MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

How do I *manage* systemic hyalohyphomycosis other than aspergillosis?

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ASIA FUNGAL WORKING GROUP
an ISHAM working group

SYSTEMIC HYALOHYPHOMYCOSIS EXCLUDING ASPERGILLOSIS MANAGEMENT ASPECT

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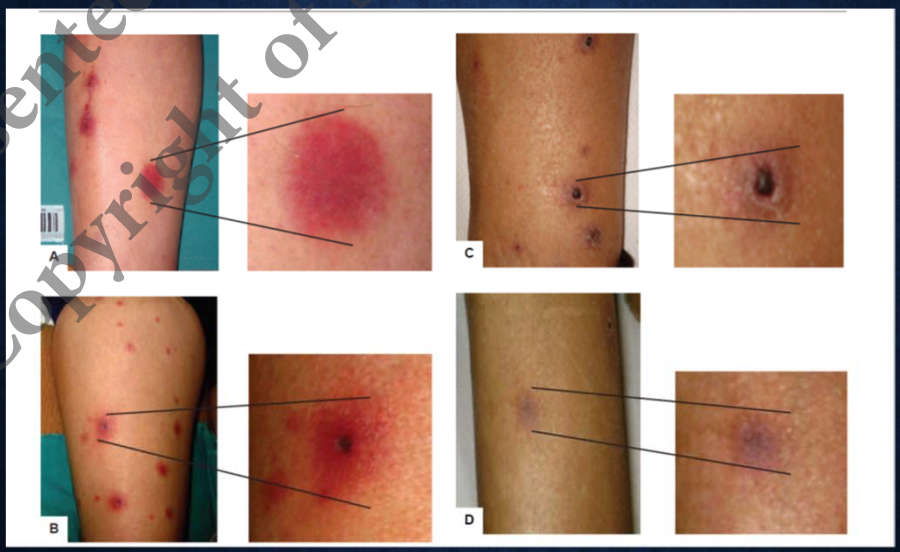
SYSTEMIC HYALOHYPHOMYCOSIS

1) Fusariosis ; more commonly seen in patients with hematological malignancy

2) Talaromycosis (penicilliosis , due to *Talaromyces marniffei*) ; most commonly observed in patients with CD4 < 100cell/uL

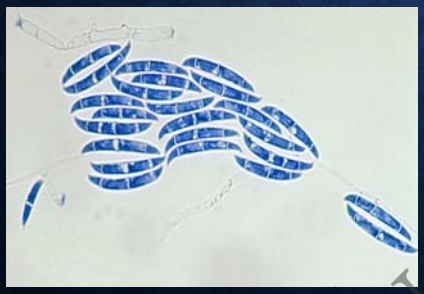


70-75 % of hematological patients with invasive fusariosis had cutaneous lesions

FUSARIUM SPP

Commonest isolates :

- F. solani 49% ,
- Fusarium oxysporum 21% ,
- Fusarium verticillioides (of the *F fujikuroi* SC) 8.8%



Alastruey-Izquierdo et, al , J. Antimicrob Chemother 2008
Muhammed et al, Medicine 2013

FUSARIUM : DRUG SUSCEPTIBILITY

- *Fusarium spp* inherently resistant to multiple –antifungals
- The optimal treatment is not well defined , as the susceptibility patterns could be species and even isolate dependent
- The susceptibility antifungal agents may not predict the individual clinical outcome of *Fusarium* infections, However ,
- there is an association between high MICs and poor response to antifungal treatment
- Low MICs do not guarantee clinical success, while high MICs are associated with lower probability of a favorable response to antifungal agent

Andes et al, Antimicrob agents chemother 2018

Itraconazole , Fluconazole , Echinocandins *: limited activities against Fusarium spp, with HIGH MIC
Exception F. temperatum : MIC to echinodandins 0.031- 4.0 µg/mL

EPIDEMIOLOGIC CUTOFF VALUES FOR FUSARIUM SPECIES COMPLEXES DETERMINED BY THE CLSI BROTH MICRODILUTION METHOD

Espinel-Ingroff et al, Antimicrob Agents Chemother 2016

MIC µg/mL	*F solani sc*	*F oxysporum sc*	*F verticillioides*
Amphotericin B	8	8	4
Voriconazole	32	16	4
Posaconazole	32	8	2
Itraconazole	32	32	NA

F solani :exhibit Higher MIC to all anti-fungals comparing to other species ; with very High azole MIC values

F oxysporum show lower MIC to azoles (voriconazole and posaconazole)

Alastruey-Izquierdo et al, JAC 2008

Invasive Fusariosis

Amphotericin B	Voriconazole	Posaconazole
Deoxycholate Ampho B (1- 1.5mg/kg/D) OR Lipid based amphotericin B (L-AMB, or ABLC 5mg/kg/D	6mg/kg 12hr for 24H then 4mg/kg 12H	Salvage therapy
Complete or partial response : 32- 46%	45-47%	48%

Host immune status
Adequate surgical debridement to control the source of infection
Dosage and serum concentration of antifungal agent

Al-Hatmi et al, J. Antimicrob. Chemother. ***2015***
Lortholary etal, Antimicrob agents chemother 2010
Raad et al, CID 2000

PRINCIPLE OF MANAGEMENT OF INVASIVE FUSARIOSIS

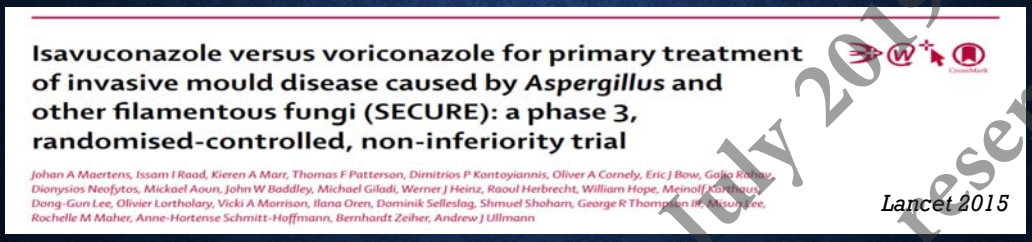
1. Adequate surgical debridement if appropriate
2. *Reversal of immunosuppression whenever possible
3. * Antifungal prophylaxis and break-through infection
4. Anti-fungal therapy- good to know the species and susceptibility results , to allow species –specific treatment

- Resolution of infection seen with reversal of myelosuppression
- Bimodal distribution (before and after) engraftment in BM transplant recipients

Eleni et al, Blood J, 1997

ISAVUCONAZOLE

- Fusarium spp show MIC of 4 µg/mL to > 16 µg/mL


Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Gotha Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Mou-Yen Yeh, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann

Lancet 2015

Only 3 out of 9 patients with invasive fusariosis had complete or partial response to Isavuconazole therapy

COMBINATION THERAPY

Anti-fungal Combination
Liposomal Amphotericin B + Voriconazole
Deoxycholate Amphotericin B + Voriconazole
Deoxycholate Amphotericin B + Terbinafine
Voriconazole + Terbinafine
Liposomal Amphotericin B + Caspofungin
Liposomal Amphotericin B + Posaconazole

- ***When monotherapy fails**
- **Response rates not better than monotherapy**

Liu et al, Medical Mycology 2011
Uemura et al, Pead Infect Dis J 2018
Horn et al, Mycoses 2014

Seven alternatives to evidence based medicine

David Isaacs, Dominic Fitzgerald

BMJ , 1999

Providence based medicine	• If the caring doctor has no idea of what to do next, the decision may be best left in the hand of the Almighty. Many are unable to resist giving God a hand with decision making
Nervousnous based medicine	• Fear of litigation is a powerful stimulus to overinvestigation and overtreatment. The only bad test is the test you didn't think of ordering .
Confidence based medicine	• This is restricted to Surgeons .

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INVASIVE TALAROMYCOSIS IN HIV

Induction
- Amphotericin B (0.6-1mg/kg/D) x 2 weeks OR
- Liposomal Amphotericin B 3-5mg/kg/D x 2 weeks OR
- IV Voriconazole 6mg/kg x 12H x 1 day, 4mg/kg x 12H x 3D at least

Consolidation
- Itraconazole 200mg BD x 10 weeks
- Voriconazole 200mg BD x 12 weeks maximum

Maintenance Secondary Prophylaxis
- Itraconazole 200mg OD till CD4 > 100cells/uL, HIV VL suppressed

Sirisanthana et al, CID 1998
IDSA 2018 : Prevention and treatment of opportunistic infections in HIV adults adolescence

IN VITRO SUSCEPTIBILITY PATTERN

- 100 % susceptible to Ampho B (MIC < 1 µg/ml
- Very low MIC to Voriconazole , Posaconazole (MIC 0.001 to < 0.125µg/mL)
- Low MIC to Itraconazole (MIC 0.016-0.50 µg/mL)
- High MIC to Fluconazole (MIC 37. 5- 75.0 µg/mL)

TABLE 1. Clinical and microbiological responses to antifungal therapeutic agents for 80 patients with disseminated *P. marneffei* infections in Chiang Mai, Thailand[a]

Treatment	No. of patients	No. of patients with clinical and microbiological outcome[b]:		
		Response	Failure	Unknown
None	12	0	9 (100%)	3
AMB	39	27 (77.2%)	8 (22.8%)	4
ITZ	16	9 (75%)	3 (25%)	4
FLZ	13	4 (36.4%)	7 (63.6%)	2

SUPPARATPINYO, et al, Antimicron agents chemother 1993
RB Singh et al, J Med Soc 2018
KP Lau et al, Antimicrob Agents chemother 2017

2018 IDSA GUIDELINES FOR PREVENTION AND TREATMENT OF OPPORTUNISTIC INFECTIONS IN ADULTS AND ADOLESCENCES : PRIMARY PROPHYLAXIS

Recommendations for Preventing and Treating *Penicillium marneffei* Infection

Preventing 1st Episode of Penicilliosis (Primary Prophylaxis)

Indication for Primary Prophylaxis:

- Patients with CD4 count <100 cells/mm^3 who reside or stay for a long period in northern Thailand, Vietnam, and Southern China, in particular in rural areas **(BI)**

Preferred Therapy:

- Itraconazole[a] 200 mg PO once daily **(BI)**

Alternative Therapy:

- Fluconazole 400 mg PO once weekly **(BII)**

Itraconazole *vs* Fluconazole as a Primary Prophylaxis for Fungal Infections in HIV-Infected Patients in Thailand

Romanee Chaiwarith[1], Apinya Fakthongyoo[1], Jutarat Praparattanapan[1], Darakorn Boonmee[1], Thira Sirisanthana[2] and Khuanchai Supparatpinyo[1,2]

Conclusions:

- Although *P. marneffei* has a reduced susceptibility in *in vitro* to fluconazole, once-weekly fluconazole is at least as effective as once-daily itraconazole as primary prophylaxis for systemic fungal infections in AIDS patients in northern Thailand

Current HIV research , 2011

TALAROMYCOSIS IN HIV: CONSOLIDATION AND SECONDARY THERAPY

- Itraconazole → NRTIs + Efavirenz
- Fluconazole → NRTIs + Efavirenz

Co-administration of EFV and Itraconazole may result in 20-50% reduction in serum itraconazole concentrationg

Carr et al, Lancet 1998
Foudraine et al, AIDS 1998

A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis

Thuy Le, M.D., D.Phil., Nguyen Van Kinh, M.D., Ph.D., Ngo T.K. Cuc, M.D.,

- Open-label, non-inferiority trial, randomized HIV-infected adults with talaromycosis,, to receive either intravenous amphotericin B deoxycholate or itraconazole capsules
- The risk of death at week 24 was 11.3% in the amphotericin group and 21.0% in the itraconazole group (95%CI, 2.8 to 16.6; P = 0.006).
- All patient was initiated on Efavirenz-based HAART ;

Relapse rate was 4 % (Itraconazole-Itraconazole) vs 1.5 (Ampho B-Itraconazole)

To initiate HAART promptly , by improving the immune function will accelerate the resolution of OIs

NEJM 2017

THANK YOU