MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Fungal infection updates 2019 – crosstalk between bench and bedside

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ASIA FUNGAL WORKING GROUP
an ISHAM working group

Fungal infection updates for 2019 – crosstalk between bench & bedside

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Emerging fungal threats to animal, plant and ecosystem health

NATURE | VOL 484 | 12 APRIL 2012

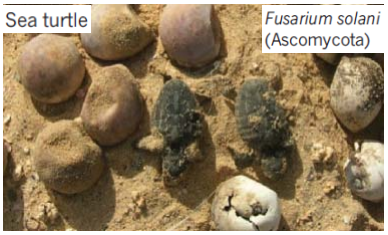
Fungi comprise the highest threat of extinction owing to infection for both animal (72% of extinctions) and plants (64% of extinctions), and this threat appears to be increasing

Bat

Bee species

Rice

Sea turtle



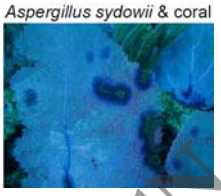
‘Planetary disasters:

- Death by volcano
- Death by solar flares
- Death by tsunami
- **Death by fungal epidemics**

Nature 8 Jan’13

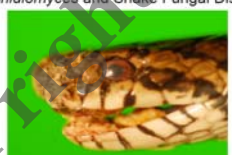
Fusarium solani & turtles

Aspergillus sydowii & coral



Nosema & honeybee CCD

Ophidiomyces and Snake Fungal Disease

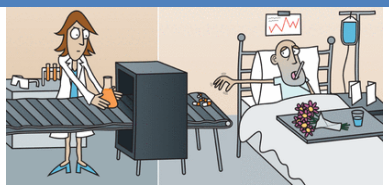


Why cross-talk required between bench & bedside?

Major three programs worldwide

- AIDS elimination
- Antibacterial stewardship
- Antifungal stewardship

Relevance of cross-talk between bench & bedside



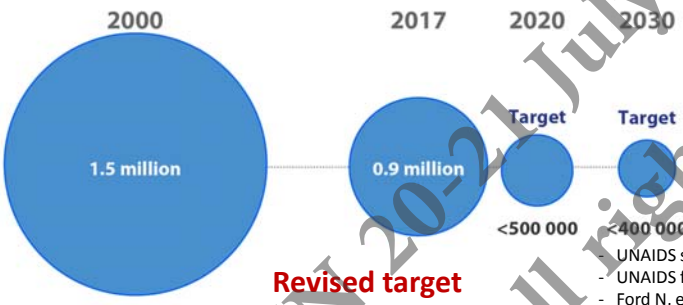
- Communicable disease had killed millions of people & destroyed many civilization
- But, AIDS has changed the course – disease identified in 1984 was up for elimination in 25 years time in 2010
- Setting trends for Sustainable Development Goal – elimination of all communicable disease by 2030
- In this ambitous goal, failure to END AIDS as pathfinder eliminable program has big stake
- Make or break opportunity

Major failure

- 2010, UNAIDS target - zero AIDS deaths by 2013

But

- By 2013, only 15% reduction in mortality, major issues
  - retention of care
  - late presentation with overwhelming infection



Revised target

- UNAIDS strategy 2010
- UNAIDS factsheet 2014
- Ford N, et al. AIDS 2016; 30: 521

Major hurdles

WHO/UNAIDS target of reducing AIDS deaths to <500,000 by 2020
(so need to achieve reduction by 50%)

Diagnose & treat HIV-TB co-infection	Hepatitis and HIV co-infection	Fungal diseases complicating HIV infection
Impactful, but still 24% of total deaths of 2013	Serious morbidity, but few patients die	Can reduce AIDS deaths by >30%

- UNAIDS strategy 2010
- UNAIDS factsheet 2014
- Ford N, et al. AIDS 2016; 30: 521

Causes of mortality – 2015 estimate

Denning DW. Phil Trans R Soc 2016; 71: 2010468

Ending AIDS by 2030 – is it possible without control of fungal disease?

Mortality 1.34 million

To control fungal disease – improvement of diagnosis & cross-talk required

HIV related, infective cause 1.0 million (74.6%)

Tuberculosis 400,000

Fungal causes 700,000

Chronic pulmonary aspergillosis, 56,000

Cryptococcosis, 232,000 (33%)

Pneumocystosis, 260,000 (37%)

Talaromycosis, 50,000 (7%)

Histoplasmosis, 80,000 (11.4%)

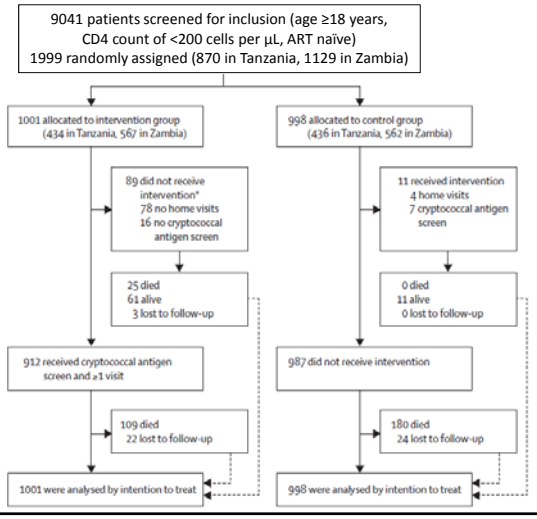
Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial

Lancet 2015; 385: 2173–82

International Standard Randomised Controlled Trial Number registry, number ISCRTN 20410413.

Sayoki Mfinanga, Duncan Chanda, S Eduard L Kivuya, Lorna Guinness, Christian Bottomley, Victoria Simms, Carol Chijioka, Ayubu Masasi, Godfather Kimaro, Bernard Ngowi, Amos Ohmuh, Peter Mwaba, Thomas S Harrison, Saidi Egwaga, Shabbar Jaffar, on behalf of the REMSTART trial team*

- Study enrolment – Feb 2012-Sept 2013
- Six urban clinics in Tanzania, & Zambia
- **Intervention group - Clinic plus community support with serum cryptococcal antigen screening + antifungal therapy for positive patients + weekly home visits for the first 4 weeks on ART (in Tanzania - + re-screening for tuberculosis at 6–8 weeks after ART initiation)**
- primary endpoint was all-cause mortality at 12 months, analysed by intention to treat



Adherence to ART

	Clinic and community support	Standard care	Rate ratio (95% CI)	p value
All				
Month 6 review	90% (421/467)	86% (375/435)	1·05 (1·00–1·10)	0·068
Month 12 review	89% (451/509)	89% (429/481)	0·99 (0·95–1·04)	0·770
Tanzania				
Month 6 review	86% (180/209)	80% (162/202)	1·07 (0·98–1·17)	0·111
Month 12 review	89% (236/265)	90% (226/250)	0·99 (0·93–1·04)	0·616
Zambia				
Month 6 review	93% (41/258)	91% (213/233)	1·02 (0·97–1·08)	0·407
Month 12 review	88% (215/244)	88% (203/231)	1·00 (0·94–1·07)	0·937

No significant difference

All cause mortality

	Clinic plus community support			Standard care			Rate ratio (95% CI)	p value
	Events	PYO	Rate (95% CI)	Events	PYO	Rate (95% CI)		
All-cause mortality								
All	134	877	15·3 (12·9–18·1)	180	843	21·3 (18·4–24·7)	0·72 (0·57–0·90)	0·004
Tanzania	66	370	17·9 (14·0–22·7)	87	359	24·2 (19·6–29·9)	0·74 (0·54–1·01)	0·073
Zambia	68	507	13·4 (10·6–17·0)	93	484	19·2 (15·7–23·5)	0·70 (0·51–0·95)	0·027

Cryptococcal Ag positive

	Clinic plus community support (n=1001)	
	Tanzania (n=434)	Zambia (n=567)
Cryptococcal antigen positive at enrolment†	22 (5%)	16 (3%)
Agreed to have lumbar puncture‡	5 (23%)	4 (25%)
CSF positive for cryptococcus§	0	3 (75%)

- **Screening & pre-emptive treatment for cryptococcal infection could substantially reduce mortality in HIV programmes in Africa**
- **Cross-talk between laboratory & AIDS physicians is essential to achieve this**

EMERGING INFECTIOUS DISEASES PERSPECTIVE Volume 23, Number 2—February 2017 P. 179

Delivering on Antimicrobial Resistance Agenda Not Possible without Improving Fungal Diagnostic Capabilities

David W. Denning, David S. Perlin, Eavan G. Muldoon, Arnaldo Lopes Colombo, Arunaloke Chakrabarti, Malcolm D. Richardson, Tania C. Sorrell

1. inaccurate diagnosis of **fungal sepsis** - resulting in inappropriate use of broad-spectrum antibacterial drugs

2. Most serious fungal infections are **'hidden'**, occurring as a consequence of other health problems such as asthma, AIDS, cancer, organ transplant & corticosteroid therapies

3. **Misdiagnosis** resulting in unnecessary antibacterial drugs

To avoid empirical therapy, we need advancement of fungal diagnosis beyond present conventional techniques

Blood culture for *Candida* isolation

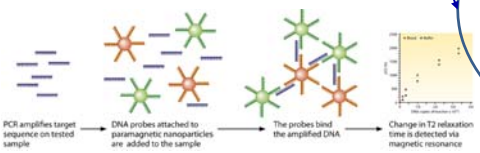
- **Current gold standard**
- 40ml blood should be cultured at any time on automated system (can culture for bacteria & fungi simultaneously)
- Sensitivity of blood culture gets limited, as *Candida* cells are rapidly eliminated from circulation
- **Sensitivity comparable to PCR (30-70%)**
- **But, blood culture positivity ~50%**
- **Drawback – median time of positivity 2-3d, may be long (8d)**

Clancy & Nguyen, Clin Infect Dis 2013; 59: 1284

T2 magnetic resonance nanoparticle mediated detection for *Candida*

- Improved turnaround
- BACTEC – 2.6d, T2 – 3-4h

- Identify only 5 *Candida* species
- Contamination
- Can't perform susceptibility
- Can't replace conventional
- Not available in developing countries

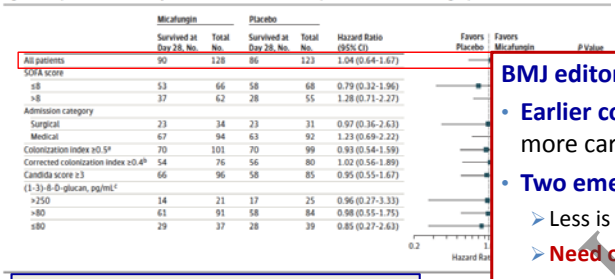


Beyda ND, *et al.* Diagn Microbiol Infect Dis 2013; 77: 324

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure
The EMPIRICUS Randomized Clinical Trial

JAMA. 2016;316(15):1555-1564. doi:10.1001/jama.2016.14655
Published online October 5, 2016.

Figure 3. Comparison of Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups



	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	P Value
All patients	90	128	86	123	1.04 (0.64-1.67)	
SOFA score						
≤8	53	66	58	68	0.79 (0.32-1.96)	
>8	37	62	28	55	1.28 (0.71-2.27)	
Admission category						
Surgical	23	34	23	31	0.97 (0.36-2.63)	
Medical	67	94	63	92	1.23 (0.69-2.22)	
Colonization index ≥0.5[a]	70	101	70	99	0.93 (0.54-1.59)	
Corrected colonization index ≥0.4[b]	54	76	56	80	1.02 (0.56-1.89)	
Candida score ≥3	66	96	58	85	0.95 (0.55-1.67)	
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	17	25	0.96 (0.27-3.33)	
>80	61	91	58	84	0.98 (0.55-1.75)	
≤80	29	37	28	39	0.85 (0.27-2.63)	

- Empiric therapy decreased the rate of new invasive fungal infections
  - 4/128 (3%) in micafungin group
  - 15/123 (12%) in placebo group (p=0.008)

BMJ editorial

- **Earlier concept** – 'some care good, more care better'
- **Two emerging themes**
  - Less is better
  - **Need of Targeted therapy**
- **Criticism**
  - Certain risk group may benefit from empiric therapy
  - The study did not include GI leakage group & acute necrotizing pancreatitis

It is easy to advice – targeted therapy (diagnose & then treat!)
(*Candida* sepsis in ICUs)

- Blood culture **positivity ~50%**
- **Colonization index** – sampling for all colonization sites daily, impractical in clinical situation, not cost effective; Moreover, near all ICU patients are colonized with *Candida* due to antibiotic
- **Ostrosky's rule** – PPV only 10%
- Do you know, **which patients to be treated with antifungal when predictive rules, candida score, blood culture fail**?

I have no answer to all your questions

But, I need cross-talk between bench & bedside to overcome some of those problems

How difficult to cope with ideal AFS?

Definition of AFS	
Right antifungal	Depends on diagnosis
Right patient	Depends on diagnosis
At right time	Early diagnosis is challenge
With right dose	TDM essential for azoles
With right route	Polyene/echinocandin i.v.
Causing least harm to the patient & future patient	Majority antifungal are toxic, drug-interaction

Updates in fungal disease in last one year

- **Candidiasis**
  - Attributable mortality of candidemia (49% → 25%, improvement of diagnosis? echinocandin effect?)
  - Ibrexafungerp: After all the years a (well tolerated) new class!
- **Aspergillus**
  - CPA & invasive aspergillosis – new guideline
- **Mucormycosis**
  - One World – One Guideline
- **New risk factors**
  - Ibrutinib and all the other TKIs and immunomodulating drugs
- **New trends**
  - Measuring guideline adherence

Cornely. O. ECCMID, 2019

More updates – relevant to bench to bedside

- Knowledge of Game changers in fungal disease
- New fungi causing fungal infections
- New concerns, new susceptible group, new risk factors & new epidemiology
- Emerging antifungal resistance
- Improvement in diagnosis
- Improved management strategies

Game-changers in recent years

HEALTH

Spread of Deadly Cryptococcal Disease in U.S. Northwest Linked to Global Warming

Mortality >30%, though the fungus is not resistant

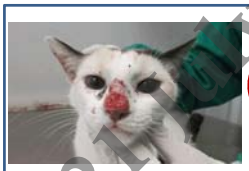
mSphere

Dating the *Cryptococcus gattii* Dispersal to the North American Pacific Northwest

Behaving as a bacterium

News

Intensive care unit closed after new deadly superbug emerges in the UK



Animal to man direct spread

Cat-Transmitted Sporotrichosis Epidemic in Rio de Janeiro, Brazil: Description of a Series of Cases

JAVMA news

AVMA

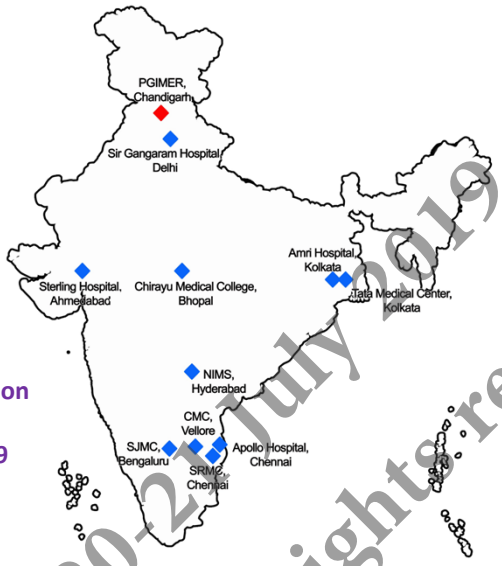
March 15, 2019

Cats spreading fungal disease to people in Brazil

New concerns, new susceptible group, new risk factors & new epidemiology

Invasive mould infection in Indian ICUs- Descriptive Epidemiology

Fungal Infection study forum (FISF)
[April 2016-September 2017]



April 2016 – Sept. 2017

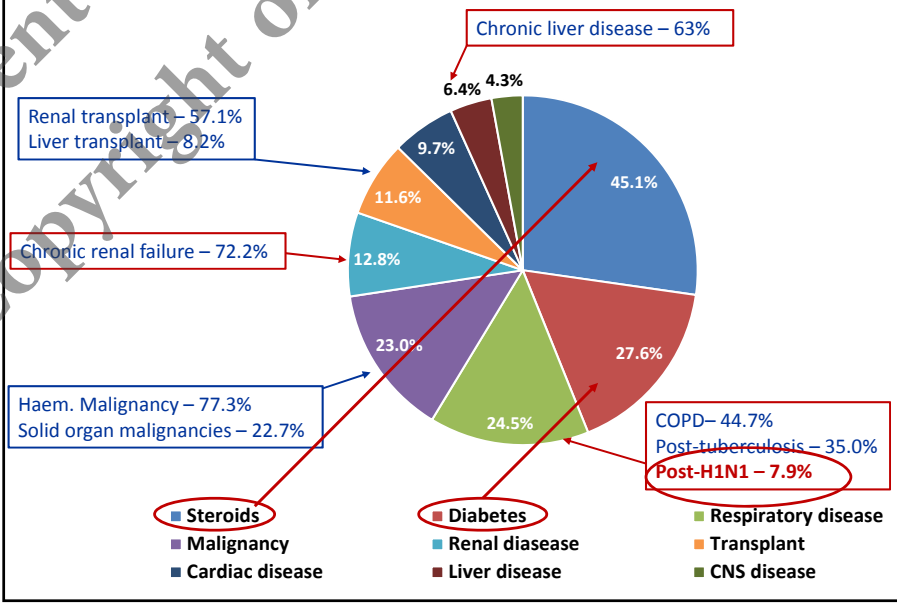
- **Total invasive mould infection (IFI) cases: 398**
- **Total ICU admissions: 41849**
- **9.5 (range 4.3- 29.0) IMI cases/1000 ICU admissions**

Overall mortality rate was 67.3%: mortality 64.5% in those treated

Chakrabarti A, *et al*. J Critical Care 2019; 51: 64-70

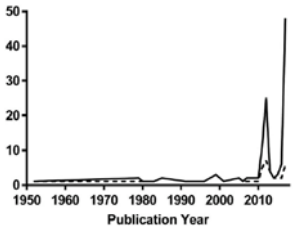
Underlying risk factors

Chakrabarti A, *et al*. J Critical Care 2019; 51: 64-70



Invasive aspergillosis linked to influenza

- Literature review – 68 cases of influenza-associated IA – 47% mortality
- Severe influenza admitted to 8 tertiary ICUs in Netherlands Dec 2015 to April 2016
- 144 patients with influenza; 23 (16%) had IA; 14/23 (61%) died



Curr Opin Infect Dis 2018, 31:471–480

Continent	Country	Publications (n = 50)
Africa		
	South Africa	1
Asia		
	Japan	6
	Korea	5
	Taiwan	4
Australia		
	Australia	1
Europe		
	Belgium	1
	France	3
	Germany	2
	Ireland	1
	Italy	1
	Poland	1
	Spain	3
	Switzerland	2
	The Netherlands	3
	United Kingdom	4
North America		
	United States of America	10

Schauwvlieghe et al, TIMM 2017

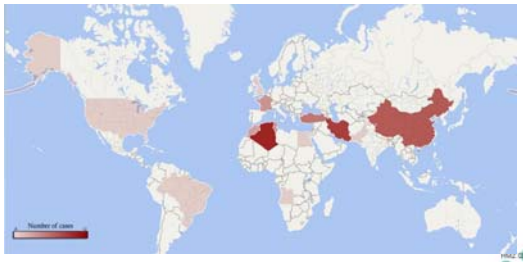
- 128 cases reported
- Mortality is very high
- Acquire the infection early after ICU admission
- Increases awareness is very important issue

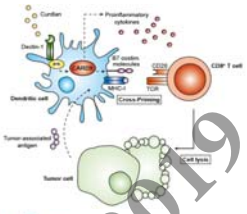
Fungi isolated [190 (single mould – 173, >1 mould - 17) 47.7%]

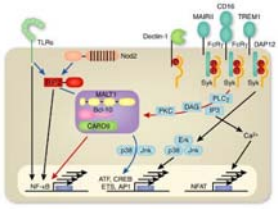
Aspergillus		**142 (82.1%)**		
	A. flavus	**67 (47.2%)**	***Fusarium***	**4 (2.3%)**
	A. fumigatus	**56 (39.4%)**	*C. lunata*	1 (0.6%)
	A. terreus	**8 (5.6%)**	*P. insidiosum*	1 (0.6%)
	A. niger	**6 (4.2%)**		
	Unidentified	5 (3.5%)	**Only smear positive**	**25 aseptate** 15 septate 4 mixture
Mucorales		**25 (14.5%)**		
Rhizopus species		**19 (11.0%)**	**Molecular**	**3**
	R. arrhizus	**11 (6.4%)**	*A. flavus*	2
	R. microsporus	1 (0.6%)	*A. fumigatus*	1
	Rhizopus spp.	7 (4.0%)		
Mucor		4 (2.3%)	**Mucormycosis – 24%**	
Apophysomyces		2 (1.2%)		

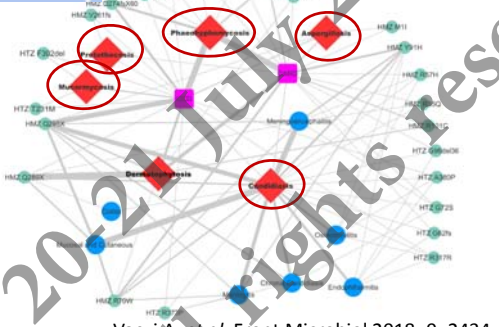
Chakrabarti A, *et al*. J Critical Care 2019; 51: 64-70

CARD 9 deficiency linked many fungal infections









Vaezi A, *et al*. Front Microbiol 2018; 9: 2434

New disease & agents

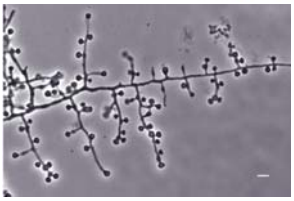
PLoS Negl Trop Dis. 2018 Jan; 12(1): e0006174.
Published online 2018 Jan 22. doi: 10.1371/journal.pntd.0006174

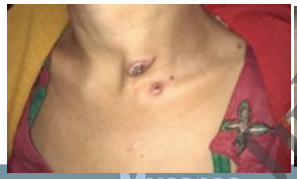
PMCID: PMC5800596
PMID: 29357352

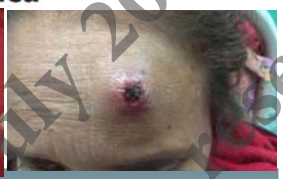
Molecular detection of airborne *Emergomyces africanus*, a thermally dimorphic fungal pathogen, in Cape Town, South Africa

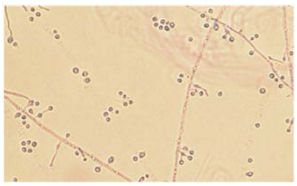
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 24, No. 4, April 2018

Emergomyces canadensis, a Dimorphic Fungus Causing Fatal Systemic Human Disease in North America









Mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Case Report | Full Access

Disseminated *Emmonsia pasteuriana* infection in India: a case report and a review

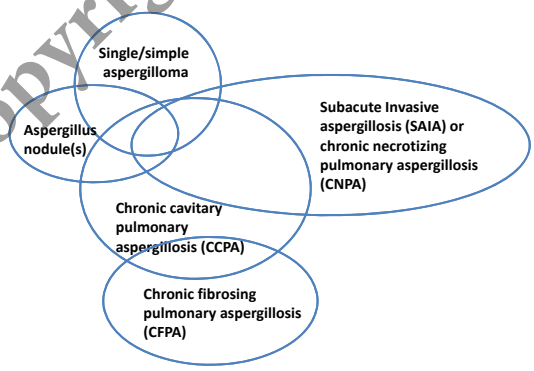
Rupali Malik, Malini R. Capoor, Ilavarasi Vanidassane, Arun Gogna, Avninder Singh, Biswajit Sen, Shivaprakash M. Rudramurthy, Prasanna Honnavar, Sunita Gupta, Arunaloke Chakrabarti

First published: 09 December 2015 | https://doi.org/10.1111/myc.12437 | Cited by: 9

Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management

Eur Respir J 2016; 47: 45–68

David W. Denning[1], Jacques Cadranel[2], Catherine Beigelman-Aubry[3], Florence Ader[4,5], Arunaloke Chakrabarti[6], Stijn Blot[7,8], Andrew J. Ullmann[9], George Dimopoulos[10] and Christoph Lange[11–14] on behalf of the European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society



- The prevalence rate - <1/100,000 population in large western European countries & the USA **to 43/100,000 in Democratic Republic of the Congo & Nigeria**
- China & India had intermediate five-year period prevalence rates of 16 and 24/100,000, respectively

Estimated annual CPA cases in India – 92,042 (7.4/100,000)

Agarwal, Denning, Chakrabarti. PLoS One 2014; 9: e114745

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 24, No. 8, August 2018

Case Definition of Chronic Pulmonary Aspergillosis in Resource-Constrained Settings

David W. Denning, Iain D. Page, Jeremiah Chakaya, Kauser Jabeen, Cecilia M. Jude, Muriel Cornet, Ana Alastruey-Izquierdo, Felix Bongomin, Paul Bowyer, Arunaloke Chakrabarti, Sara Gago, John Guto, Bruno Hochhegger, Martin Hoenigl, Muhammad Irfan, Nicholas Irurhe, Koichi Izumikawa, Bruce Kirenga, Veronica Manduku, Samihah Moazam, Rita O. Oladele, Malcolm D. Richardson, Juan Luis Rodriguez Tudela, Anna Rozaliyani, Helmut J.F. Salzer, Richard Sawyer, Nasilele F. Simukulwa, Alena Skrahina, Charlotte Sriruttan, Findra Setianingrum, Bayu A.P. Wilopo, Donald C. Cole, Haileyesus Getahun

Required criteria†	Details
Symptoms for ≥3 mo	Hemoptysis and/or persistent cough, and/or weight loss; other symptoms are common, but not required, notably fatigue, chest pain, dyspnea, and sputum production
Radiologic features	Progressive cavitation on chest imaging and/or intracavitary fungal ball and/or pleural thickening or pericavitary fibrosis or infiltrates all adjacent to cavities
Microbiological evidence of *Aspergillus* infection	Positive *Aspergillus*-specific IgG and/or sputum microscopy results showing hyphae consistent with *Aspergillus* and/or *Aspergillus* growth on ≥2 sputum or other respiratory samples
Mycobacterial infection ruled out with smear, GeneXpert, and/or mycobacterial culture‡	It is possible for mycobacterial infection and CPA to be present concurrently, but this diagnosis requires characteristic radiological findings on CT scan that are not present with pulmonary TB including pleural thickening, a fungal ball or other intracavitary material, or marked pericavitary infiltrates in addition to a positive *Aspergillus* IgG antibody test

*CPA, chronic pulmonary aspergillosis; CT, computed tomography; TB, tuberculosis.
†All 4 criteria are required.
‡GeneXpert (http://www.cepheid.com/us/cepheid-solutions/systems/genexpert-systems/genexpert-iv).

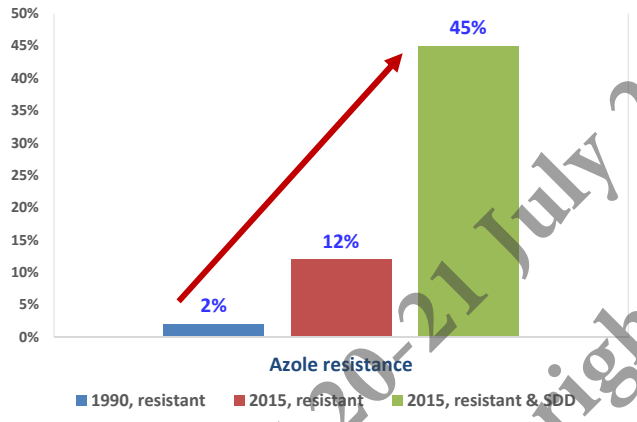
Antifungal resistance

Azole susceptibility profile

n = 918; 27 centers

- *C. tropicalis* – 5-41.6%
- *C. albicans* - 9.4-40%

(Including resistant & SDD)



Chakrabarti *et al.* Intensive Care Med 2015; 41: 285

Azole susceptibility in other Asian countries

Organism	Fluconazole (R + SDD)	Voriconazole (R + SDD)	Itraconazole (R + SDD)	reference
Malaysia				
C. albicans	**5.6%**	**1.4%**	**2.8%**	J Med Microbiol 2011; 60: 1312
C. tropicalis	**7.4%**	**0.0%**	**3.7%**	
C. parapsilosis	**7.1%**	**1.4%**	**14.3%**	
C. glabrata	**16.6%**	**0.0%**	**16.6%**	
China				
C. tropicalis	**14.1%**	**7.1%**	**96.1%**	JAC 2013: 68: 778
C. albicans	**34.6%**	**7.7%**	**40.4%**	JAC 2014; 69: 162
C. tropicalis	**37.3%**	**10.4%**		
C. parapsilosis	**51.8%**	**7.2%**		

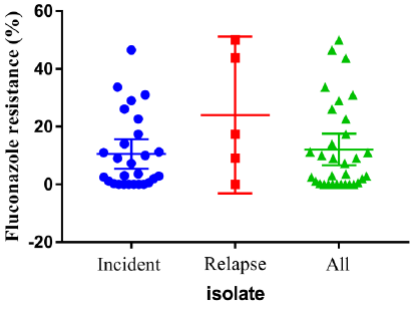
Azole resistance in *A. fumigatus*

- Increasingly recognised : clinical, environmental isolates
- Varies with geography (2-15%; maybe more)
- Low incidence in Asian countries
- **Is it a global phenomenon or restricted in certain geographical location like north Europe?**

Verweij et al, Clin Infect Dis. 2016; 62: 362; Stensvold CR, et al. Curr Fungal Infect Rep 2012; 6: 178

Fluconazole resistance in *Cryptococcus neoformans*

- A total of 4,995 *Cryptococcus* isolates from 3,210 patients were evaluated



- **Mean prevalence of resistance is 12.1%**
- Mean fluconazole resistance was **10.6%** (95% CI: 5.5% - 15.6%) **for the incident isolates** (n=4,747), and **24.1%** (95% CI: -3.1% - 51.2%) **for the relapse isolates** (n=248).

Bongomin F, *et al*. Mycoses. 2018; 61: 290

Progress in diagnosis

Avancement in diagnosis

- Direct detection of **biomarkers** or fungal pathogen **nucleic acid for diagnosis.**
- **Identification** of positive cultures to genus or species level by **MALDI or nucleic acid**
- **Molecular typing and phylogeny** for outbreak and cluster analysis.
- **Rapidly identify the mechanisms of antifungal resistance**.

Proteomic vs. genomic approach

Proteomic approach

- Identification from growth – MALDI (very promising)
- Detection in clinical sample – promising, but success limited
- Limitation
  - presence of biomarker in pg
  - No scope of prior amplification before detection

Genomic approach

- Pre-amplification possible
- Higher sensitivity & specificity, low turn-around time
- Better in patient on prophylaxis, as GM released in active growth
- Limitation
  - Contamination & not standardized yet

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry for the rapid identification of yeasts causing bloodstream infections

A. K. Ghosh, S. Paul, P. Sood, S. M. Rudramurthy, A. Rajbanshi, T. J. Jillwin and A. Chakrabarti

Clin Microbiol Infect 2015; 21: 372–378

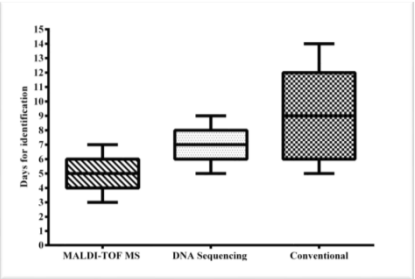
MALDI-TOF correctly identified 98.9% as compared to PCR-sequencing

Matrix-assisted laser desorption/ionization–time of flight mass spectrometry: protocol standardization and database expansion for rapid identification of clinically important molds

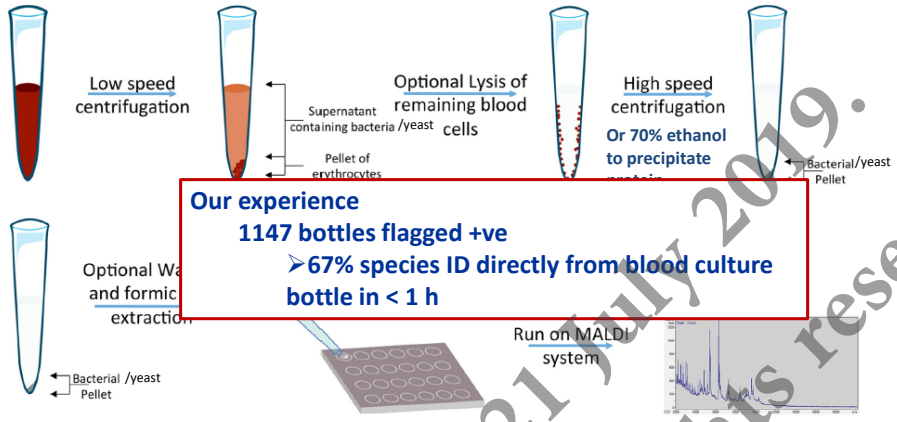
Future Microbiol. 2017 Dec;12:1457-1466.

Saikat Paul[1], Pankaj Singh[1], Shivaprakash M Rudramurthy[1], Arunaloke Chakrabarti[1] & Anup K Ghosh*[,1]

Comparison of TAT for mycelial fungi



Culture – independent same-day identification



Our experience

1147 bottles flagged +ve

➢**67% species ID directly from blood culture bottle in < 1 h**

Protocols

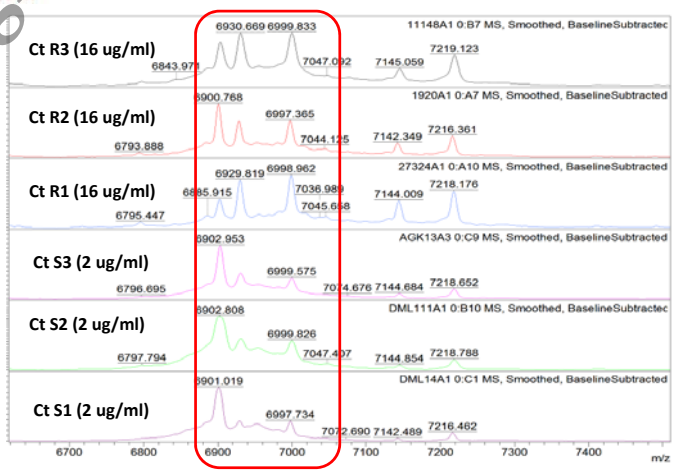
-Removal of red cells	- distilled water/SDS or ammonium chloride/saponin
-Protein precipitation	- 70% ethanol washing
-Protein solubilization	- trifluoroacetic acid or formic acid+acetonitrile

Faron ML, *et al*. J Clin Microbiol 2017; 55: 3328

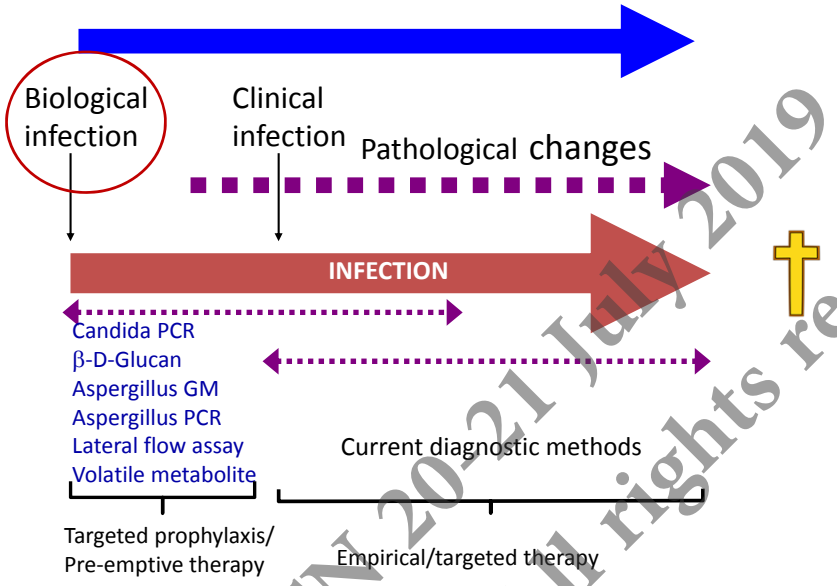
Medical Mycology, 2018, 56, 234–241

Rapid detection of fluconazole resistance in *Candida tropicalis* by MALDI-TOF MS

Saikat Paul, Pankaj Singh, Shamanth A S, Shivaprakash M, Rudramurthy, Arunaloke Chakrabarti and Anup K Ghosh*



But what would be real success?



Biomarker tests

Existing benchmark tests

- CRP & Procalcitonin ?
- Serum galactomannan
- BAL galactomannan
- Serum Beta-D gulcan

(Caution: may need 'expert' interpretation)

New biomarkers

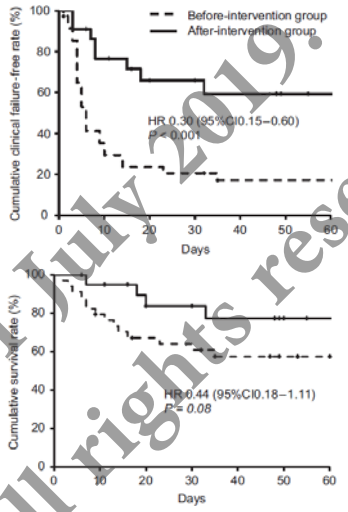
- Aspergillus PCR
- Aspergillus GM + PCR
- Aspergillus Lateral flow
- BAL Beta-D glucan
- Mucorales PCR from blood
- Breath Volatile metabolites
- Many potential POCT

J Clin Pharm Ther. 2019;44:454–462.

The impact of implementing an antifungal stewardship with monitoring of 1-3, β-D-glucan values on antifungal consumption and clinical outcomes

Syuri Ito-Takeichi[1,2] | Takashi Niwa[1,2] | Ayasa Fujibayashi[1,2] | Keiko Suzuki[1] | Hirotoshi Ohta[2] | Ayumi Niwa[2] | Mayumi Tsuchiya[2] | Masayo Yamamoto[2] |

- Daily reviews of antifungal agents & monitoring βDG
- Parental antifungal use significantly reduced compared to that before intervention (*P* = 0.006)
- **60-day clinical failure in patients with *Candida* bloodstream infection was significantly reduced, from 80.0% to 36.4% (*P* < 0.001)**
- **60-day mortality associated with candidaemia reduced, from 42.9% to 18.2% (*P* = 0.081)**
- Antifungal adverse events significantly lower in the after-intervention group than in the before-intervention group (51.4% vs 13.6%, *P* = 0.004)



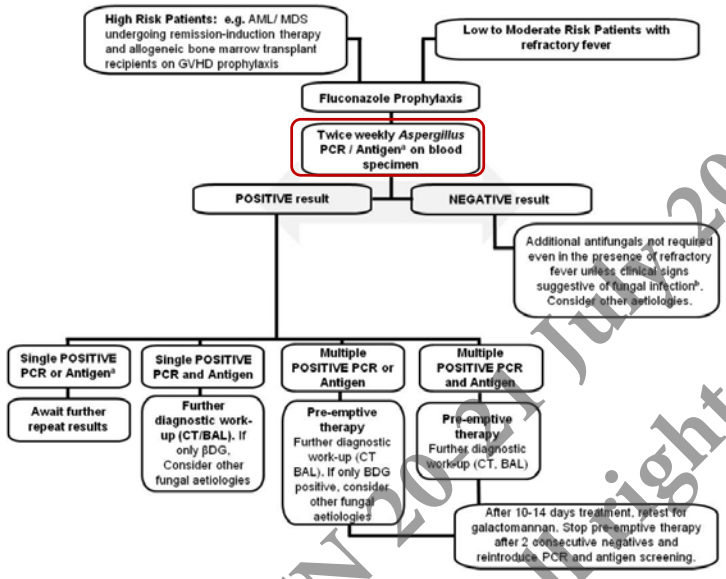
Diagnosis of aspergillosis – comparison GM/BDG/PCR

White PL *et al.* Clin Infect Dis 2015; 61: 1293

Characteristic	GM-EIA	B-D-glucan	PCR
Methodological recommendation	Single commercial assay with SOP: **Platelia Aspergillus antigen** (BioRad)	5 commercial assays: **Fungitell** (Associates of Cape Cod) **Fungitec G-Test MK** (Seikagaku Corporation) **B-G Star** (Maruha Corporation **B-Glucan Test Wako** (Wako Pure Chemicals) **Dynamiker Fungus** (1–3)-β-D-Glucan Assay (Dynamiker Biotechnology Co, Ltd)	**Pathonostics Aspergenius, Roche Septifast, Myconostica MycAssay, Ademtech Mycogenie, Renishaw Fungiplex,** Procedural recommendations for DNA extraction **(EAPCRI)**
Quality control	Internal – BioRad Proficiency panel	No	Independent – QCMD & EAPCRI Panels
Sensitivity %	Blood: 79.3 BAL: 83.6–85.7	Blood: IA: 56.8–77.1	Blood: 84–88 BAL: 76.8–79.6
Specificity %	Blood: 80.5–86.3 BAL: 89.0–89.4	Blood: 81.3–97.0	Blood: 75–76 BAL: 93.7–94.5
False positive	Yes	Yes	Yes
False negative	Yes	Yes	Yes
Clinical utility	Yes	Limited	yes

Screening strategy

Barnes RA, *et al*. Med Mycol 2018; 56: S60

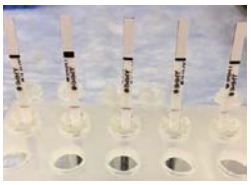


Mycoses. 2019;62:230–236.

Point-of-care diagnosis of invasive aspergillosis in non-neutropenic patients: *Aspergillus* Galactomannan Lateral Flow Assay versus *Aspergillus*-specific Lateral Flow Device test in bronchoalveolar lavage

Jeffrey D. Jenks[1] | Sanjay R. Mehta[1] | Randy Taplitz[1] | Saima Aslam
Sharon L. Reed[1,2] | Martin Hoenigl[1]

Aspergillus specific LFA

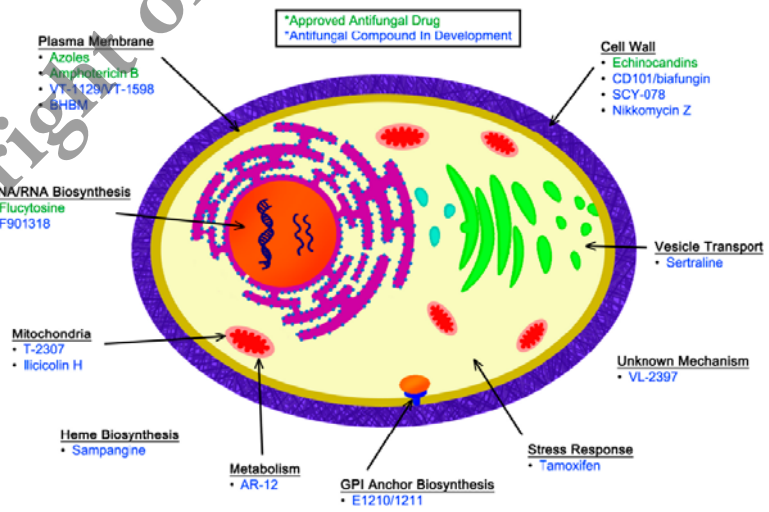


Aspergillus GM LFA

- 82 patients evaluated
- Both point-of-care tests showed comparable performance,
- Sensitivities & specificities in the 60%-70% range when used alone & increasing to 80% when used in combination

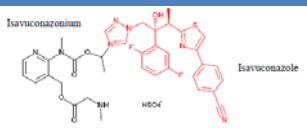
Management

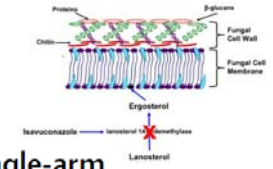
Existing & new (in development) antifungal agents



Pianalto &Alspaugh. J Fungi 2016; 2: 26

Isavuconazole





Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis

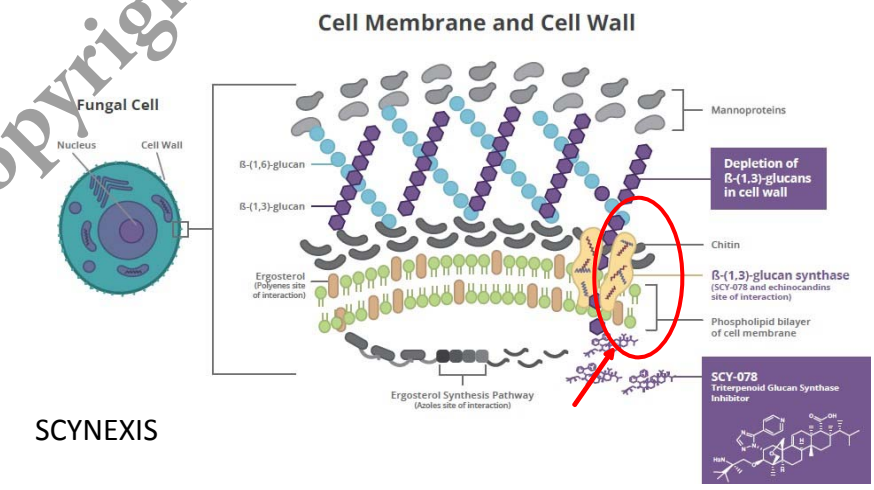
	Isavuconazole	Amphotericin B	p value
Crude all-cause mortality, n/N (%; 95% CI)*	7/21 (33%; 14·6–57·0)	13/33 (39%; 22·9–57·9)	p=0·775†
Weighted all-cause mortality (%;‡ 95% CI)*	33%; 13·2–53·5	41%; 20·2–62·3	p=0·595§
Crude mortality by matching covariates, n/N (%)			
Haematological malignancy	5/11 (45%)	7/18 (39%)	NA
Severe disease¶	6/12 (50%)	8/13 (62%)	NA
Surgical treatment‖	4/9 (44%)	3/13 (23%)	NA

Primary treatment with isavuconazole-treated cases (VITAL) versus amphotericin B-treated controls (FungiScope). *95% CI are based on an exact binomial distribution (crude) or normal approximation (weighted). †Calculated from Fisher's exact test. ‡Weights were applied according to the ratio of the number of controls matched to each case. §Calculated from a χ^2 test. ¶CNS involvement or disseminated disease (defined as disease involving >1 non-contiguous organ). ‖Resection or debridement at the site of infection at treatment start (SD 7 days).

Marty FM, *et al*. Lancet Infect Dis 2016; 16: 828

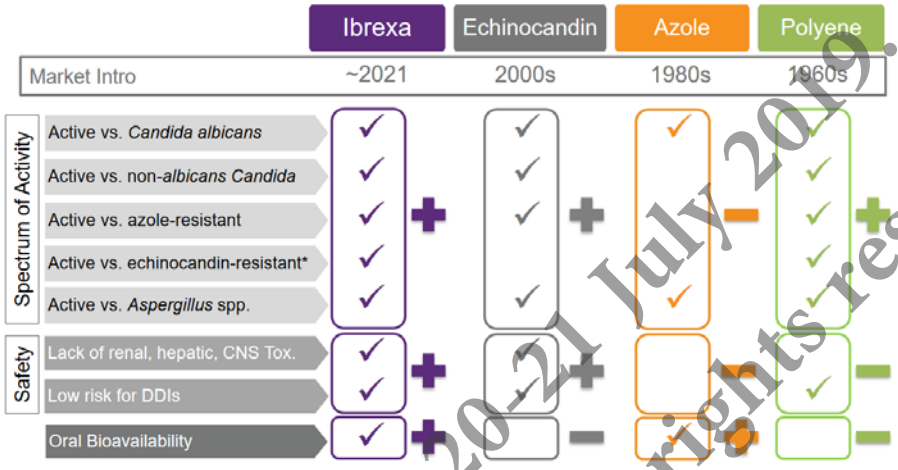
Ibrexafungerp (Formerly SCY-078): a novel antifungal agent

Structurally distinct from other glucan synthesis inhibitors, e.g. echinocandins



SCYNEXIS

Ibrexafungerp: glucan synthase inhibitor

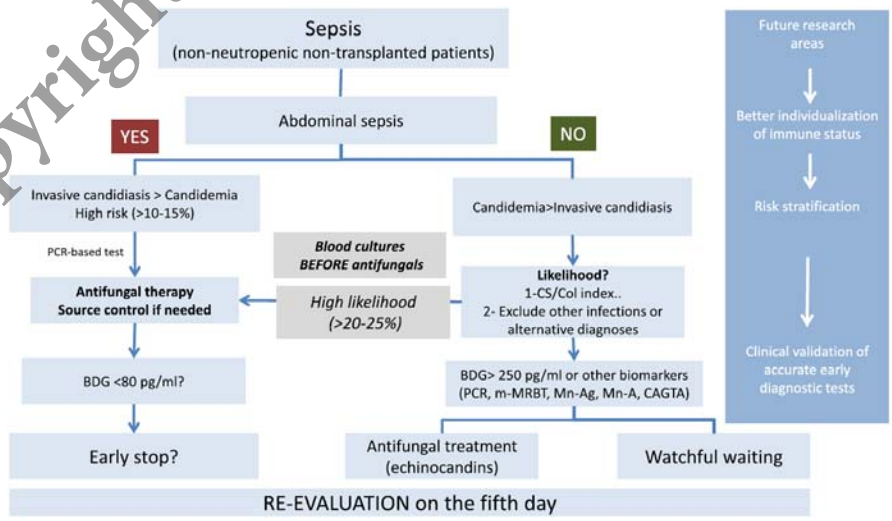


Cornely OA et al. ECCMID 2019: L0010.

ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients

Intensive Care Med (2019) 45:789–805

Ignacio Martin-Loeches[1,2*], Massimo Antonelli[3], Manuel Cuenca-Estrella[4], George Dimopoulos[5], Sharon Einav[6], Jan J. De Waele[7], Jose Garnacho-Montero[8,9], Souha S. Kanj[10], Flavia R. Machado[11], Philippe Montravers[12], Yasser Sakr[13], Maurizio Sanguinetti[14], Jean-Francois Timsit[15,16] and Matteo Bassetti



Points to consider while managing

QUESTIONS TO START "EARLY"

1) Is the patient at high risk of invasive candidiasis?
(e.g. Colonisation, abdominal surgery, broad-spectrum antibiotic therapy, CVC, ICU stay > 4 days)

2) Are the clinical conditions "stable"?
(e.g. Suspected infection with stable haemodynamics OR Sepsis/Septic shock)

3) Have I evaluated the results of biomarkers?
(e.g. Two consecutive BDG results > 80 pg/ml cut-off; Association with PCT < 2 ng/ml)

4) Can I take into account other non-culture assays?
(e.g. PCR, T2MR, MALDITOF)

EFFECTIVE "EARLY" ANTIFUNGAL TREATMENT IN ICU

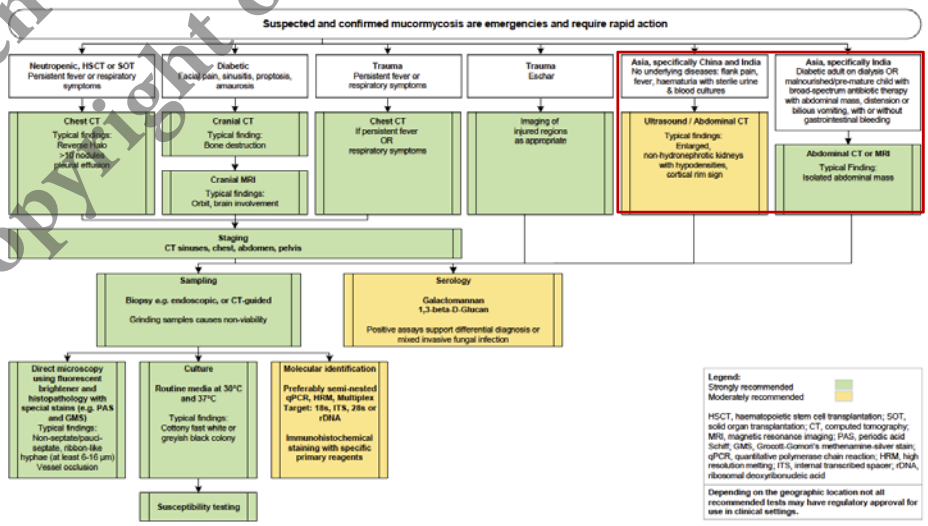
1) Have I requested and checked biomarkers?
(e.g. Serial measurements of BDG < 80 pg/ml; Association with Mannan, antimannan antibodies, or CAGTA)

2) Is it still reasonable to continue antifungal treatment?
(e.g. Other source of infections, results from standard cultures, adequate source control)

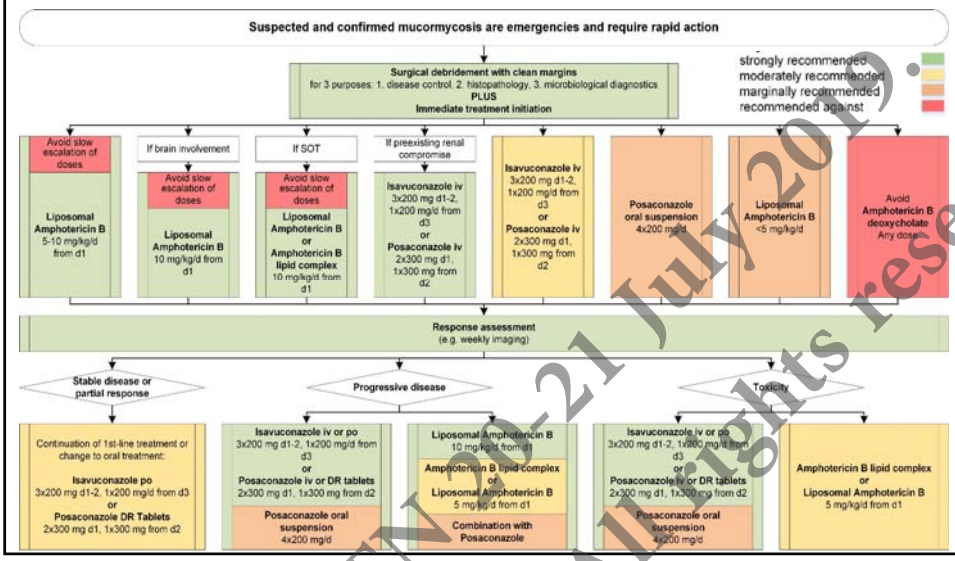
QUESTIONS TO STOP "EARLY"

Cortegiani A, Bassetti M. ICU Management & Practice 2018; 18 (4)

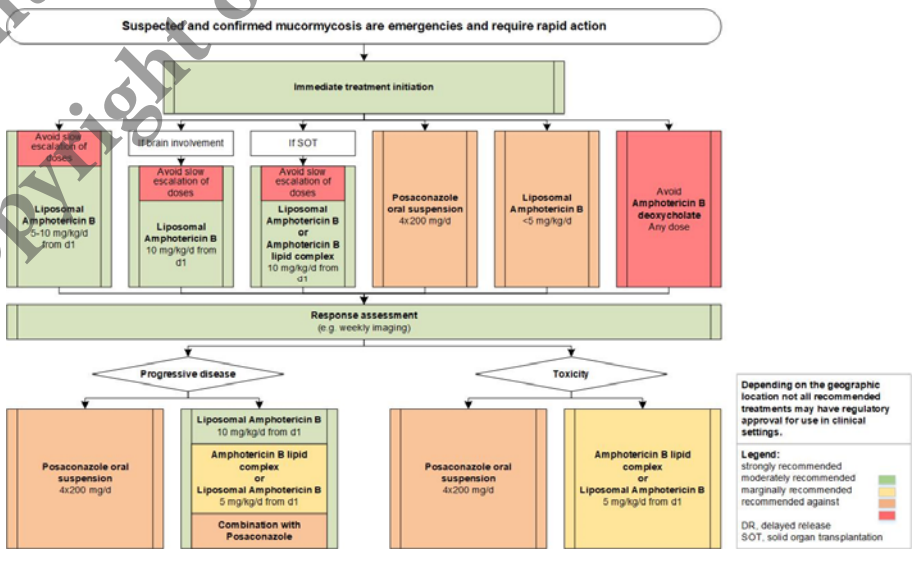
Mucormycosis world guideline – diagnostic pathway



Mucormycosis treatment pathway – all options available



Treatment pathway when isavuconazole not available



Equal *Candida* score

(adherence to guideline)

EQUAL Candida Score 2018: An **E**CMM Score Derived From Current Guidelines to Measure **QUAL**ity of Clinical Candidemia Management

EQUAL Candida Score 2018 [1,2]

Diagnosis	Initial blood culture (40mL) [3,4]	3
	Species identification [3,4]	3
	Susceptibility testing [3,4]	2
	Echocardiography [3,5]	1
	Ophthalmoscopy [5,6]	1
Treatment	Echinocandin treatment [3,5]	3
	Step down to fluconazole depending on susceptibility result [3,5]	2
	Treatment for 14 days after first negative follow-up culture [3,5]	2
	CVC carriers*: CVC removal [3,5,7] ≤ 24 hours from diagnosis	3
	CVC carriers*: CVC removal [3,5,7] > 24 < 72 h hours from diagnosis	2
Follow-Up	Follow-up blood culture (at least one per day until negative) [3,5]	2

* CVC carriers receive extra points, total score thus differs in Non-CVC vs. CVC carriers

Background

The EQUAL Candida Score weighs and aggregates factors recommended for the ideal management of candidemia and provides a tool for antifungal stewardship as well as for measuring guideline adherence. Current guidelines provided by the *European Society for Clinical Microbiology and Infectious Diseases*[4,5] and by the *Infectious Diseases Society of America*[3] were reviewed and the strongest recommendations for management quality selected as basis for this scoring tool.

Maximum Score

	Non-CVC carriers	CVC carriers
Diagnosis	10	10
Treatment	7	10
Follow-up	2	2
Total	19	22

References

1. Mellinghoff et al. *Mycoses* 2018; 2. Koehler et al. *Mycoses* 2014; 3. Pappas et al. *Clin Infect Dis* 2016; 4. Cuenca-Estrella et al. *Clin Infect Dis* 2012; 5. Comely et al. *Clin Microbiol Infect* 2012; 6. Munoz et al. *Diagn Microbiol Infect Dis* 2017; 7. Andes et al. *Clin Infect Dis* 2012.

Whether a high score correlates with outcome remains to be explored

Mellinghoff SC, *et al.* Mycoses 2018; 61: 326

Fungal Infections Related to New Immunotherapies & Biologicals

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

VIEWPOINTS

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

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]

Blood 2018; 131: 1955

LYMPHOID NEOPLASIA

Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib

David Ghez,[1] Anne Calleja,[2] Caroline Protin,[3] Marine Baron,[4] Marie-Pierre Ledoux,[5] Gandhi Damaj,[6] Mathieu Dupont,[7] Brigitte Dreyfus,[8] Emmanuelle Ferrant,[9] Charles Herbaux,[10] Kamel Laribi,[11] Ronan Le Calloch,[12] Marion Malphettes,[13] Franciane Paul,[14] Laetitia Souchet,[4] Malgorzata Truchan-Graczyk,[15] Karen Delavigne,[16] Caroline Dartigeas,[17] and Loïc Ysebaert,[3] on behalf on the French Innovative Leukemia Organization (FILO) CLL group

Summary

- Game changers in fungal diseases – cryptococcosis in temperate climate, outbreak of sporotrichosis in Brazil, global outbreak of C. auris infection
- Reason – fungal adaptation, host changes due to morbidity
- New susceptible hosts, new diseases bothering us
- Antifungal resistance is also emerging
- Improvement of diagnosis – MALDI, biomarkers, fungal PCR
  - New initiatives – genetic susceptibility, POCT (lateral flow, proximity ligation assay, microarray, nano technology, T2)
- **Asian laboratories** – investment required, LFA – cheaper option
- New antifungals are in pipeline, local management strategies required
- Most important – cross-talk between laboratory & clinicians
- **Think of fungus in your patient!**

Autopsy study in critically ill patients

- **893 post-mortem examinations were performed**
- **2.8% were diagnosed with invasive aspergillosis.**
- **60% were never diagnosed for IA ante-mortem**
- Most common comorbid conditions were **corticosteroid treatment (56%), COPD (44%),** immunosuppression (24%) & haematological malignancy (20%).
- 92% had three or more risk factors
- Critically ill patients with pulmonary infiltrates, treated with high doses intravenous corticosteroids (even for a short period of time), particularly COPD patients who developed worsening respiratory insufficiency were at the highest risk of IA

Tejerina EE, et al, Mycoses. 2019;online