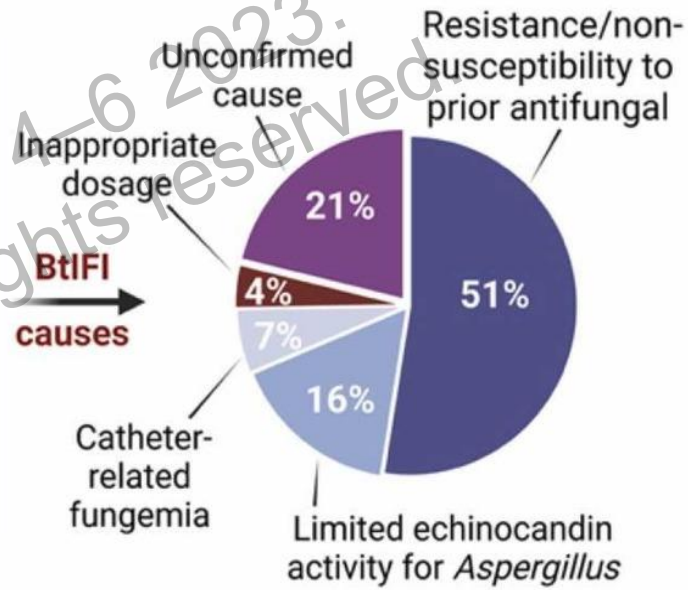
54 aspergillosis
62% of non-*fumigatus Aspergillus*

23 candidemia
87% of non-*albicans Candida* species

7 mucormycosis
64% among biopsy proven BtIFI

6 other molds and **5 other yeasts**

BtIFI causes

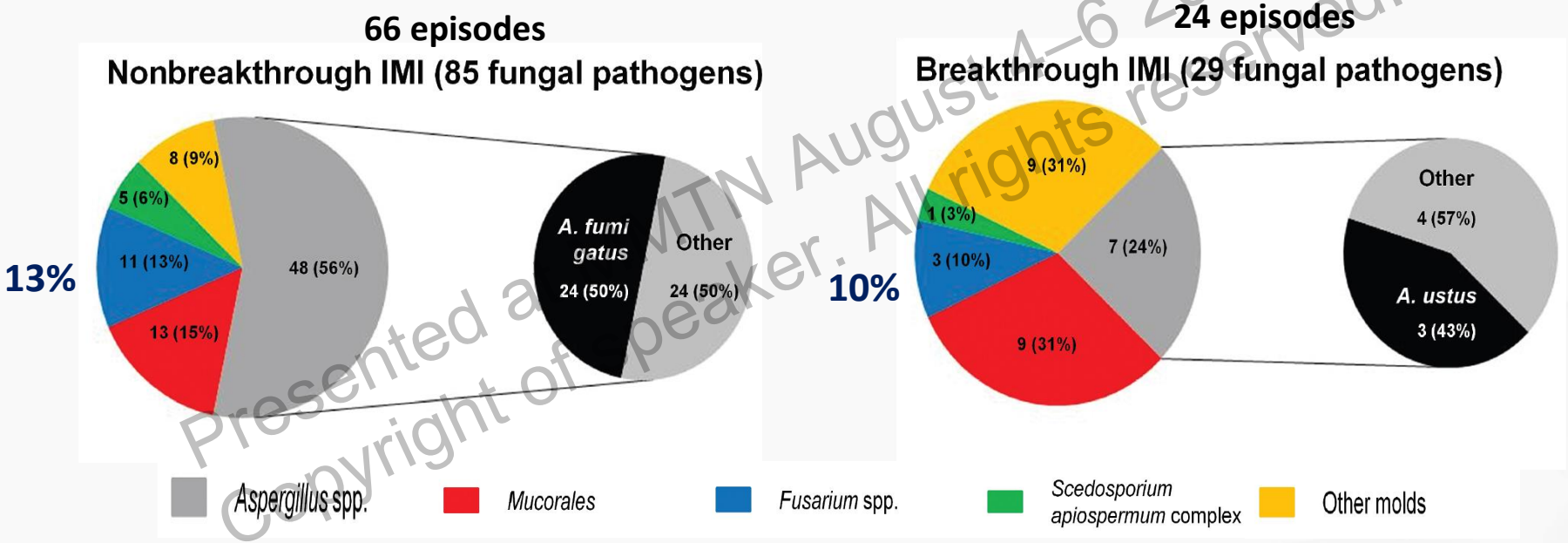


Prior antifungal determined BtIFI **epidemiology,** and **100-day mortality** was **47%**

Conclusions: BtIFI are mainly caused by non-*fumigatus Aspergillus*, non-*albicans Candida*, Mucorales and other rare species of mould and yeast. Due to high mortality, aggressive diagnostic and therapeutic approach is needed

Puerta-Alcalde P, et al. J Infect. 2023;87:46

Invasive mold infections in patients receiving azole prophylaxis



Lamoth F, et al. *Clin Infect Dis* 2017;64:1619 (Switzerland)

Characteristics of breakthrough invasive mold infections

Fungal species	MIC [µg/ml]			Antifungal prophylaxis trough Level [µg/ml])	IMI classification [2] (site)	Underlying disease	Treatment (outcome)
	VOR	POS	AmB				
Fusarium solani complex [1]	>16	>16	2	POS (NA)	Proven (sinus, blood, skin)	HM (neutropenia)	VOR / AMB (no follow-up)
Fusarium solani complex [1]	>16	>16	2	VOR (NA)	Proven (lung, blood)	HM (HSCT, neutropenia)	MCF (failure)
Fusarium spp [1], *Purpureocillium lilacinum*, *Aspergillus versicolor* complex	8 0.25 NA	>16 1 NA	2 >16 NA	POS (1.2)	Probable (lung)	SOT (lung)	13

Lamoth F, et al. *Clin Infect Dis* 2017;64:1619 **Abbreviations**: VOR, voriconazole; POS, posaconazole; AmB, amphotericin B; IMI, invasive mould infections

Aspergillosis versus Fusariosis

Similarities

- Sino-pulmonary portal of entry
- Image: nodules with halo sign, centrilobular micronodules, cavitary lung lesions, tree-in-bud infiltrates, consolidations
- Histopathology: vascular invasion, acute branching septate hyphae
- Biomarkers: serum galactomannan, 1,3-beta-D-glucan
- Outcome
  - High morbidity/mortality
  - Relapse following myelosuppression
  - Bimodal occurrence after HSCT
- Hospital reservoirs

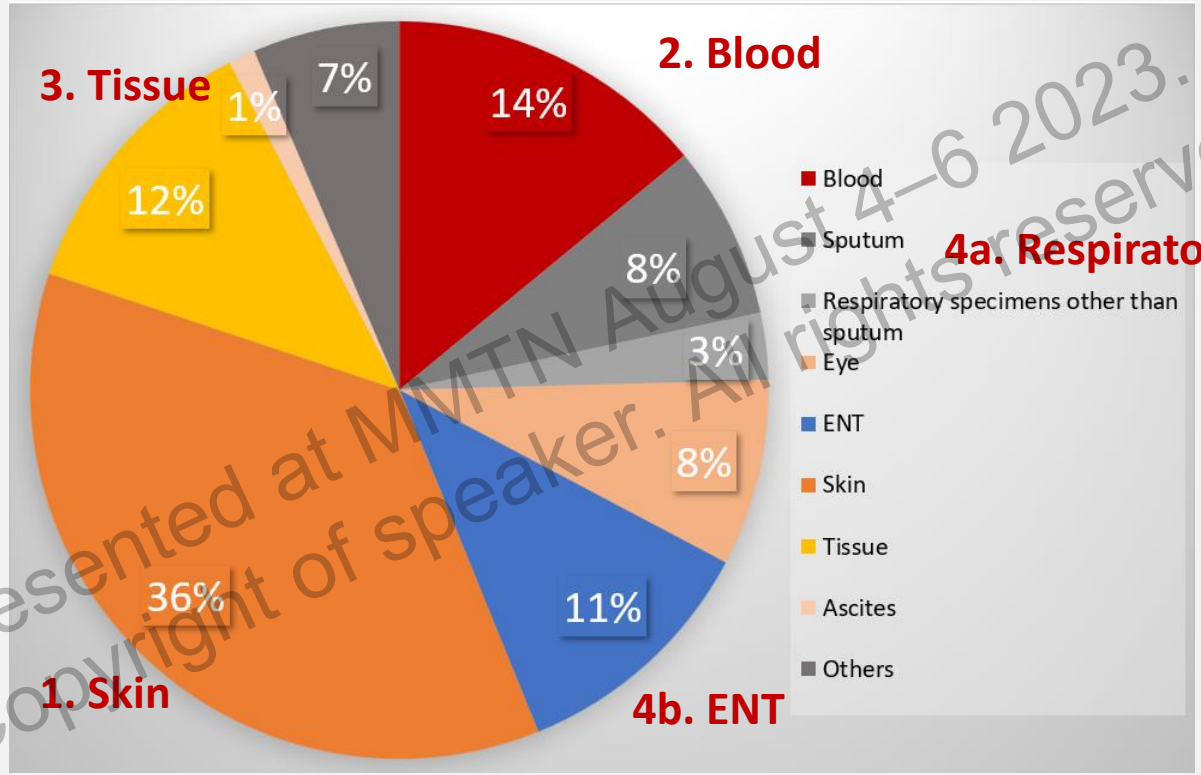
Differences*

- The bloodstream: 50-70% positive blood cultures (vs. contamination)
- The skin 60-70%
  - Frequent portal of entry for localized lesions (onychomycosis, trauma)
  - Multiple lesions at different stages of evolution, at times painful; subcutaneous nodules; ecthyma-like lesions; bullae or target lesions surrounded by a thin rim of erythema
- Many complained of myalgia
- Resistance to antifungals

* Characteristics associated with fusariosis

Nucci M, et al. Clin. Infect. Dis. 2002;35:90; J Fungi (Basel). 2021;7:815.

Distribution of *Fusarium* clinical isolates



NTUH, 2011-2021, N=171

Diagnostic stewardship for invasive fusariosis

EQUAL Score Quality indicator	Strength of recommendation	Level of evidence	Equal score points
Chest/Sinus CT in the case of persistent or recurrent fever (fusariosis less likely to have halo sign)	A	IIh	2
Blood cultures	A	IIu	2
Skin (more frequently) or other tissue			
Direct examination	A	IIu	2
Culture	A	II	2
Histopathology	A	II	2
Serology			
Serum galactomannan serum	B	IIu	1
Serum 1,3-beta-D-glucan	C	II	1
Species identification			
PCR or MALDI-TOF MS	B	IIu	1
Antifungal susceptibility tests (CLSI or EUCAST)	C	IIu	1

Guarana M, et al. *Mycoses* 2021;64:1542; Nucci M, et al. J Fungi (Basel). 2021;7:815

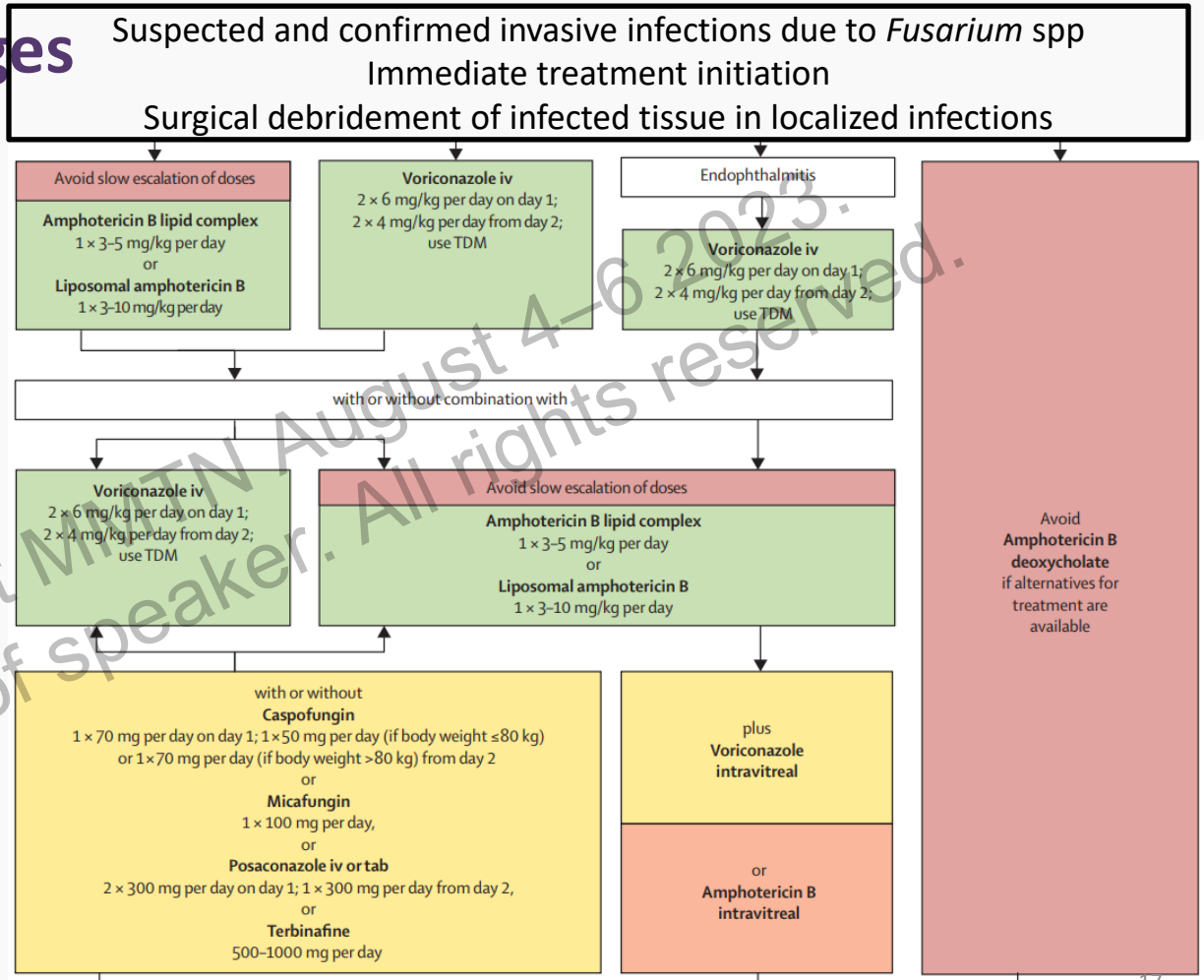
Direct exam of a skin biopsy is the fastest way of establishing the diagnosis

Therapeutic challenges

There are no randomized trials evaluating the efficacy of antifungal drugs for the treatment of invasive fusariosis

Primary combination therapy, with a potential early step down to monotherapy later (once minimum inhibitory concentrations of the azole and polyenes become available) is an approach we strongly recommend

- The severity of the disease
- MICs for azoles and polyenes are often high
- Difficulties in achieving voriconazole trough concentrations within the targeted range



IV, intravenously; **tab**, tablets; **TDM**, therapeutic drug monitoring
Hoenigl M, *et al. Lancet Infect Dis* 2021

Primary antifungal therapy and 6-week death rate in 88 patients with invasive fusariosis

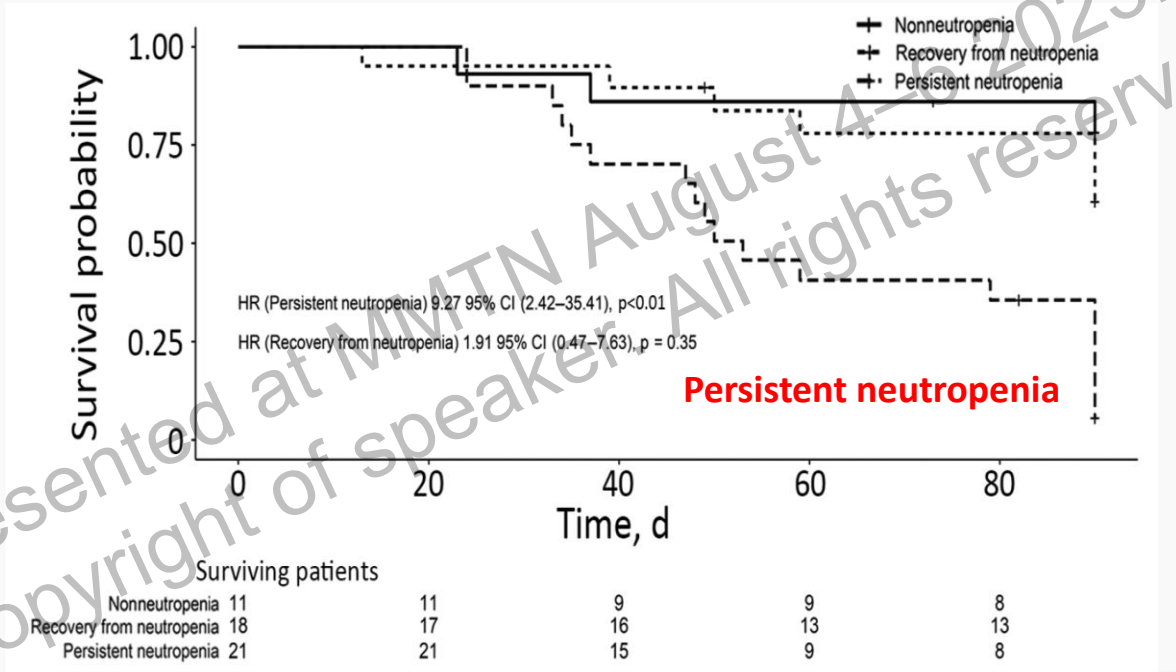
Treatment	No. (%)	6-week death rate (%)
Monotherapy	52 (59.1)	**32.7**
Voriconazole	27 (30.7)	29.6
Liposomal amphotericin B	16 (18.2)	31.3
Deoxycholate amphotericin B	5 (5.7)	60.0
Amphotericin B lipid complex	3 (3.4)	33.3
Posaconazole	1 (1.1)	–
Combination therapy	36 (40.9)	**33.3**
Liposomal amphotericin B + voriconazole	23 (26.1)	21.7
Deoxycholate amphotericin B + voriconazole	9 (10.2)	55.6
Other[a]	4 (4.5)	–

22 centers from seven countries (Austria, Brazil, Chile, Italy, the Netherlands, Spain and the USA)

Resolution of neutropenia was associated with a greater likelihood of clinical success

Nucci M, *et al.* Do high MICs predict the outcome in invasive fusariosis? *J Antimicrob Chemother* 2021;76:1063

Persistent neutropenia was the only risk factor for death, regardless of antifungal therapy



Adjusted Kaplan-Meier curves obtained from the stratified Cox regression model for 90-day survival in 50 patients treated for invasive fusariosis, Spain, 2000–2015. HR, hazard ratio.

Perez-Nadales E, *et al. Emerg Infect Dis* 2021;27:26 (Spain)

Recommendation for management

EQUAL Score	Quality indicator	Strength of recommendation	Level of evidence	Equal score points
Treatment, fist line	Voriconazole IV, switch to PO once stable	A	IIu	2
	Liposomal amphotericin B or amphotericin B lipid complex	A	IIu	2
	Combination therapy with voriconazole and a lipid formulation of amphotericin B	A	IIu	2
Ancillary therapies	Surgical debridement of necrotic tissue	A	II	2
	G-CSF or GM-CSF	B	IIu	1
	Granulocytic transfusions	C	III	1
Follow-up	Galactomannan in serum (if positive at diagnosis)	A	II	2

Guarana M, et al. *Mycoses* 2021;64:1542

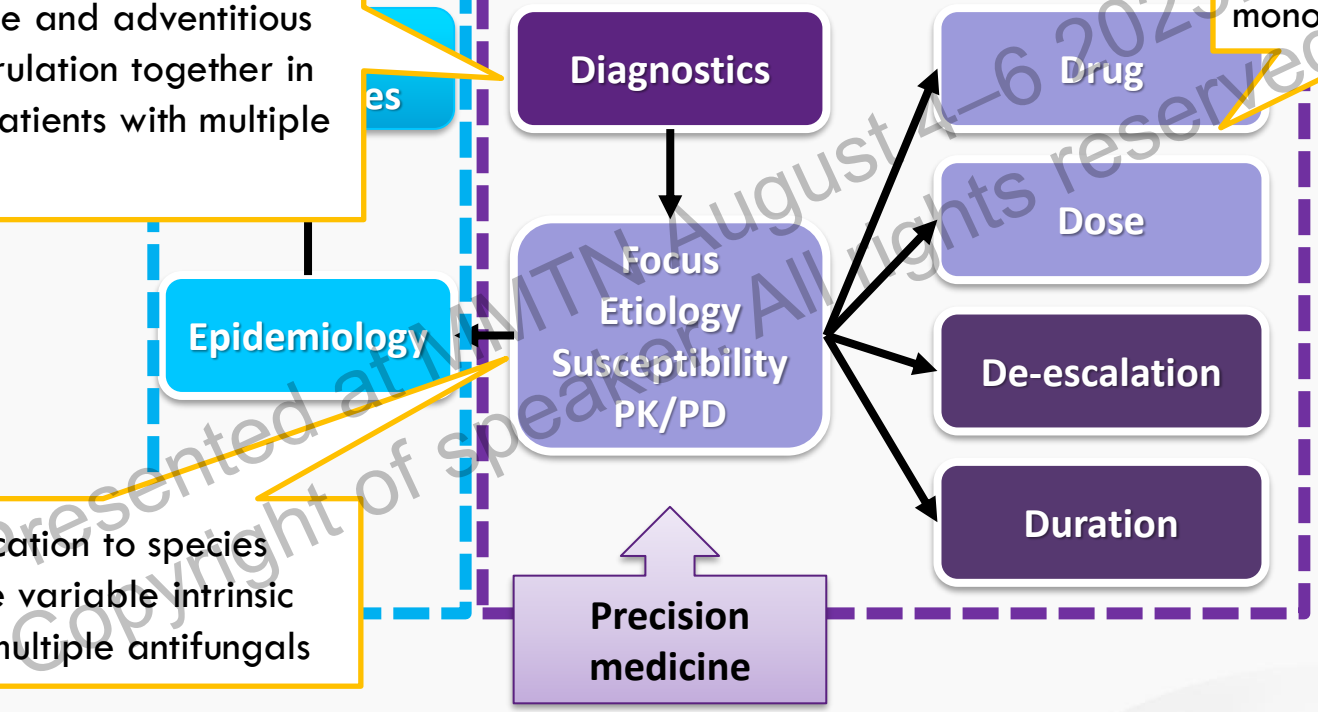
Take home messages

Elements of antimicrobial stewardship and delivering precision therapy

Primary combination therapy, with a potential early step down to monotherapy later

Hyaline hyphae and adventitious yeast-like sporulation together in the high-risk patients with multiple skin lesions

Rapid identification to species level given the variable intrinsic resistance to multiple antifungals



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 2022;77:2579

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Thank you