Introduction to Medical Mycology
Magnitude of the problem

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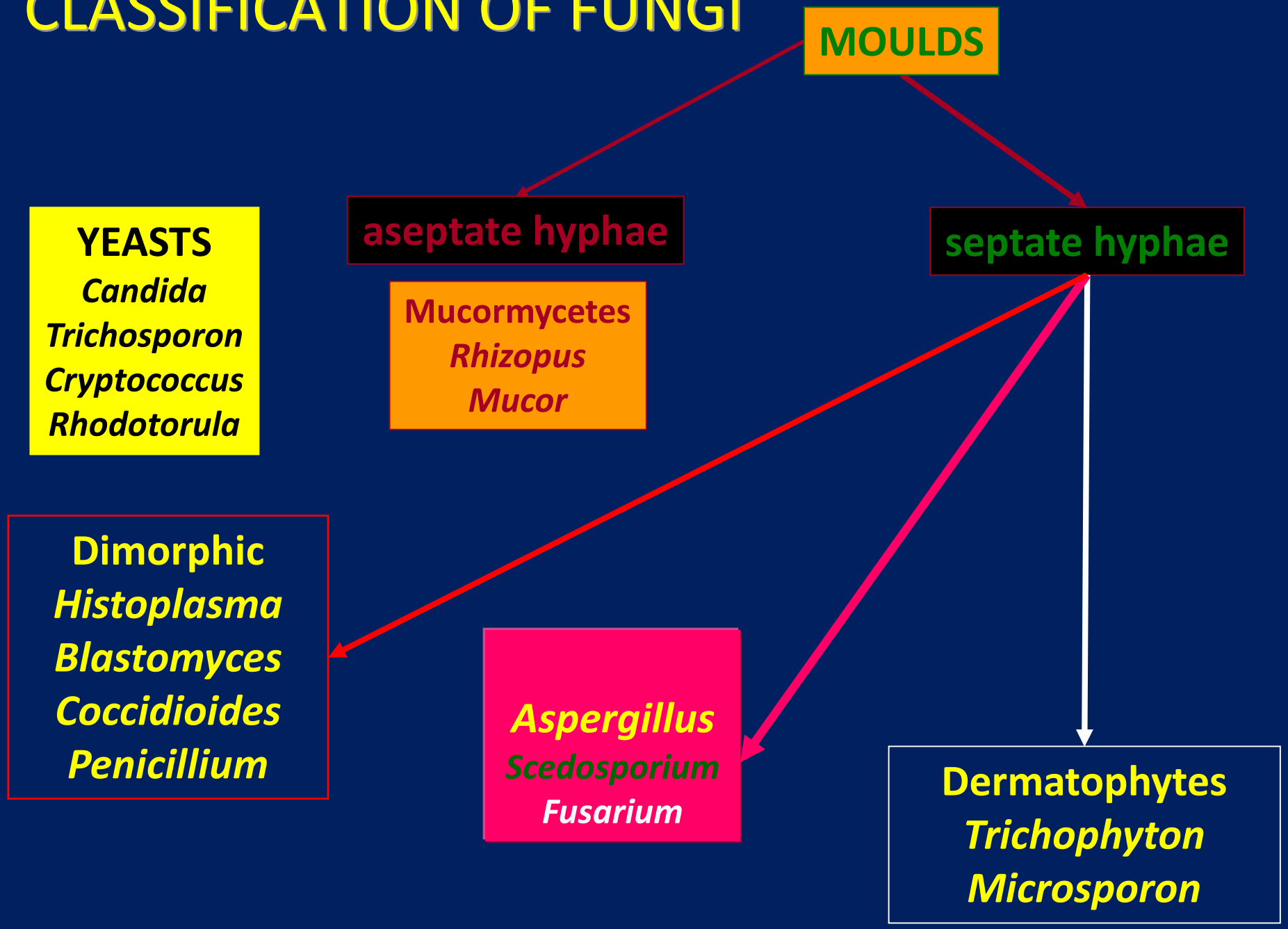
Disclosures

Consultancy, speakerfee, grants

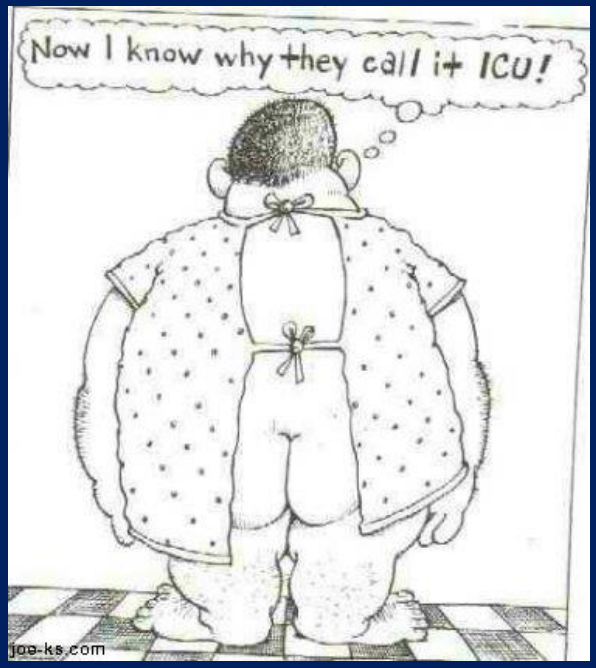
Astellas,Basilea,Gilead,Merck

The Fungal kingdom

CLASSIFICATION OF FUNGI

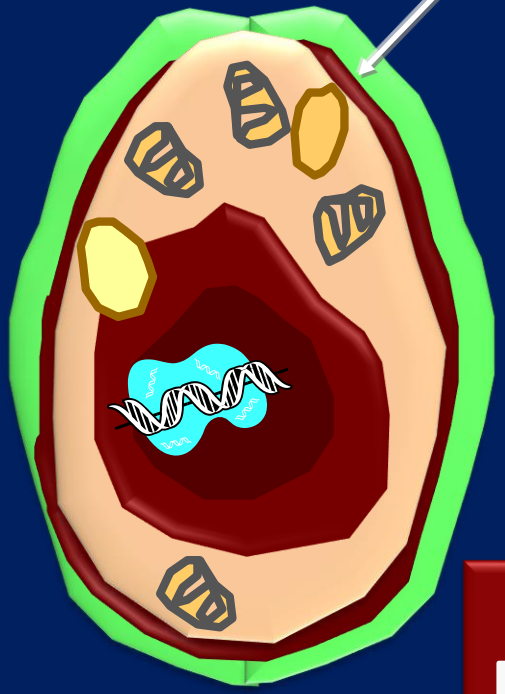


FUNGUS : PLANT OR ANIMAL?



NO CHLOROPHYL!

cell membrane
-ergosterol



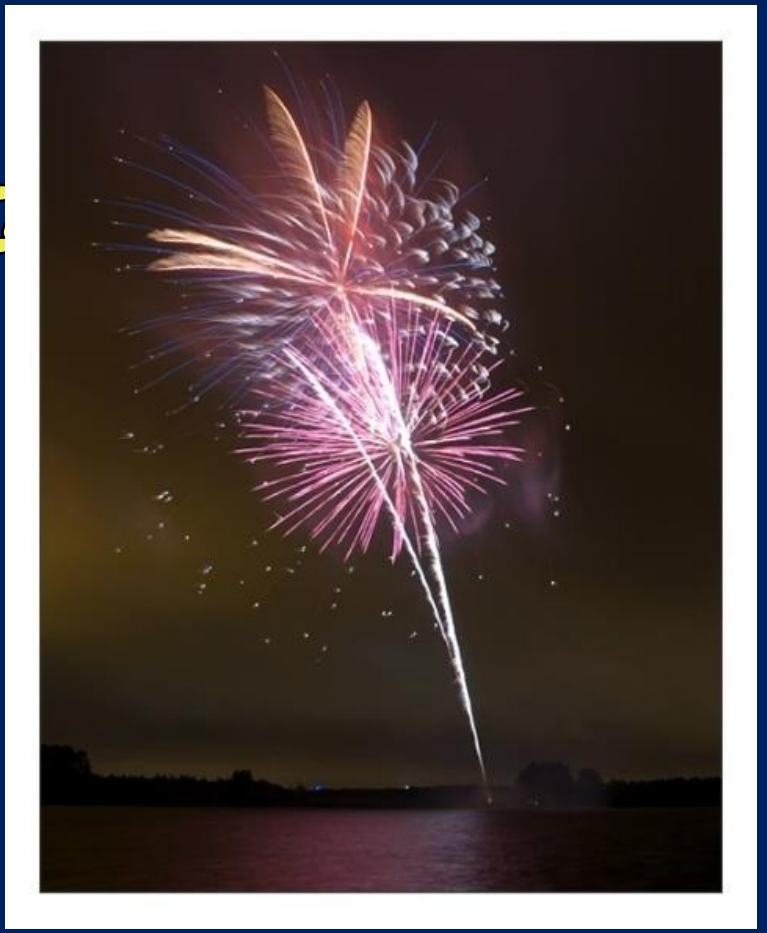
cell wall
-chitin
-mannoproteins
-ß-glucan

eukaryotic

FOR GROWTH CARBON FROM ORGANIC MATERIAL IS NEEDED

THE DIFFERENCE

YEAST



MOULD

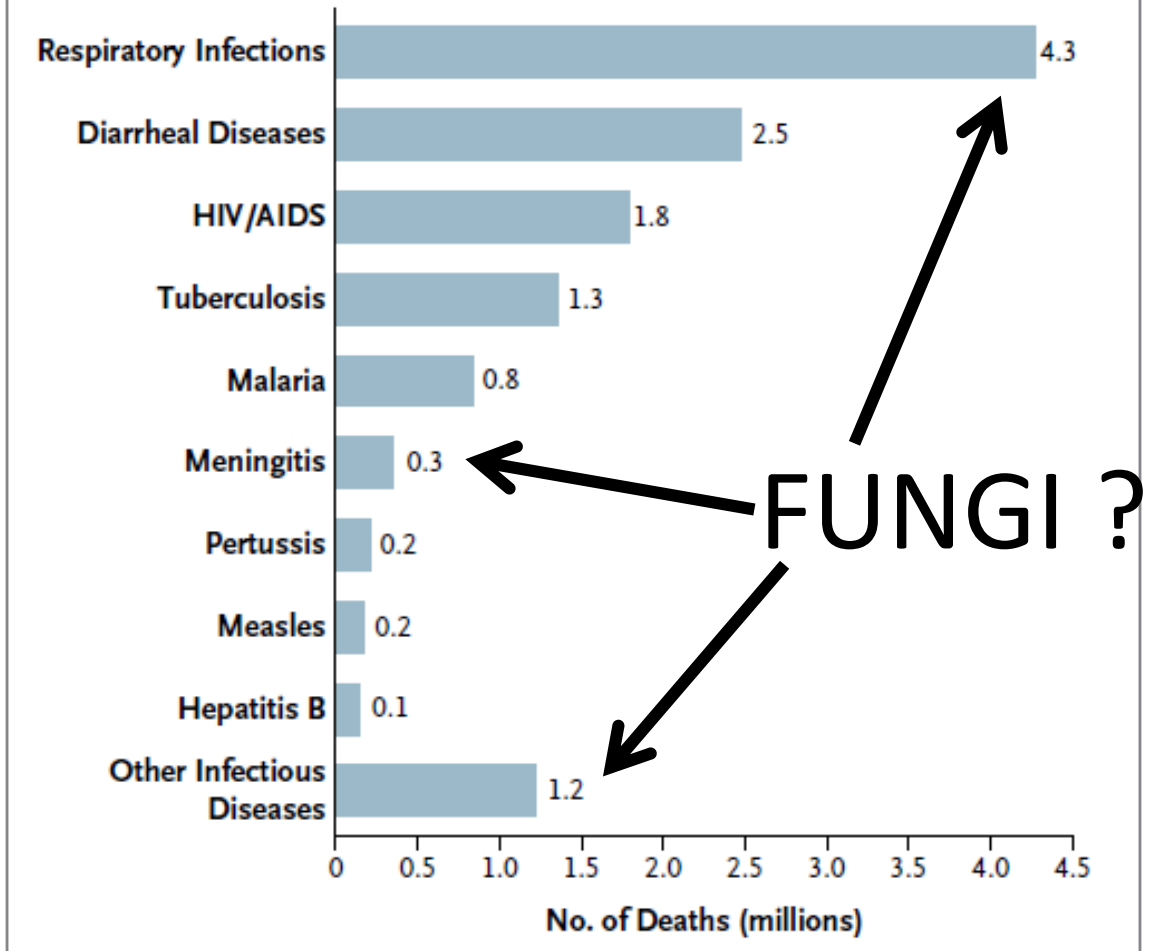


Figure 1. Leading Causes of Global Deaths from Infectious Diseases.

Of an estimated 58.8 million annual deaths worldwide, approximately 15.0 million (25.5%) are believed to be caused by infectious diseases. Cause-specific mortality estimates are provided by the World Health Organization.[43,44] The data do not include deaths from secondary infectious causes, such as rheumatic fever and rheumatic heart disease, liver cancer and cirrhosis, or other chronic diseases.

LEADING INTERNATIONAL FUNGAL EDUCATION

http://www.life-worldwide.org/awareness-advocacy/

N Engl J Med 2012;366:454-61.

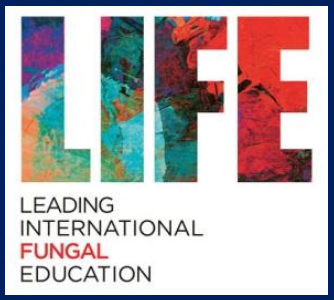
Hidden Killers: Human Fungal Infections

Gordon D. Brown,[1]* David W. Denning,[2]* Neil A. R. Gow,[1]* Stuart M. Levitz,[3]* Mihai G. Netea,[4]* Theodore C. White[5]*

Table 1. Statistics of the 10 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

IMPACT OF FUNGAL INFECTIONS: DEATHS



Cryptococcal meningitis

> **600,000** deaths annually.

Invasive aspergillosis

100,000 deaths annually

Chronic pulmonary aspergillosis

450,000 deaths per year.

Candida bloodstream infection

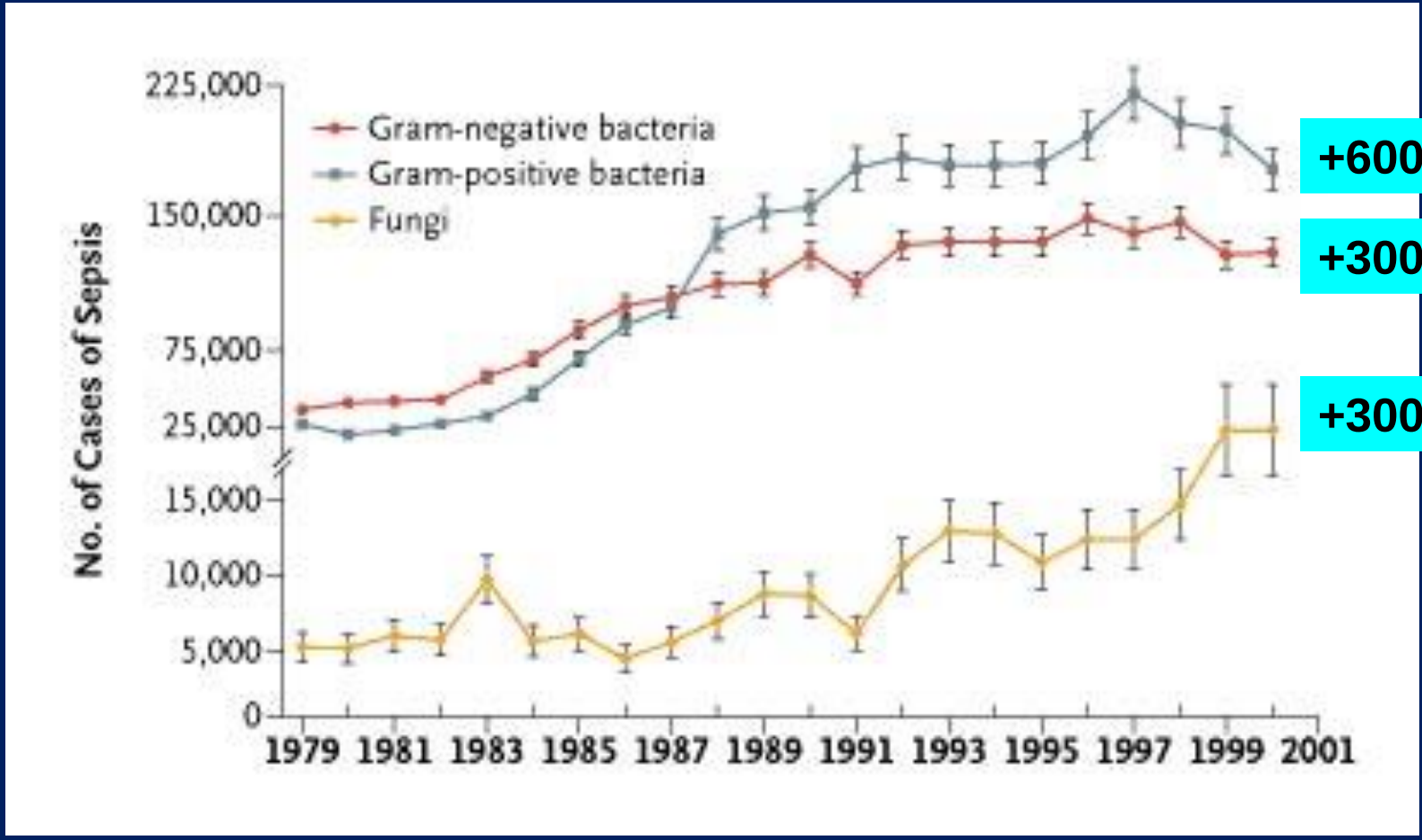
120,000 deaths per year

http://www.life-worldwide.org/awareness-advocacy/

Magnitude of the problem

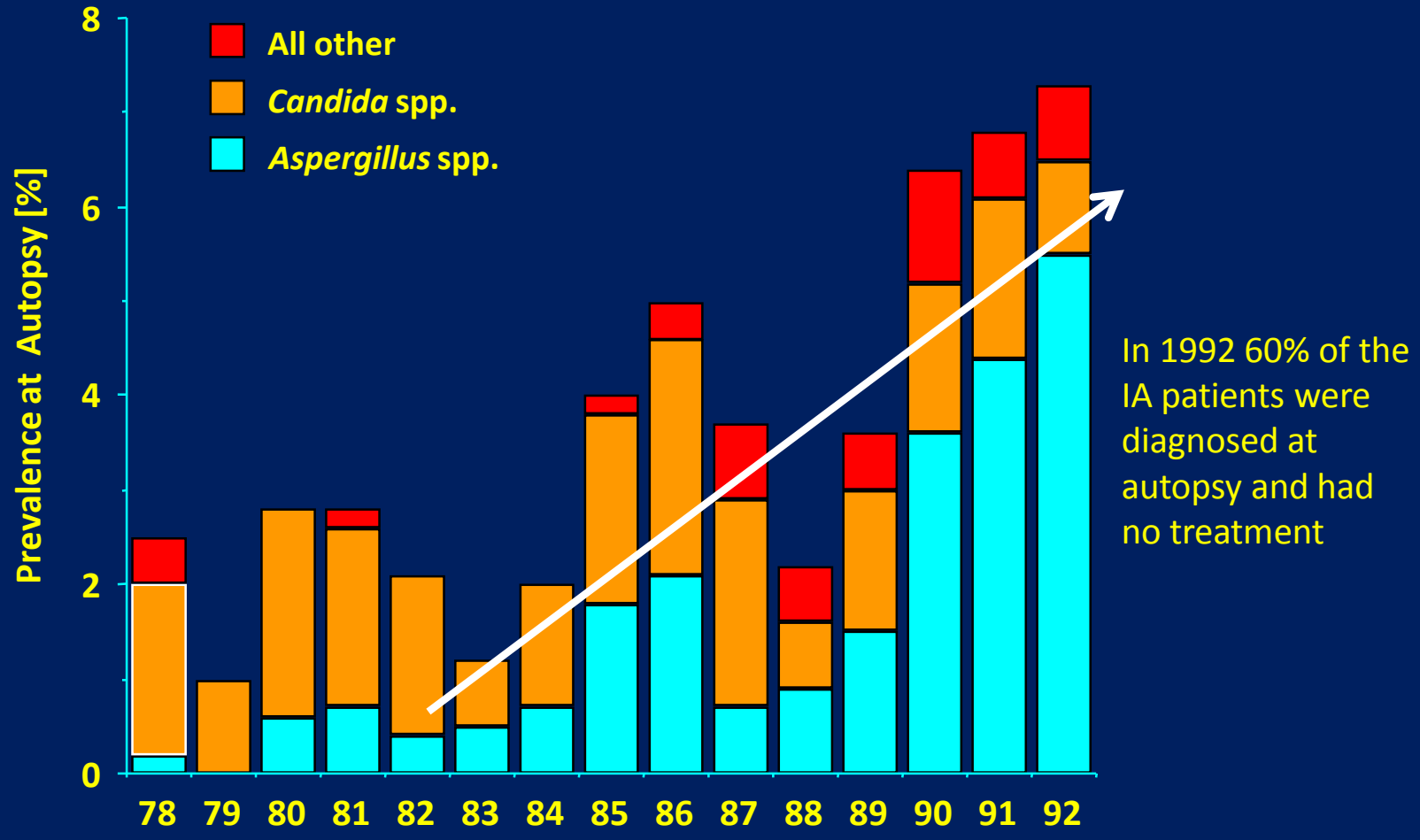
- Increasing cases of invasive fungal infections
- Poor performing diagnostic tools
- Increasing use of prophylaxis and empirical therapy
- Replacement of sensitive species by resistant ones
- Increasing awareness of the role of fungi in allergy
- Increasing drug and hospitalisation costs

Increasing rate of candidosis in the USA



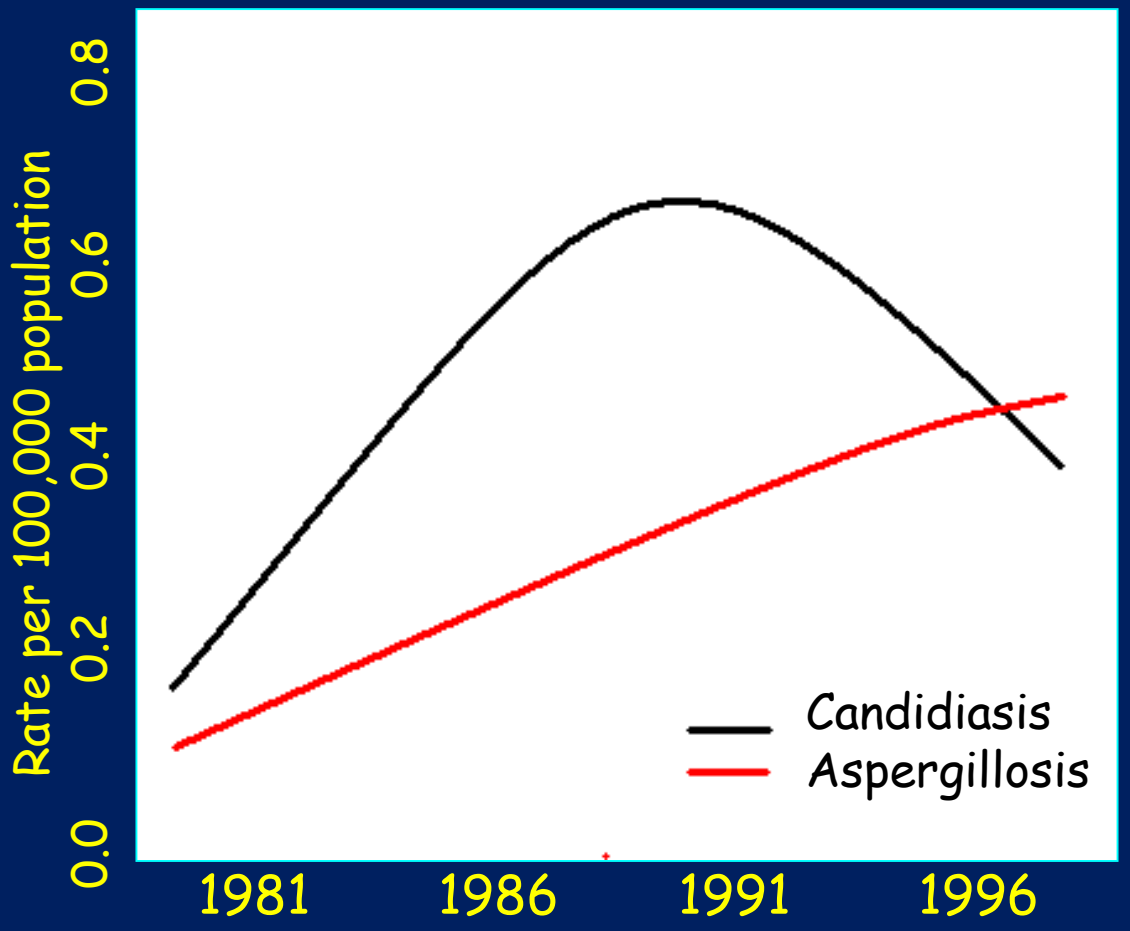
Martin et al, NEJM 2003;348:1546

Prevalence of invasive aspergillosis at autopsy



Groll et al, J Infect 1996;33:23-32.

Changing incidence of fatal invasive mycoses in non-HIV patients in USA



McNeil *et al*, Clin Infect Dis 2001;33:641

Epidemiological facts of *Aspergillus* infections

- **Cancer patients** with chemotherapy-induced neutropenia
- **Transplant recipients** receiving immunosuppressive therapy
- Prolonged **intensive care** treatment
- **COPD**, **Post-tuberculosis** and **CF** patients are targets

PULMONARY ASPERGILLOSIS FOLLOWING POST-INFLUENZAL BRONCHOPNEUMONIA TREATED WITH ANTIBIOTICS

BY

J. D. ABBOTT, M.D., Dip.Bact.

H. V. J. FERNANDO, M.B., B.S.

K. GURLING, M.D., M.R.C.P.

AND

B. W. MEADE, M.B., B.S.

(From King's College Hospital and Medical School, London)

The association of fungus infections with antibiotic therapy is now well recognized. Although many references are to be found in the American literature, few examples have been recorded in this country. We therefore think the following case of pulmonary aspergillosis

DISSEMINATED ASPERGILLOSIS AND MONILIASIS ASSOCIATED WITH AGRANULOCYTOSIS AND ANTIBIOTIC THERAPY

BY

N. E. RANKIN, M.B., B.S.

From the Department of Pathology, the Royal Infirmary, Gloucester)

ulmonary aspergillosis and local infections with onilia are not rare, but the disseminated forms are uch less common. The use of antibiotics in the resence of these fungous infections is dangerous. The llowing case is of interest because both fungi were resent in the lesions.

Case Report

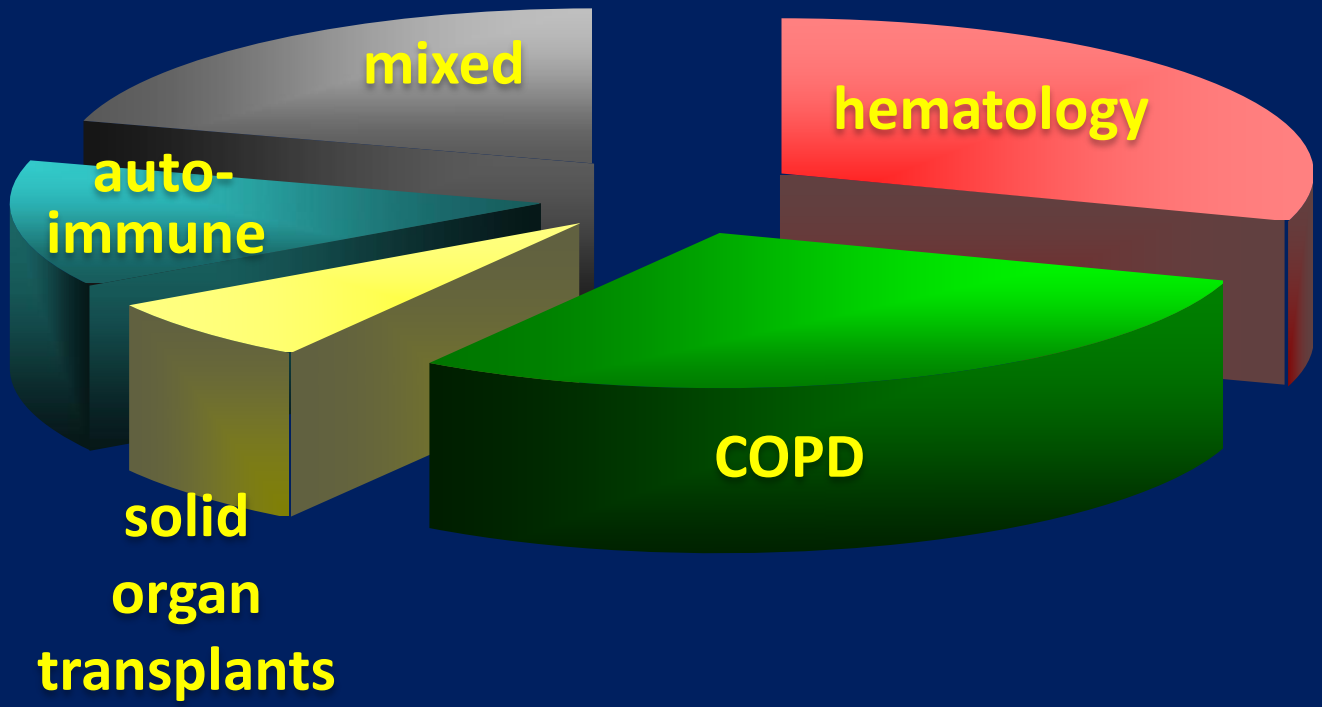
A window cleaner aged 45 was seen on April 3, 195[illegible] ith an abscess of the thigh. He was treated with sulphon mides, and was admitted on April 18 for evacuation of the

ASPERGILLUS INFECTIONS IN ICU UNITS

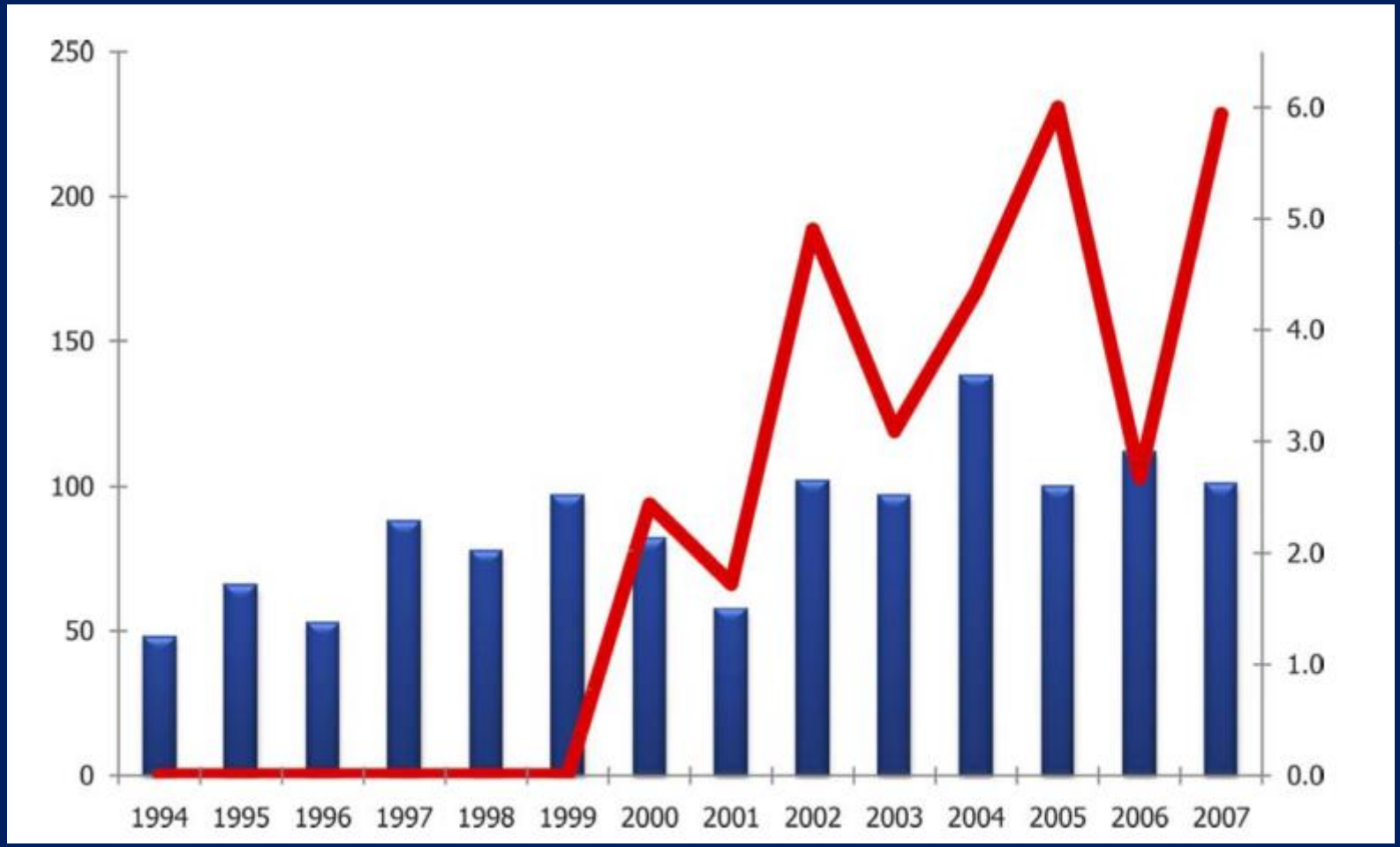
Meersseman et al. Clin Microbiol Infect 2004;10,Suppl 3:266

1850 admissions 2000-2003

6.9%



Acquired resistance in *A. fumigatus* at the Radboud University Medical Center



4.9%

2013

94% TR_{34}/L98H

PLoS Med 2008;5:e219

J Antimicrob Chemother 2012; **67**: 362–366
doi:10.1093/jac/dkr443 Advance Access publication 25 October 2011

Clinical isolates

Antimicrobial Chemotherapy

Isolation of multiple-triazole-resistant *Aspergillus fumigatus* strains carrying the TR/L98H mutations in the *cyp51A* gene in India

Anuradha Chowdhary[1]*, Shallu Kathuria[1], Harbans S. Randhawa[1], Shailendra N. Gaur[2], Corné H. Klaassen[3] and Jacques F. Meis[3,4]

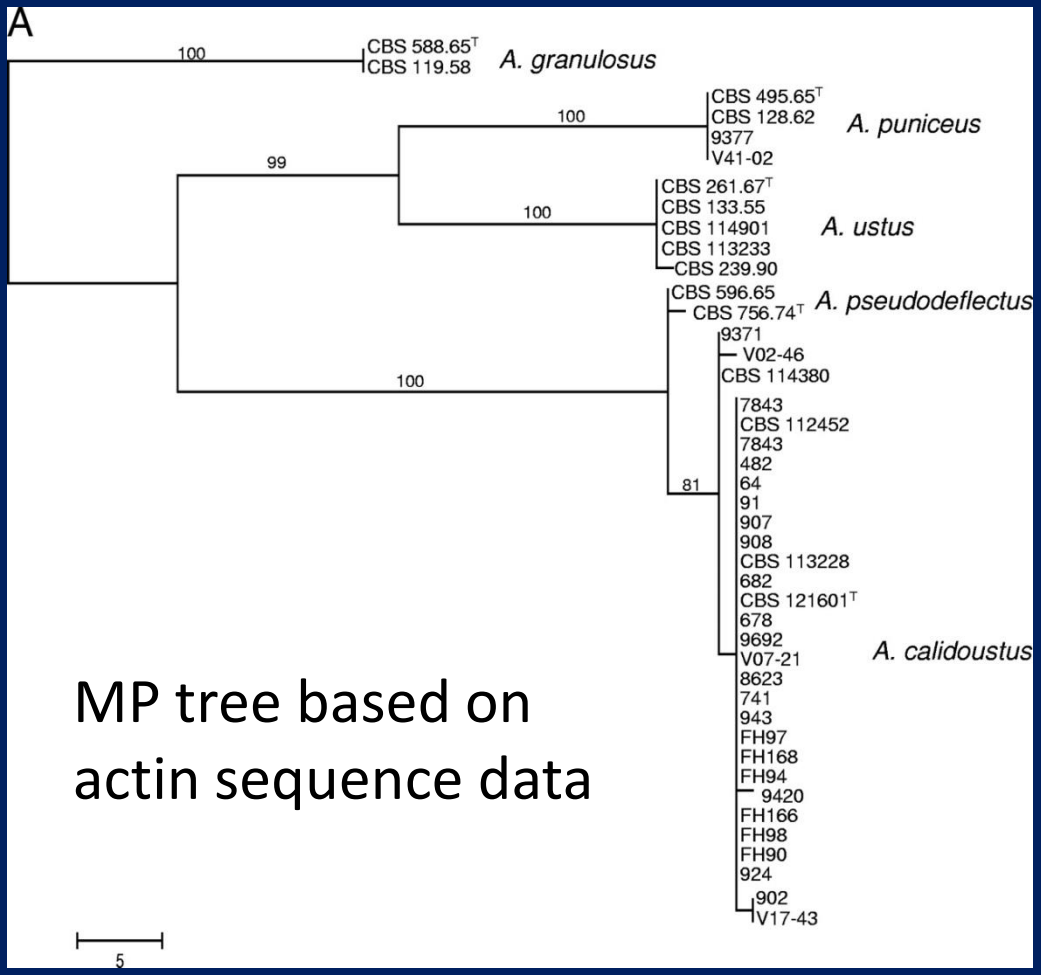
OPEN ACCESS Freely available online

PLOS ONE

Clonal Expansion and Emergence of Environmental Multiple-Triazole-Resistant *Aspergillus fumigatus* Strains Carrying the TR_{34}/L98H Mutations in the *cyp*51A Gene in India

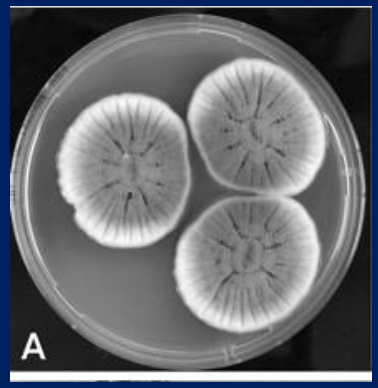
Anuradha Chowdhary[1]*, Shallu Kathuria[1], Jianping Xu[2], Cheshta Sharma[1], Gandhi Sundar[1], Pradeep Kumar Singh[1], Shailendra N. Gaur[3], Ferry Hagen[4], Corné H. Klaassen[4], Jacques F. Meis[4,5]

Aspergillus calidoustus former *A. ustus*



MP tree based on actin sequence data

Vagra et al. Euk Cell 2008



Antifungal agent	MIC (mg/liter [range]) (*n* = 20)
Amphotericin B	1-2
5-FC	8->64
Itraconazole	>16 (16)
Voriconazole	8-16
Posaconazole	>16
Terbinafine	0.031-0.125
Caspofungin	0.25-4

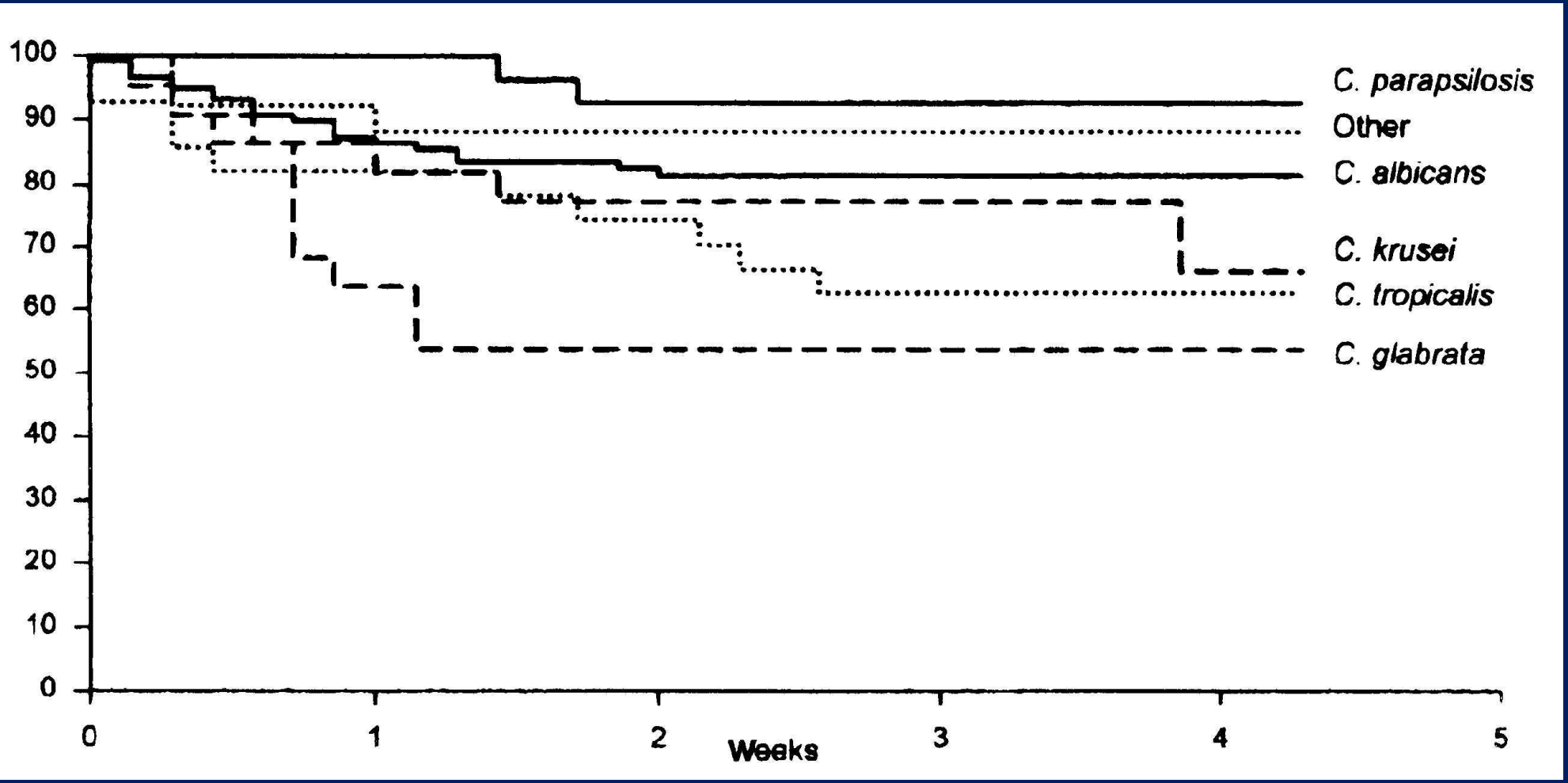
Invasive fungal infection –current mortality rates

	Mortality
Aspergillosis	
Pulmonary aspergillosis	50-75%
Cerebral aspergillosis	95%
Candidosis	
Candidaemia	40%

Antifungal susceptibility in *Candida* spp.

Usually susceptible	Less susceptible	Resistant
<u>Fluconazole</u>		
C. albicans	*C. tropicalis*	*C. glabrata*
C. parapsilosis		*C. krusei*
All others		
<u>Amphotericin B</u>		
C. albicans	*C. lusitaniae*	*C. krusei*
C. tropicalis		*C. glabrata*
C. parapsilosis		
<u>Caspofungin</u>		
C. albicans	*C. parapsilosis*	*C. glabrata*
		emerging
C. tropicalis	*C. guilliermondii*	
C. glabrata	*C. lusitaniae*	
C. krusei		

Candidaemia – Survival According To Species



Viscoli C et al. Clin Infect Dis 1999.

Candida species causing bloodstream infection worldwide and India

Species	USA (n=4570)	Europe (n=7659)	L. America (n=1710)	Asia (n=5803)	India (n=2592)
C. albicans	**52**	**61**	**42**	**32**	**16**
C. glabrata	**20**	**15**	**5**	**8**	**5**
C. parapsilosis	12	12	**22**	13	4
C. tropicalis	12	7	18	**25**	**37**
C. krusei	2	2	3	3	5
C. guilliermondii	0	1	3	5	11
Other *Candida* species	3	3	7	13	23

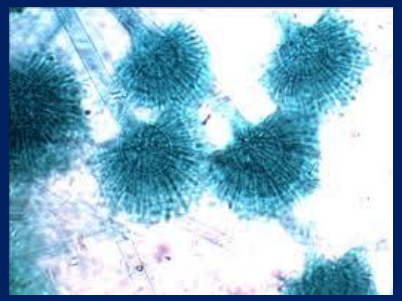
Slide Dr. A. Chakrabarti

Int J Infect Dis 2010; 14: e954
Scand J Infect Dis 2009; 41: 275
J Postgrad Med 2005; 51: S16

The threat of opportunistic fungal infections

Opportunistic fungi
Include all species from

A (Aspergillus)
To
Z (Zygomycetes)



- **Candidosis**
- **Aspergillosis**
- **Mucormycosis**

>80%

- *Fusarium* spp.
- *Scedosporium* spp.
- *Trichosporon* spp.
- *Penicillium* spp.

TOP 10 NEW SPECIES 2014

International Institute for Species Exploration
SUNY-ESF

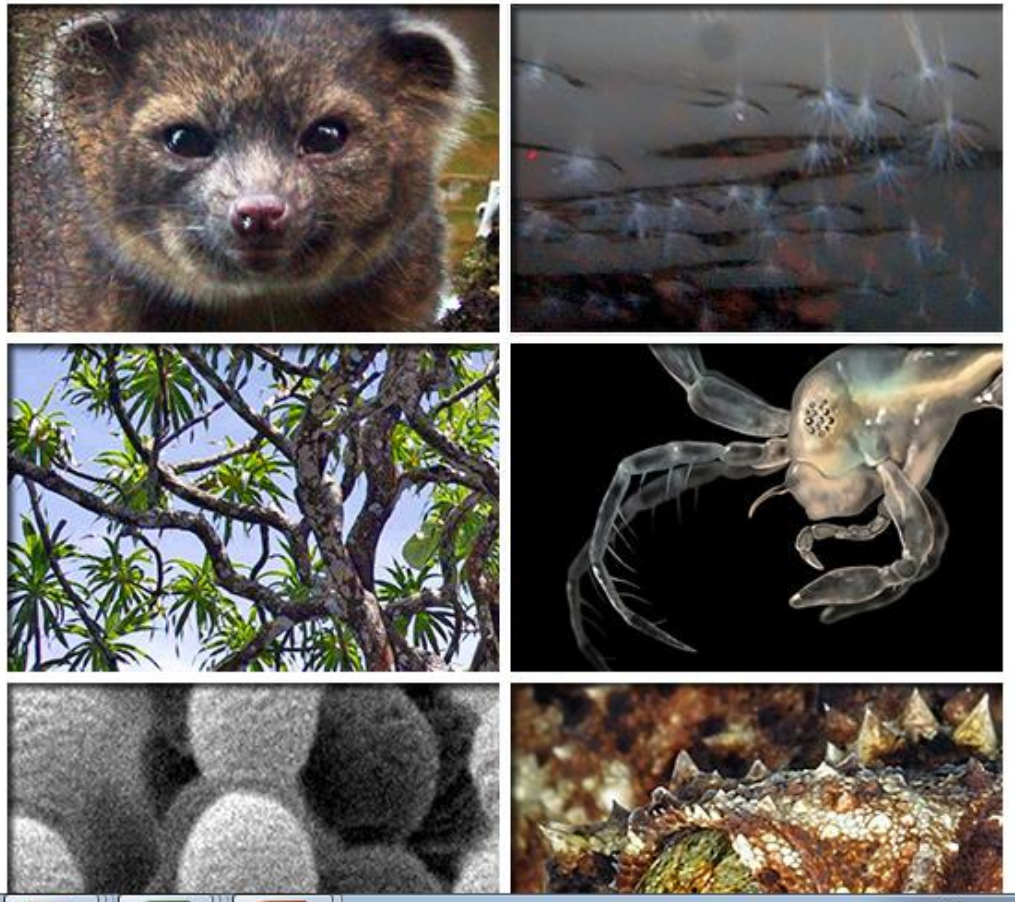
Top 10 New Species for 2014

An appealing carnivorous mammal, a 12-meter-tall tree that has been hiding in plain sight and a sea anemone that lives under an Antarctic glacier are among the species identified by the **SUNY-ESF International Institute for Species Exploration** (IISE) as the top 10 species discovered last year.

The 2014 Top Ten

Species are not ranked, and are presented in alphabetical order by scientific name.

- **Olinguito** *(Bassaricyon neblina)*
- **Kaweesak's Dragon Tree** *(Dracaena kaweesakii)*
- **ANDRILL Anemone** *(Edwardsiella andrillae)*
- **Skeleton Shrimp** *(Liropus minusculus)*
- **Orange Penicillium** *(Penicillium vanoranjei)*
- **Leaf-tailed Gecko** *(Saltuarius eximius)*
- **Amoeboid Protist** *(Spiculosiphon oceana)*
- **Clean Room Microbes** *(Tersicoccus phoenicis)*
- **Tinkerbell Fairyfly** *(Tinkerbella nana)*
- **Domed Land Snail** *(Zospeum tholussum)*



Orange Penicillium

Scientific Name: Penicillium vanoranjei

Country of Discovery: Tunisia

Distinguished by the bright orange color it displays when produced in colonies, this fungus was named as a tribute to the Dutch royal family, specifically His Royal Highness the Prince of Orange. It was reported in a journal published by the National Herbarium of the Netherlands. The newcomer was isolated from soil in Tunisia. This species also produces a sheet-like extra-cellular matrix that may function as protection from drought.

Persoonia 2013;31: 42–62

	Case 1	Case 2	Case 3
Age/Sex	12/F	45/F	54/M
Clinical summary	AML, on induction chemotherapy	COPD, on steroids	COPD, on steroids, uncontrolled diabetes mellitus
Present clinical diagnosis	Suspected pulmonary aspergillosis	CPA	CPA
VRC: indication	Empirical therapy for IPA	Therapy for CPA	Therapy for CPA
VRC: started after admission on day	17	12	7
Symptoms	Intermittent fever	Intermittent fever since 1.5 years, cough	Dyspnoea, anorexia, weight loss, intermittent fever since 4 years
Radiology	Nodule, upper lobe of right lung; enhancing ring lesions in liver and spleen	Diffuse, bilateral pulmonary infiltrates	Cavitating consolidation, middle lobe, lingual and bilateral upper lobes of the lung
Site of Infection	Liver, spleen and lung	Lung	Lung
Duration of VRC therapy (days)	38	59	49
Clinical specimen	Liver aspirate	FNAB, BAL, sputum	FNAB, sputum
In vitro AFST (MIC/MEC µg/mL)			
VRC	2	>16	2
AMB	≤0.03	0.5	0.5
ITC	0.5	2	1
POS	0.125	0.5	0.125


12 YEAR
F
9/6/2013 9:36:07 AM
DIRRGCI1389156
LOC: -55.50
THK: 6
HFS
R
L
RD: 246
Tilt: 0
mA: 38
KVp: 110
Acq no: 2
Z: 1
C: -700
W: 700
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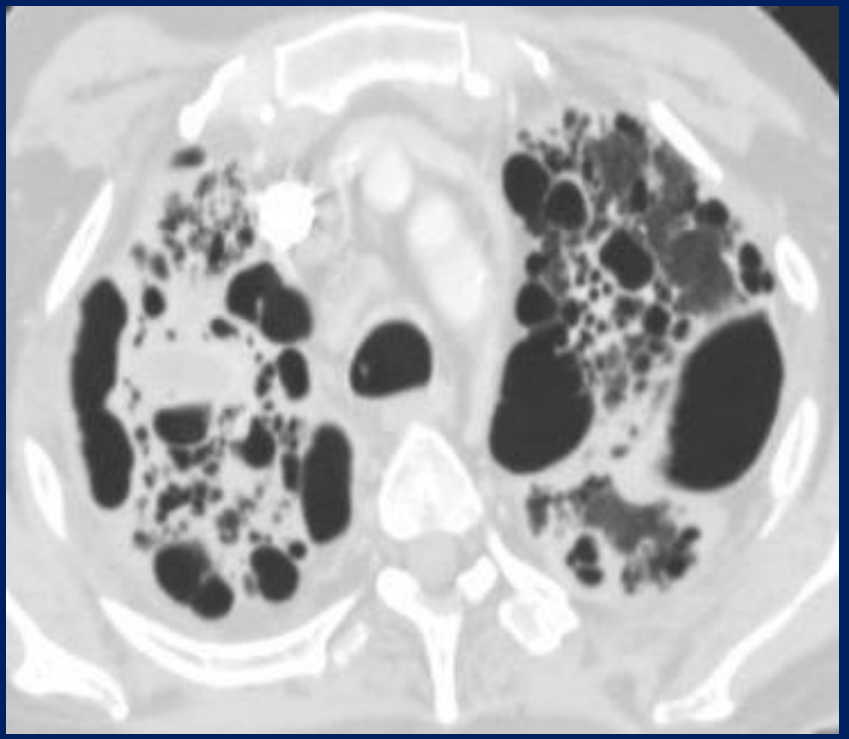
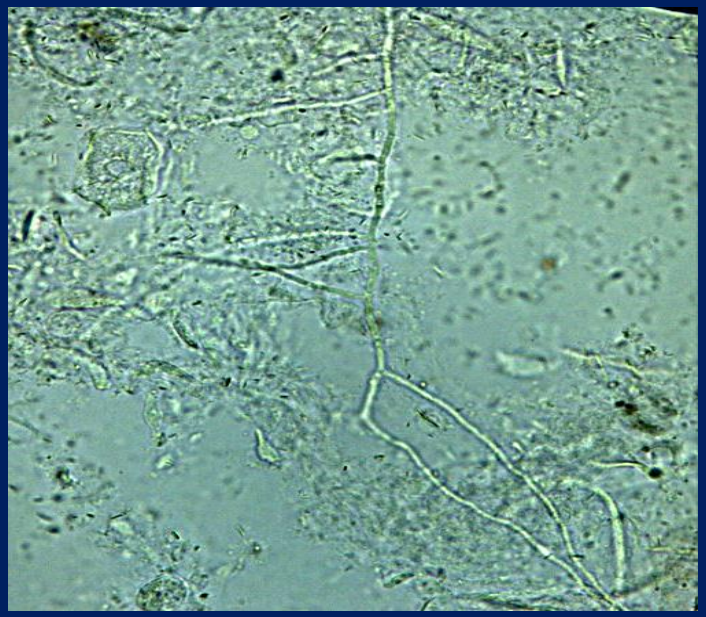
cm





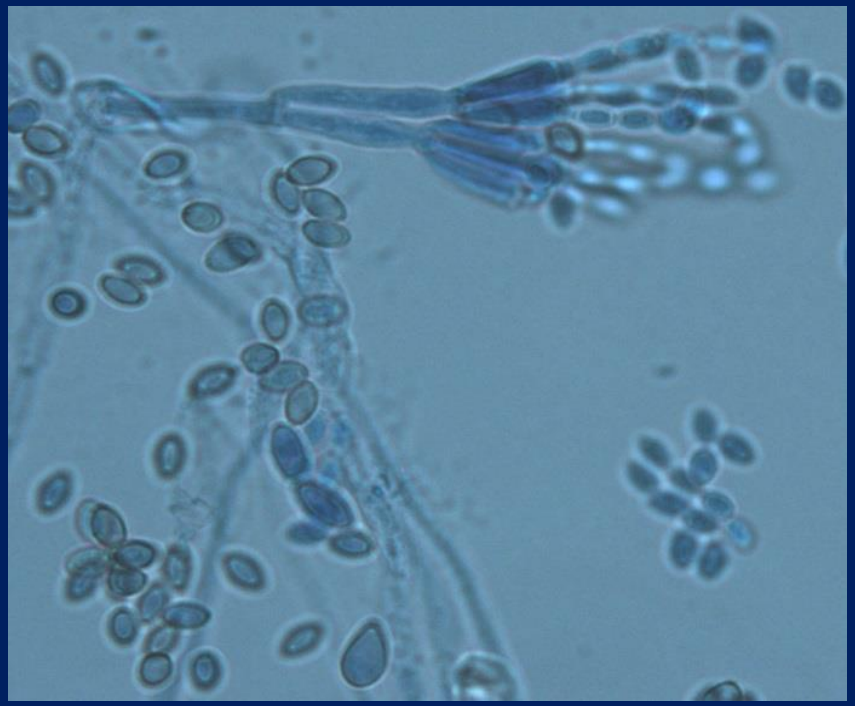
Probable diagnosis?

1. Aspergillosis (azole resistant)
2. Scedosporiosis
3. Fusariosis
4. Penicilliosis
5. Invasive filamentous fungal infections

Voriconazole-Resistant *Penicillium oxalicum*: An Emerging Pathogen in Immunocompromised Hosts

Anuradha Chowdhary,[1] Shallu Kathuria,[1] Kshitij Agarwal,[2] Neelam Sachdeva,[3] Pradeep K. Singh,[1] Sandeep Jain,[3] and Jacques F. Meis[4,5]

Open Forum Infectious Diseases



New *Candida* species in complex

C. albicans → *C. dubliniensis* <10%

→ *C. africana* <1%

C. glabrata → *C. bracarensis* <2.2%

→ *C. nivariensis* <0.5%

C. haemulonii

→ *C. auris* < 0.1%

C. parapsilosis → *C. orthopsilosis* 1.4%

→ *C. metapsilosis* 1.7%

Outbreaks of unusual cases of fungemia

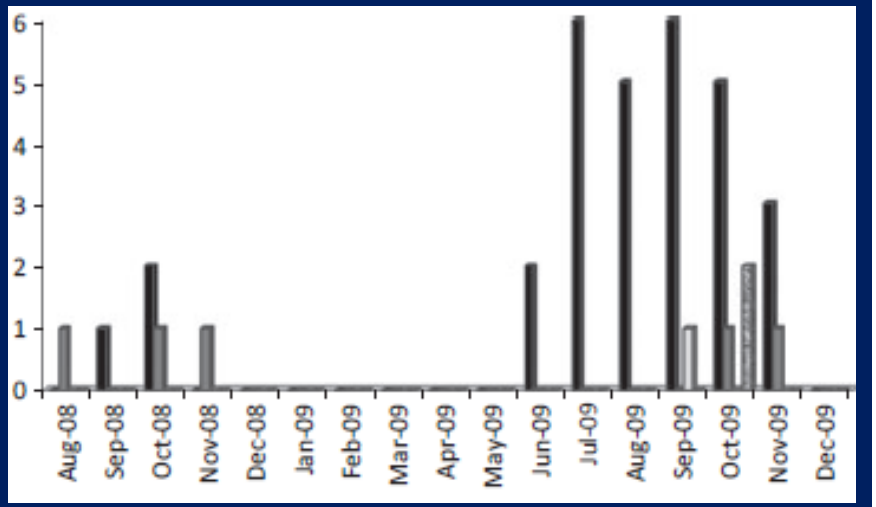
- ***Pichia anomala***
- ***Kodamaea ohmeri***
- ***Candida haemulonii***
- ***Pichia fabianii***
- ***Candida auris***

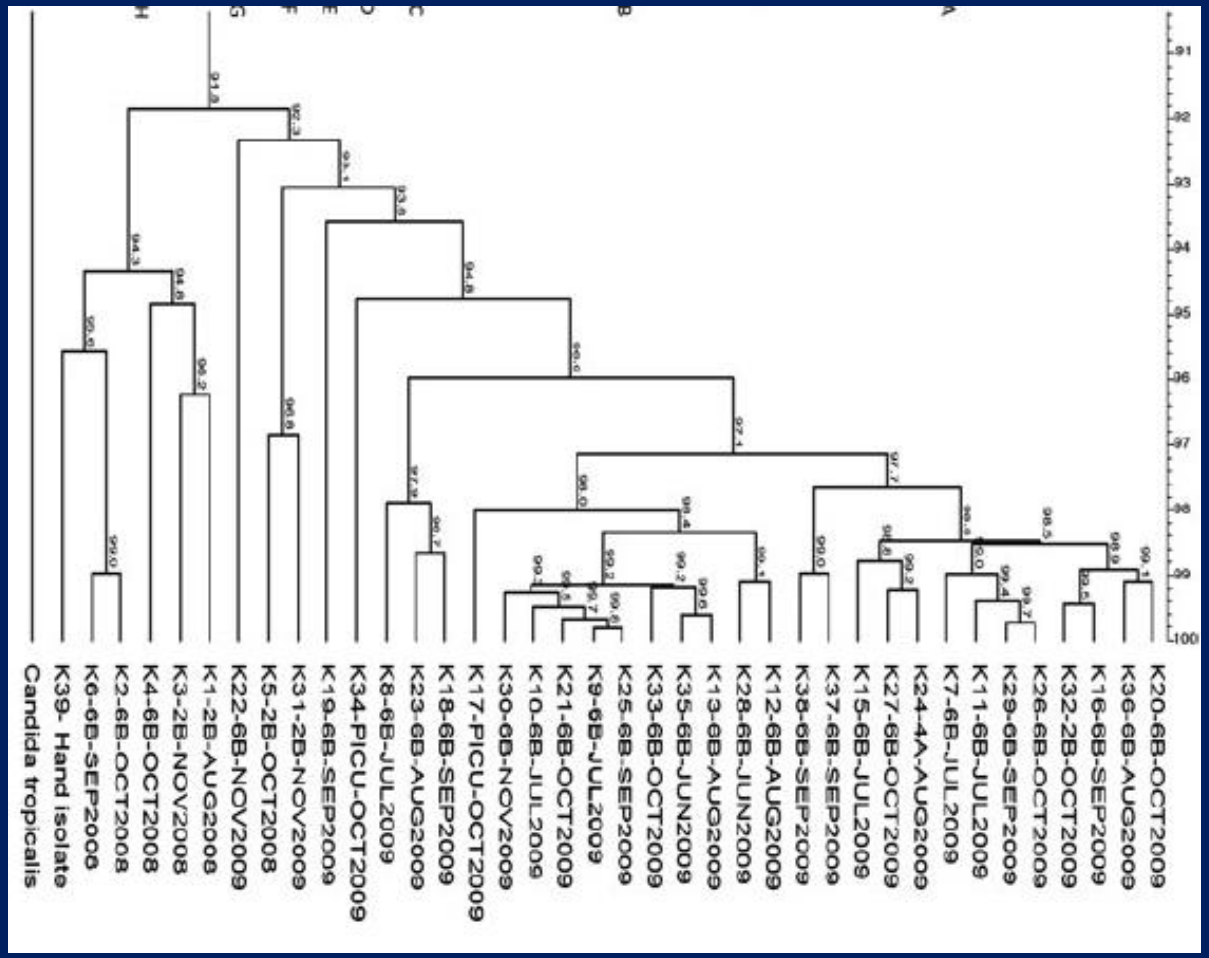
- *C. guilliermondii*
- *C. lusitaniae*
- *C. dubliniensis*
- *C. inconspicua*
- *C. famata*
- *C. rugosa*
- *C. norvegensis*

Clin Microbiol Infect. 2014; 20 (2) :83-9.

Epidemiological study of a large cluster of fungaemia cases due to *Kodamaea ohmeri* in an Indian tertiary care centre

A. Chakrabarti[1], S. M. Rudramurthy[1], P. Kale[1], P. Hariprasath[1], M. Dhaliwal[1], S. Singhi[2] and K. L. N. Rao[3]





New Clonal Strain of *Candida auris*, Delhi, India

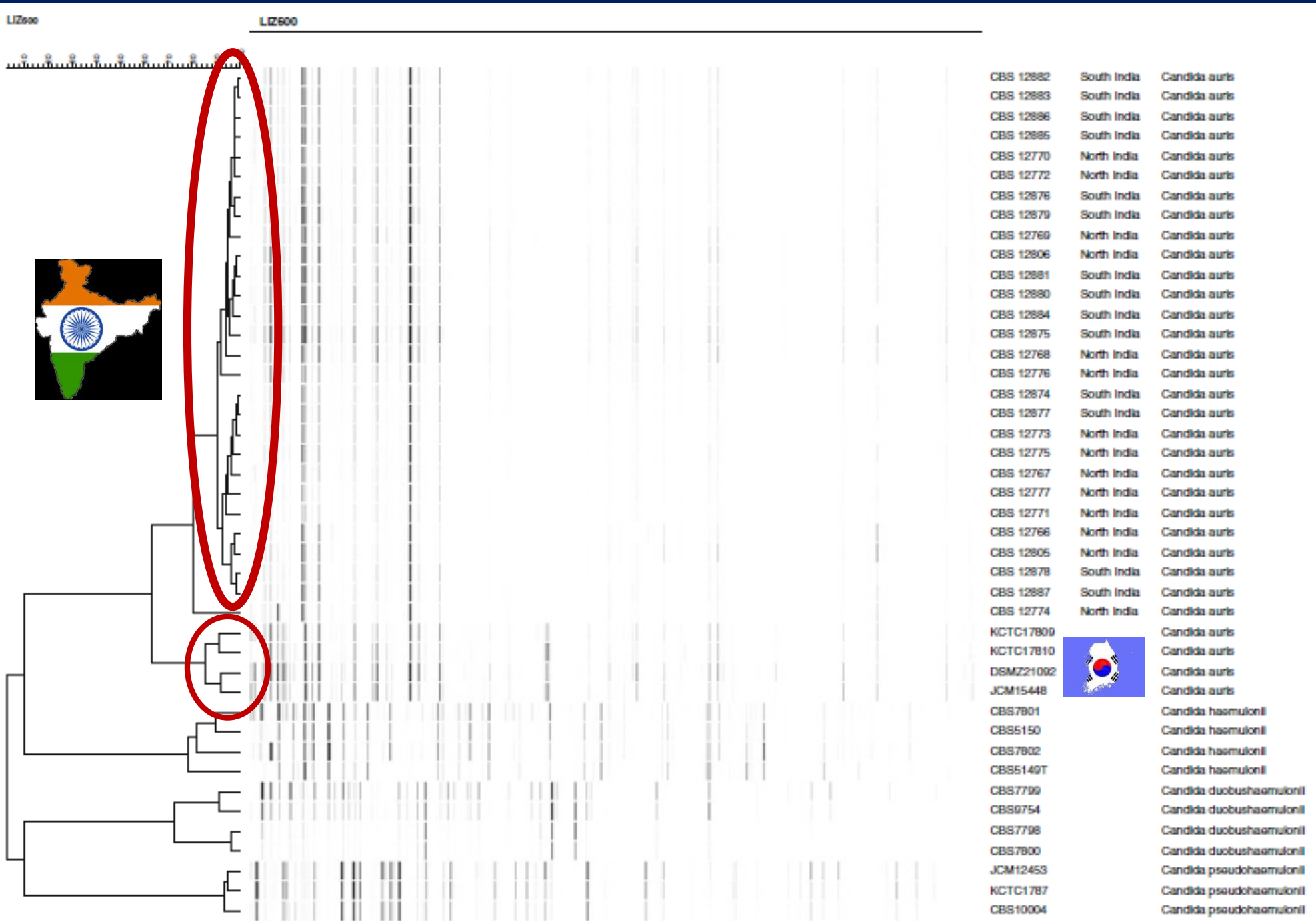
Anuradha Chowdhary, Cheshta Sharma, Shalini Duggal, Kshitij Agarwal, Anupam Prakash, Pradeep Kumar Singh, Sarika Jain, Shallu Kathuria, Harbans S. Randhawa, Ferry Hagen, and Jacques F. Meis

Emerging Infectious Diseases Vol. 19, No. 10, October 2013

Multidrug-resistant endemic clonal strain of *Candida auris* in India

A. Chowdhary · V. Anil Kumar · C. Sharma · A. Prakash · K. Agarwal · R. Babu · K. R. Dinesh · S. Karim · S. K. Singh · F. Hagen · J. F. Meis

Eur J Clin Microbiol Infect Dis (2014) 33:919–926


LIZ600
CBS 12882 South India Candida auris
CBS 12883 South India Candida auris
CBS 12886 South India Candida auris
CBS 12885 South India Candida auris
CBS 12770 North India Candida auris
CBS 12772 North India Candida auris
CBS 12876 South India Candida auris
CBS 12879 South India Candida auris
CBS 12769 North India Candida auris
CBS 12806 North India Candida auris
CBS 12881 South India Candida auris
CBS 12880 South India Candida auris
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CBS 12768 North India Candida auris
CBS 12776 North India Candida auris
CBS 12874 South India Candida auris
CBS 12877 South India Candida auris
CBS 12773 North India Candida auris
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CBS 12766 North India Candida auris
CBS 12805 North India Candida auris
CBS 12878 South India Candida auris
CBS 12887 South India Candida auris
CBS 12774 North India Candida auris
KCTC17809 Candida auris
KCTC17810 Candida auris
DSMZ21092 Candida auris
JCM15448 Candida auris
CBS7801 Candida haemulonii
CBS5150 Candida haemulonii
CBS7802 Candida haemulonii
CBS5149T Candida haemulonii
CBS7799 Candida duobushaemulonii
CBS9754 Candida duobushaemulonii
CBS7798 Candida duobushaemulonii
CBS7800 Candida duobushaemulonii
JCM12453 Candida pseudohaemulonii
KCTC1787 Candida pseudohaemulonii
CBS10004 Candida pseudohaemulonii

ESCMID† and ECMM‡ joint clinical guidelines for the diagnosis and management of rare invasive yeast infections

Clin Microbiol Infect 2014; **20** (Suppl. 3): 76–98

M. C. Arendrup[1], T. Boekhout[2,3,4], M. Akova[5], J. F.Meis[6,7], O. A. Cornely[8], O. Lortholary[9,10] and on behalf of the ESCMID EFISG study group and ECMM*

- ✓ ***Geotrichum***
  - ➢ *candidum*
- ✓ ***Kodamaea ohmeri***
- ✓ ***Malassezia***
  - ➢ *furfur, globosa , pachydermatis* and *restricta*
- ✓ ***Pseudozyma* spp.**
- ✓ ***Rhodotorula***
  - ➢ *glutinis, minuta* and *mucilaginosa*
- ✓ ***Saccharomyces***
  - ➢ *cerevisiae* and *boulardii*
- ✓ ***Saprochaete***
  - ➢ *S. capitatae* (*Magnusiomyces (Blastoschizomyces) capitatus* formerly named *Trichosporon capitatum* or *Geotrichum (Dipodascus) capitatum*) and *Saprochaete clavata*.
- ✓ ***Sporobolomyces***
- ✓ ***Trichosporon***
  - ➢ *asahii, asteroides, dermatis, inkin, jirovecii , loubieri , mucoides* and *mycotoxinivorans*

Not rare per se

but

Rare as invasive pathogens

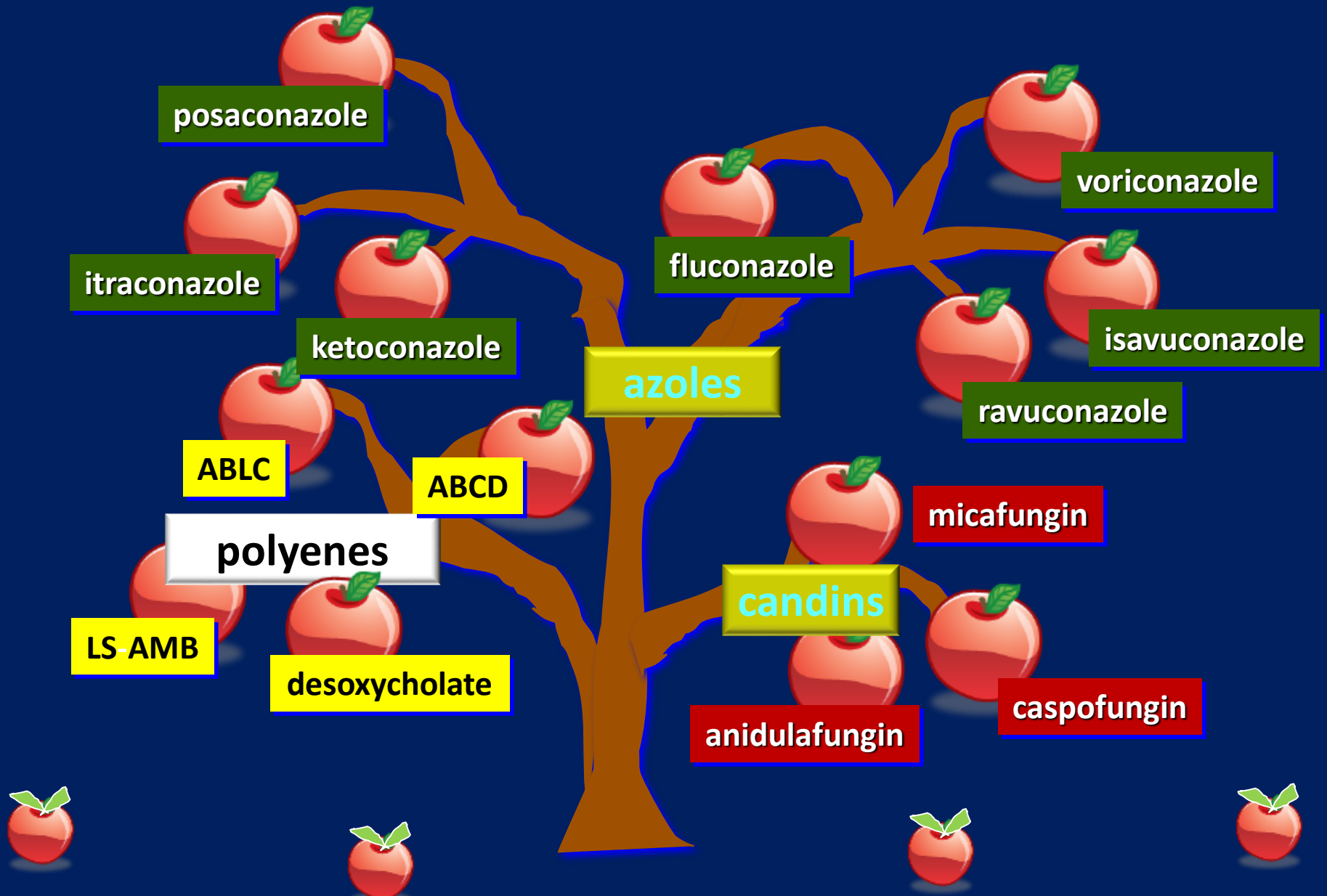
Identification to the species level

Genus	Motivation	SoR	QoE	Method
Cryptococcus	Inter-species MIC variation documented	B	II	ITS 1 + 2 (2nd option D1/D2 domain); MALDI-TOF promising
Geotrichum	Can be confused w other spp	B	II	ITS 1 + 2 (2nd option D1/D2 domain); MALDI-
K. ohmeri	Can be confused w *C. guillermondii* MIC differs (eg low candin MIC)	B		+ 2
Malassezia	Mainly important in outbreak investigation			I-TOF
Pseudozyma	To gain experience			n)
Rhodotorula	Less important for clin management	C		domain)
Saccharomyces	Less important for clin management	C	II	Biochemical tests or MALDI-TOF
Saprochaete	Can be confused w other spp.	B	II	ITS 1 + 2 (2nd option D1/D2 domain); MALDI-TOF promising
Sporobolomyces	Can be confused w other spp.	B	II	ITS 1 + 2 (2nd option D1/D2 domain)
Trichosporon	Inter-species MIC variation documented	B	II	ITS 1 + 2 (2nd option D1/D2 domain); IGS1 necessary for some species; MALDI-TOF promising

Species ID obligatory in outbreak investigation

Clin Microbiol Infect 2014; **20** (Suppl. 3): 76–98

THE ANTIFUNGAL APPEL TREE - 2014




YIELD
INTERSTATE
80
BUMP
NO OUTLET
RAIL ROAD CROSSING
20 M.P.H.
20 M.P.H.
WEST
DO NOT ENTER
SPEED LIMIT 25
STOP AHEAD
R R
STOP
ONE WAY
CLOSED

YIELD OF GUIDELINE APPLICATION

Linder et al. Dtsch Artzebl Int 2011; 108:155-162

84.410 patients
diabetes type II
guideline-based

23.180 patients
diabetes type II
controls

Stroke
Vascular complications
Neuropathy
Renal failure
Ischemic heart disease

22%

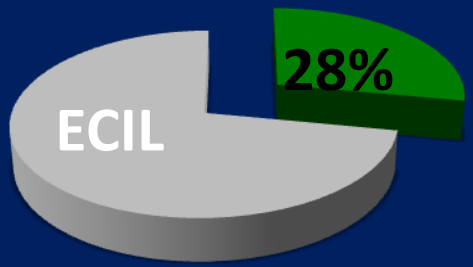
24%

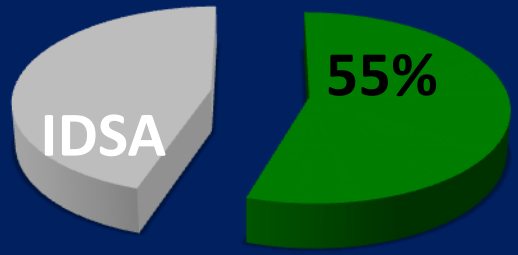
IMPACT OF ADHERENCE TO GUIDELINES AND SURVIVAL

Pagano et al. J Antimicrob Chemother 2010; 65:2013-2018

136 patients with proven/probable invasive aspergillosis

ADHERENCE TO GUIDELINES





SURVIVAL at day 120

	ADHERENCE	NO ADHERENCE
ECIL	18%	28%
IDSA	21%	30%

HAPPY WITH GUIDELINES?

ADVANTAGES:

- **Evidence based**
- **Limits subjectivity**
- **Easily available**
- **Saves time**
- **Standard therapy guaranteed**
- **Comparability data**
- **Evaluation possible**
- **Cost control possible**

HAPPY WITH GUIDELINES?

BUT

- **Good evidence limited**
- **Offers pseudo-objectivity**
- **Missing recent data**
- **Reduces reflection**
- **Little space for individual needs**
- **Comparison of data in different populations**
- **Administrator paradise**

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Conclusions

- Fungi are her to stay and are a major threat in advancement of medicine
- Rare yeasts and filamentous fungi increasingly encountered
- Rare due to low virulence not rare per se

  →How to interpret “overall” outcome (did the patient die with or because of the infection)

- Rapid taxonomic changes; molecular ID necessary
- Especially for epidemiological purposes including outbreak investigation
- Guidelines are made by busy doctors; let your clinical judgement also take control

Trends in Medical Mycology (magnitude of solution)

- EXPECT the UNEXPECTED
- New and Emerging Species
- Molecular Identification
- Molecular Epidemiology
- Emerging Resistance