Clinical profile of cryptic *Aspergillus* species

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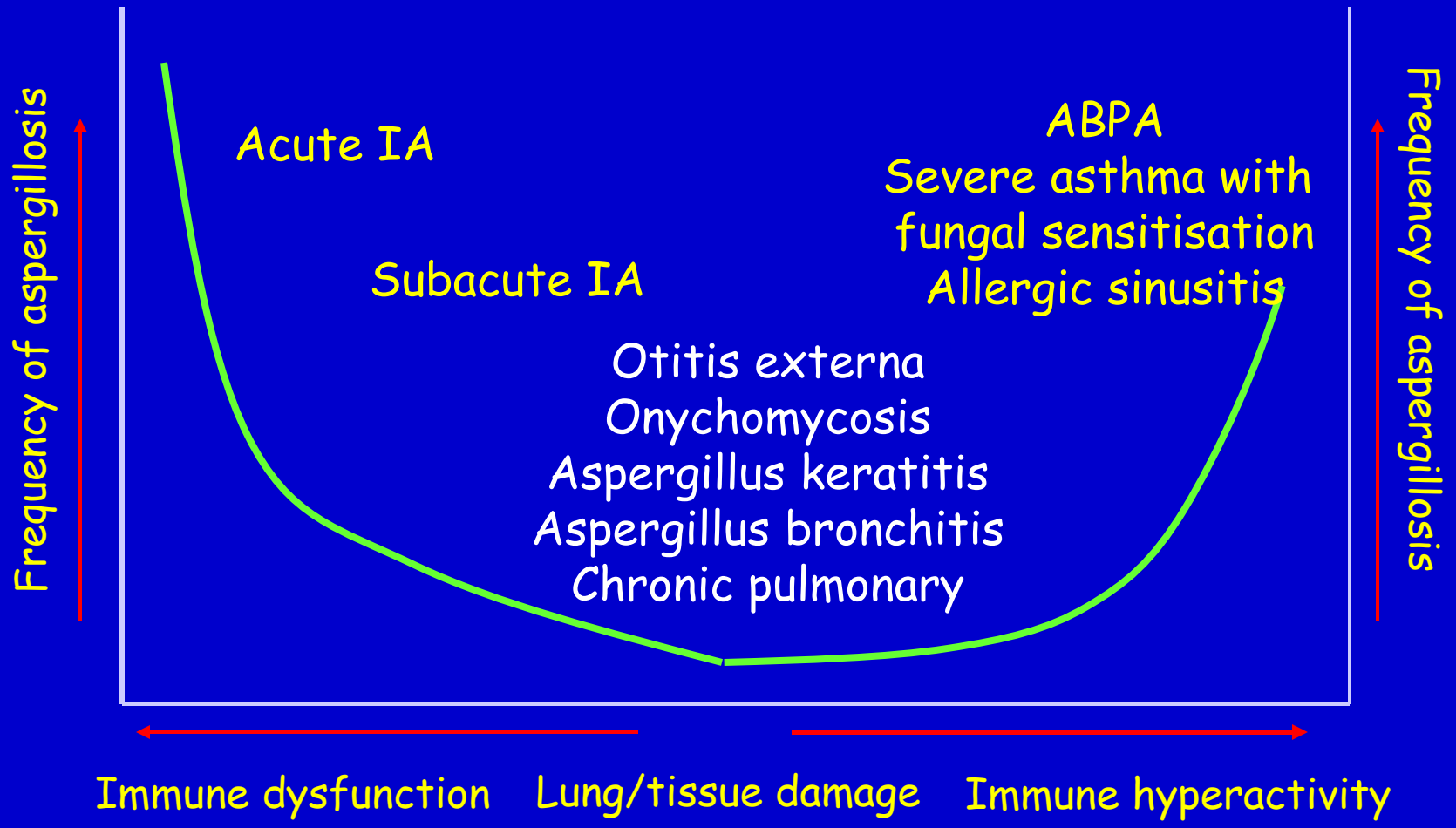
The University of Manchester

Infections caused by *Aspergillus* spp.

- Superficial i.e. otitis externa, onychomycosis (fungal nail disease), keratitis (corneal infection), wound infection and Aspergillus bronchitis
- Chronic fungal infections such as chronic pulmonary aspergillosis, granulomatous rhinosinusitis
- Allergic i.e. allergic bronchopulmonary aspergillosis (ABPA), severe asthma with fungal sensitisation (SAFS) and allergic fungal sinusitis
- Invasive and life-threatening i.e. invasive aspergillosis

Interaction of *Aspergillus* with the host

A unique microbial-host interaction



After Casadevall & Pirofski, Infect Immun 1999;67:3703

Aspergillus keratitis

- Usually *A. flavus or A. fumigatus*
- ~50% of keratitis fungal, and ~50% of these are due to *Aspergillus*.
- 1-12 million affected worldwide, especially in India, Nepal, Sri Lanka, Myanmar.
- Usually farmers and labourers, occasionally contact lens wearers

Unusual *Aspergilli* causing keratitis

Aspergillus	A. clavatus, A. fischerianus, A. flavipes, A. flavus, A glaucus, A. fumigatus, A. janus[b], A. niger, A. terreus, A. nidulans[b], A. oryzae, A. wentii[b] Aspergillus viridinutans

Thomas PA. Clin Microbiol Infect 2013;19:210

Aspergillus otitis externa

- Almost always *A. niger* complex
- Acute otitis affects 1 in 250 persons annually
- Chronic otitis affects 3-5% of the population (200-350 million)
- ~10% are fungal in origin

Unusual *Aspergilli* and otitis externa

- In Turkey, *Aspergillus niger* (180), *Aspergillus fumigatus* (95), *Aspergillus terreus* (32), *Aspergillus flavus* (23), *Aspergillus* spp. (14).
- In Hungary, 14 *A. niger* complex strains identified. 2010-2011. All were *A. awamori* and *A. tubingensis*
- *A. fresenii*, or an unnamed sister species responsible
- Invasive otitis externa caused by *Neosartorya pseudofischeri*

Degeril, Mikrobiyol Bul 2012:46:79; Szigeti G, Mycopathologia 2012;174:143. Hubka V, Med Mycol 2012:50:601; Balajee SA, J Clin Microbiol 2005:43:5996

Aspergillus onychomycosis

- Almost always toenails
- 0.5-3% of all cases of onychomycosis, ~20% of non-dermatophyte infections
- ? More common in diabetics
- 10's to 100's millions with onychomycosis worldwide
- ? 1 million cases

Unusual *Aspergilli causing* onychomycosis

- Usually toenails, but fingernails reported
- *A. fumigatus, A. niger, A. flavus* and *A. versicolor* relatively common
- *A. terreus* may be implicated. Found in Argentina, London, Italy, Denmark and Mexico.
- Rarer species include *A. sydowi, A. insulicola, A. westerdijkiae, A. tritici, A. nomius*, Cervini section, *A. ochraceus, A. candidus, A. alliaceus, A. versicolor, A. tamarii, A. ochraceopetaliformis* and *A. persii.*

Fernandez M, Mycoses 2013; 56:177

Patterns of onychomycosis caused by *Aspergilli*

Table II. Clinical presentations associated with different organisms

	DLSO* n (%)	SWO* n (%)	PSO n (%)
Scopulariopsis brevicaulis	27 (30.7)	—	10 (62.5)
Aspergillus species	23 (26.1)	12 (25.5)	6 (37.5)
Acremonium species	15 (17.0)	21 (44.7)	—
Fusarium species	13 (14.8)	13 (27.7)	—
Onychocola canadensis	4 (4.5)	1 (2.1)	—
Nattrassia mangiferae	4 (4.5)	—	—
Scytalidium dimidiatum	1 (1.1)	—	—
Alternaria species	1 (1.1)	—	—
	88 (100)	47 (100)	16 (100)

DLSO, Distal and lateral subungual onychomycosis; *PSO*, proximal subungual onychomycosis; *SWO*, superficial white onychomycosis.
*Mixed DLSO-SWO infections were counted as one each of DLSO and SWO.

Gupta A, J Am Acad Dermatol 2012;66:494

Patterns of onychomycosis caused by *Aspergilli*

Fig 4. Proximal subungual onychomycosis featuring periungual inflammation caused by *Aspergillus niger*.

Fig 3. Deep superficial white onychomycosis caused by *Aspergillus flavus*.

Gupta A, J Am Acad Dermatol 2012;66:494

Patterns of onychomycosis caused by *Aspergilli*

A. candidus

A. alliaceus

Gianni C, Dermatol 2004;209:104

Patterns of onychomycosis caused by *Aspergilli*

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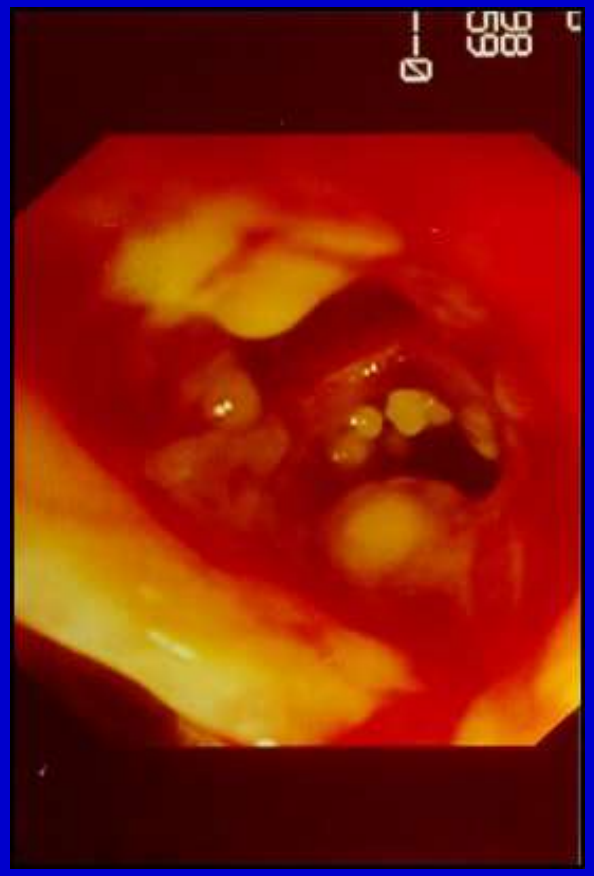
Gupta A, J Am Acad Dermatol 2012;66:494

Aspergillus bronchitis

- Complicates cystic fibrosis and bronchiectasis
- Recurrent infection and/or mucus plugging
- Superficial invasion of the bronchial wall.
- 8,600 UK CF patients, 5,000 adults.
- *Aspergillus* bronchitis affects ~1,500; globally about 11,000 cases
- Burden of *Aspergillus* bronchitis in non-CF patients unclear

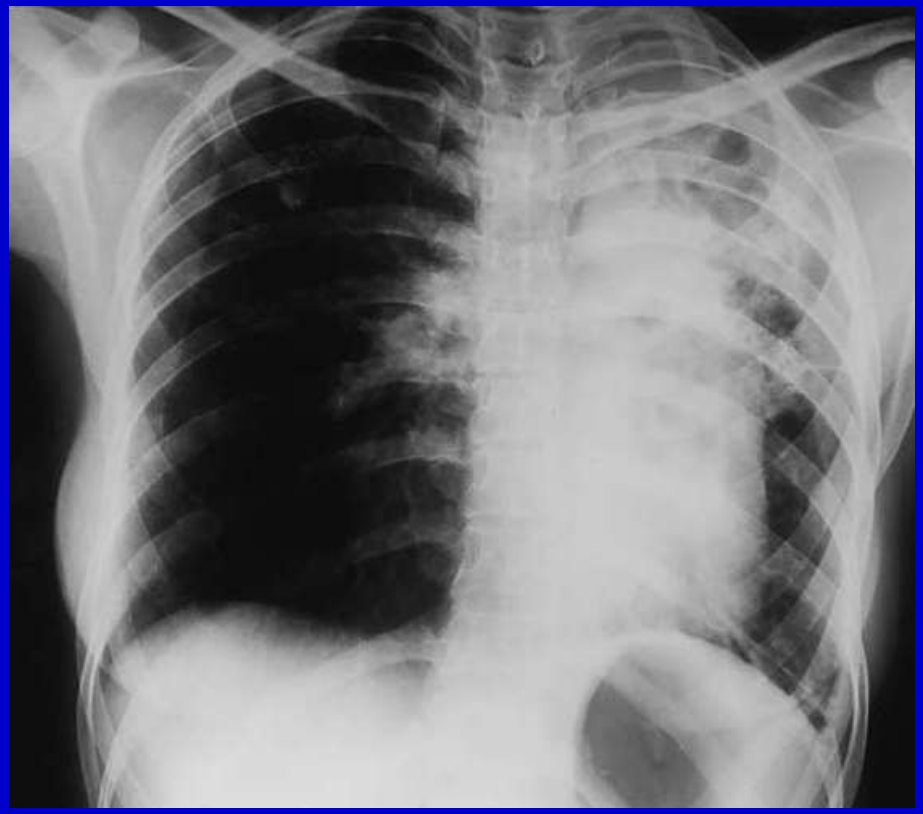


Aspergillus bronchitis and colonisation

- *Aspergillus* bronchitis may be caused by *A. fumigatus*, *A. flavus*, *A. terreus* or *A. niger*.
- *Aspergillus lentulus* was found occasionally during a 10-year follow-up study of one CF patient also colonized by *A. fumigatus*.
- *Neosartorya pseudofischeri* was isolated from three patients in Europe.
- *A. calidoustus* found in airways from transplant patients.

Symoens F, Med Mycol 2010;48; S1-10; Baddley JW, J Clin Microbiol 2009;47:3271; Egli A , Tranplant 2012;94:403

Chronic pulmonary aspergillosis



Chronic pulmonary aspergillosis

- 4 patterns of disease – chronic cavitary, chronic fibrosing, simple aspergilloma and *Aspergillus* nodule.
- Vast majority of cases due to *A. fumigatus*
- Reports of occasional cases due to *A. niger*, *A. flavus* and *A. nidulans*
- 1 aspergilloma caused by *A. tubingensis*

Pulmonary *Aspergillus niger* intracavitary colonization. Report of 23 cases and a review of the literature

Luiz Carlos Severo, Geraldo Resin Geyer, Nelson da Silva Porto, Mário Bernardes Wagner, Alberto Thomaz Londero

Laboratório de Microbiologia Clínica, IPD -Santa Casa, Annes Dias, 285 Porto Alegre 90020-090 RS, Brasil

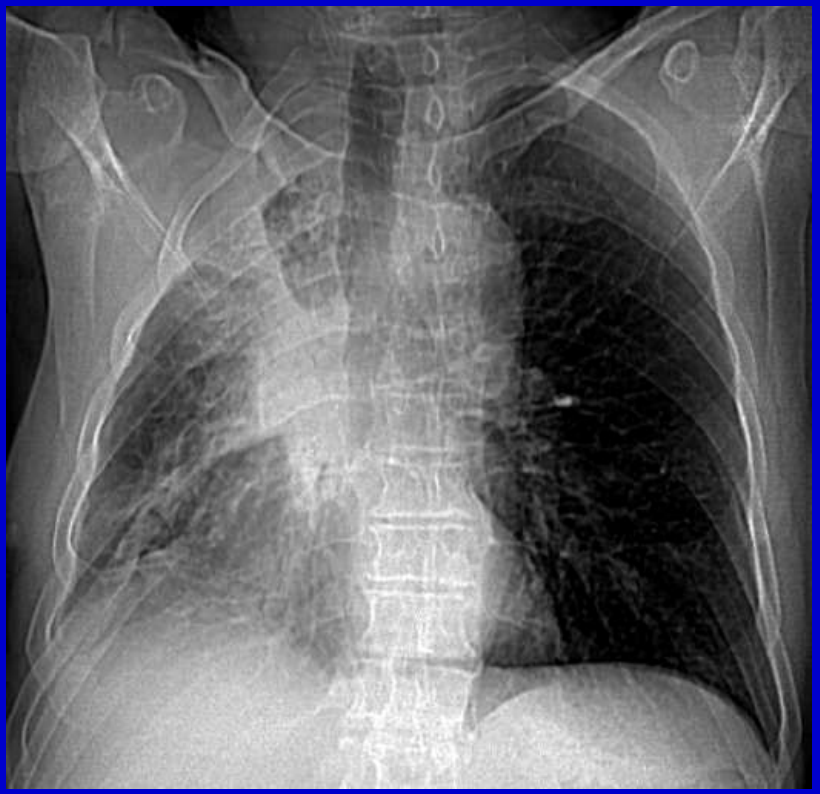
- 19 TB, 7 diabetes
- Serum precipitins (ID) against *A. niger* antigens in 18 (78%)
- *A. niger* conidial head in tissue sections
- 25% have pulmonary oxalosis, 1 systemic oxalosis

Table 2: Comparison of signs and symptoms observed in patients reported in the literature with our patients affected by *Aspergillus niger* intracavitary colonization.

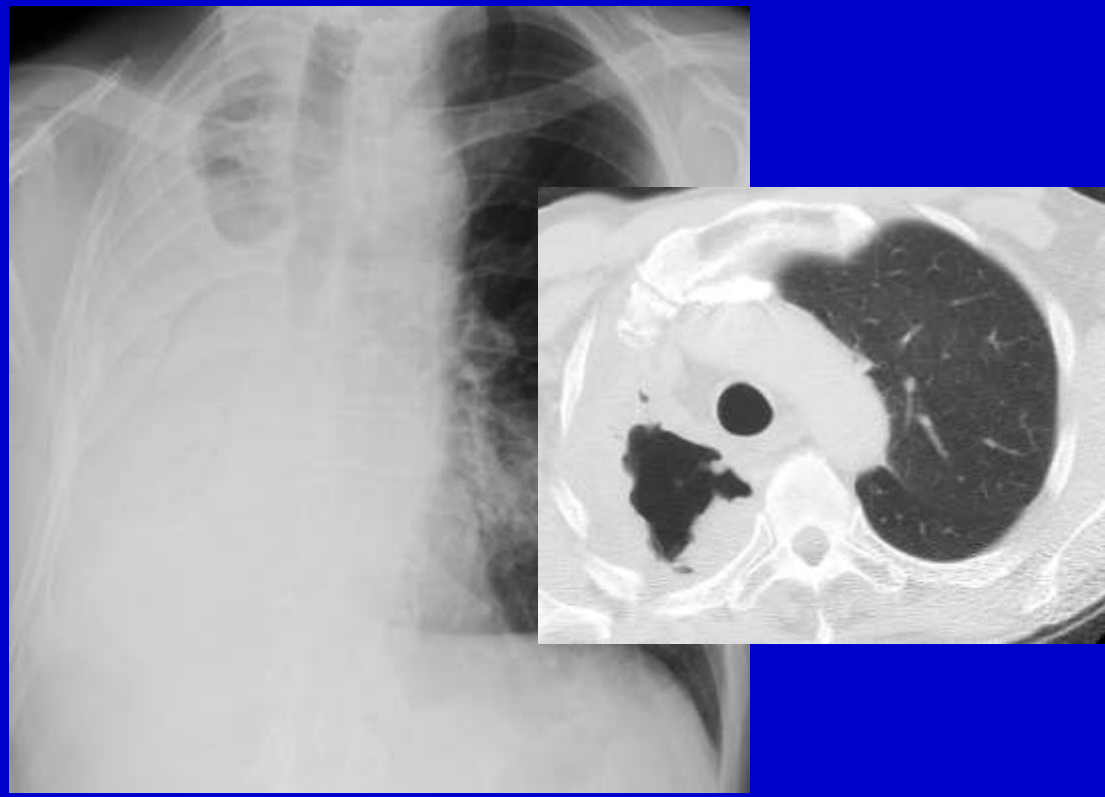
Symptoms and signs	Literature (n=40)		Our series (n=23)	
	n	% (95% CI)*	n	% (95% CI)
Cough and expectoration	26	65.0 (48.3-78.9)	21	91.3 (70.5-98,5)
Hemoptysis	22	55.0 (38.7-70.4)	19	82.6 (60.5-94.3)
Fever	13	32.5 (19.1-49.2)	5	21.7 (8.3-44.2)
Weight loss	6	15.0 (6.2-30.5)	10	43.5 (24.0-65.1)
Weakness	3	7.5 (2.0-21.5)	6	26.1 (11.1-48.7)
Cachexia	2	5.0 (0.9-18.2)	2	8.7 (1.5-29.5)
Breathlessness	4	10.0 (3.3-24.6)	7	30.4 (14.1-53.0)
Cyanosis	1	2.5 (0.1-14.7)	1	4.3 (0.2-24.0)
Chest pain	1	2.5 (0.1-14.7)	4	17.4 (5.7-39.6)
Anorexia	4	10.0 (3.3-24.6)	0	0.0 (0.0-17.8)

Severo LC, Rev Iberoam Micol 1997:14:104

Chronic pulmonary aspergillosis caused by *A. calidoustus*



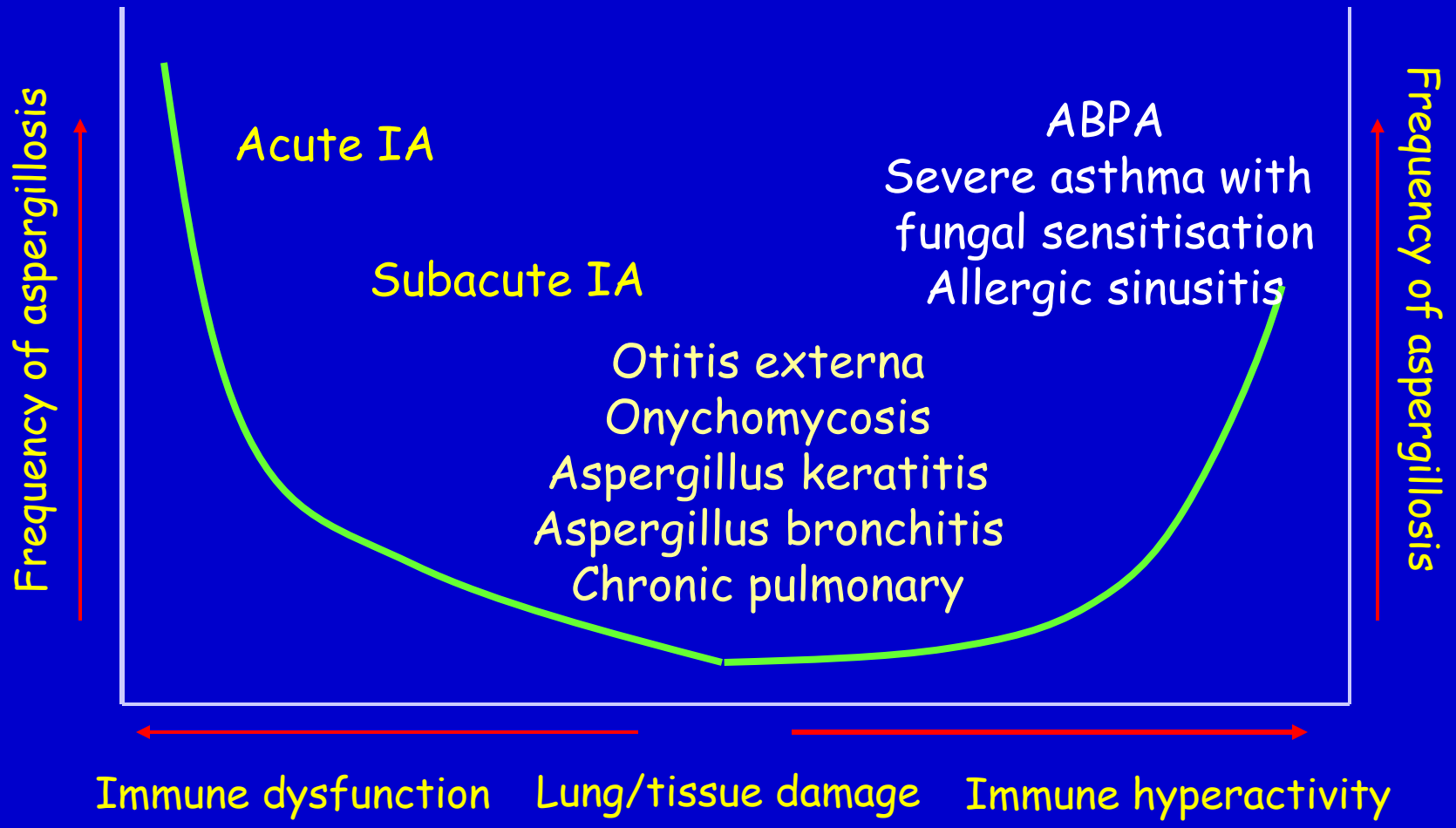
November 2008



December 2008

Interaction of *Aspergillus* with the host

A unique microbial-host interaction



After Casadevall & Pirofski, Infect Immun 1999;67:3703

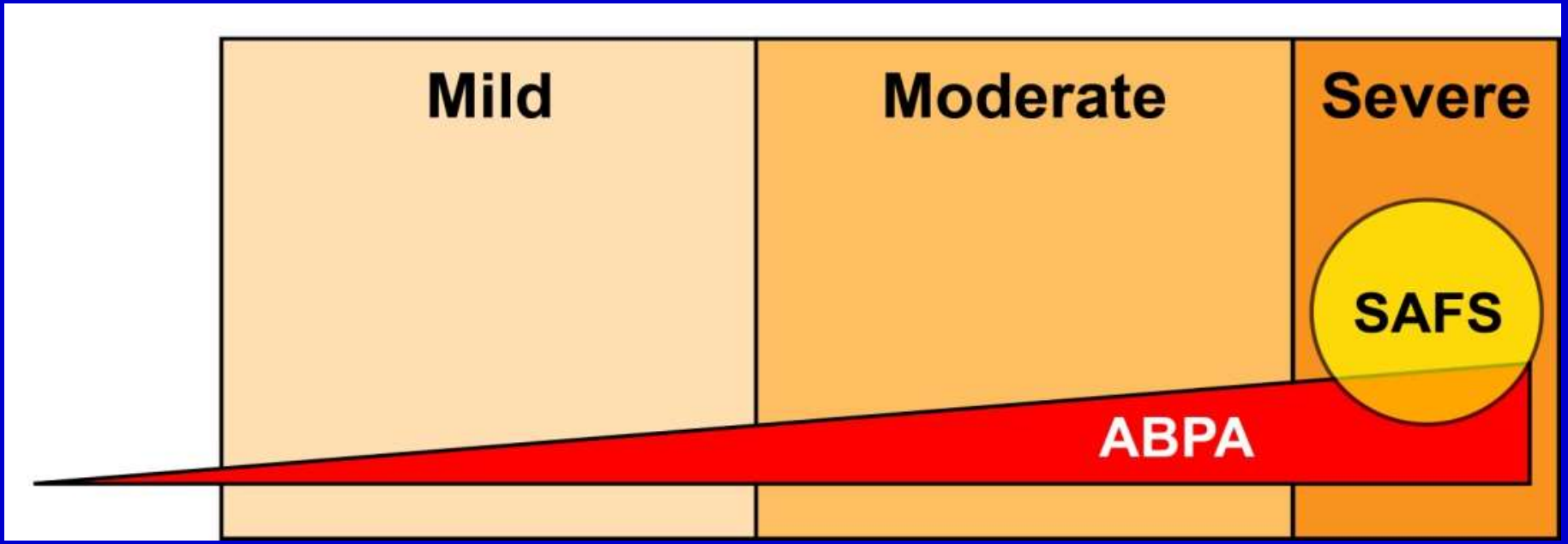
ABPA and severe asthma

Fungal exposure in asthmatics is related to:

- Life-threatening asthmatic attacks (ie thunderstorm asthma)
- Severe asthma and hospital admission
- Increased wheezing and symptoms
- Loss of medication control
- Allergic bronchopulmonary mycosis
- Eosinophilic fungal rhinosinusitis

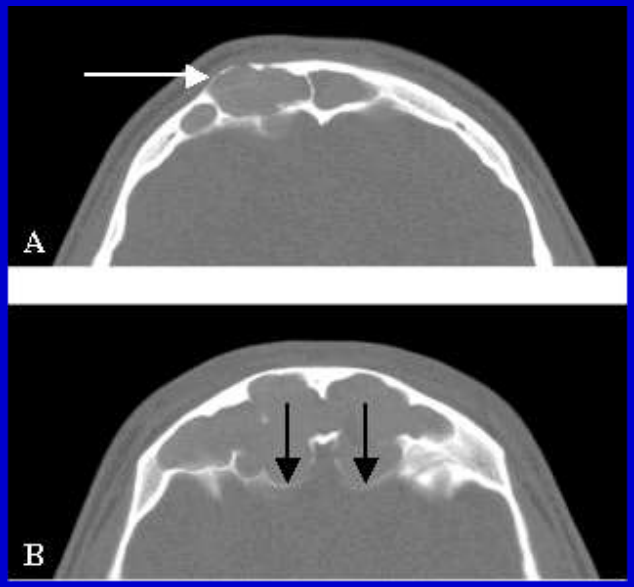
O'Hollaren, N Engl J Med 1991; 324: 359; and many others

ABPA versus SAFS



Denning et al, Med Mycol 2013:51:361

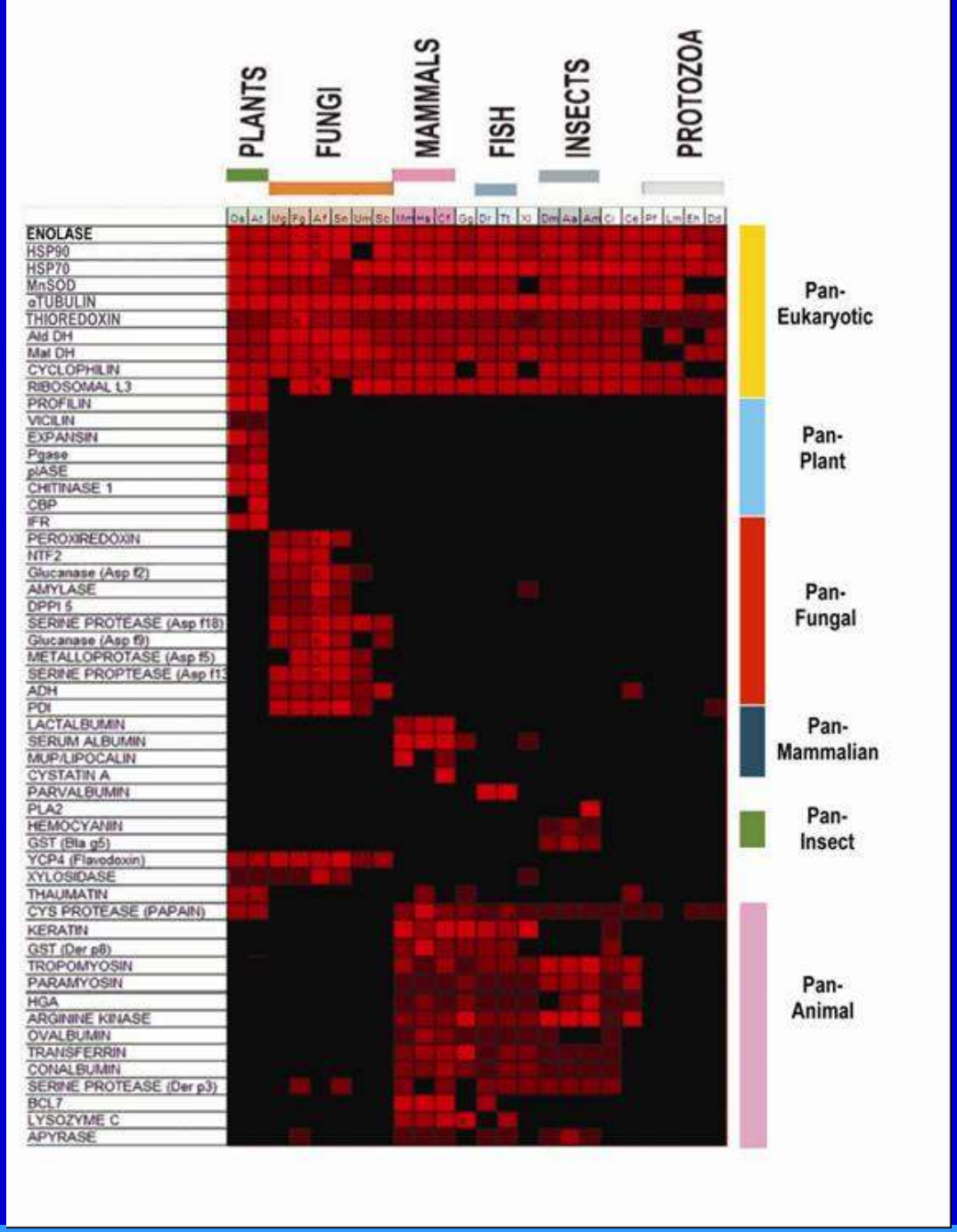
Allergic Aspergillus sinusitis



Clinical features = nasal obstruction, recurrent sinus infections, loss of smell and nasal polyps

Aspergillus precipitins IgG antibody) positive in 85% of original series

Genomic analysis of allergens



Bowyer et al, BMC Genomics 2006;7:251

Approved allergens

On Allergome.org – 190 of 6965 entries are '*Aspergillus*', 71 to 'fumigatus'.

9		Asp c		Aspergillus, *Aspergillus clavatus*, Fungi, Molds, *Trichocomaceae*
10		Asp cl		Aspergillus, *Aspergillus clavatonanicus*, Fungi, Molds, *Trichocomaceae*
11		Asp f		Aspergillus, *Aspergillus fumigatus*, Fungi, Molds, *Neosartorya fumigata*, *Sartorya fumigata*, *T*
12		Asp fl		Aspergillus, *Aspergillus flavus*, Fungi, Molds, *Trichocomaceae*
13		Asp gi		Aspergillus, *Aspergillus giganteus*, Fungi, Molds, *Trichocomaceae*
14		Asp lo		Aspergillus, *Aspergillus longivesica*, Fungi, Molds, *Trichocomaceae*
15		Asp me		Aspergillus, *Aspergillus melleus*, Fungi, Molds, *Trichocomaceae*
16		Asp n		Aspergillus, *Aspergillus niger*, Fungi, Molds, *Trichocomaceae*
17		Asp o		Aspergillus, *Aspergillus oryzae*, Fungi, Molds, *Trichocomaceae*
18		Asp oc		Aspergillus, *Aspergillus ochraceus*, Fungi, Molds, *Trichocomaceae*
19		Asp r		Aspergillus, *Aspergillus restrictus*, Fungi, Molds, *Trichocomaceae*
20		Asp rh		Aspergillus, *Aspergillus rhizopodus*, Fungi, Molds, *Trichocomaceae*
21		Asp sa		Aspergillus, *Aspergillus phoenicis*, *Aspergillus saitoi*, Fungi, Molds, *Trichocomaceae*
22		Asp sp		Aspergillus, *Aspergillus spp*, Fungi, Molds, *Trichocomaceae*
23		Asp sy		Aspergillus, *Aspergillus sydowii*, Fungi, Molds, *Trichocomaceae*
24		Asp t		Aspergillus, *Aspergillus terreus*, Fungi, Molds, *Trichocomaceae*
25		Asp v		Aspergillus, *Aspergillus versicolor*, Fungi, Molds, *Trichocomaceae*
26		Aspe ni		Aspergillus, *Aspergillus nidulans*, *Emericella nidulans*, Fungi, Molds, *Trichocomaceae*
27		Neo fi		*Aspergillus fischeri*, *Aspergillus fischerianus*, Fungi, Molds, Neosartorya, *Neosartorya fischeri*,

Multiple Admissions

Mean sensitization score (mm)
(Mean and 95% CI)

20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0

P= <0.0001

No Hospital Admission

Single Admission

Multiple Admissions

No Hospital Admission

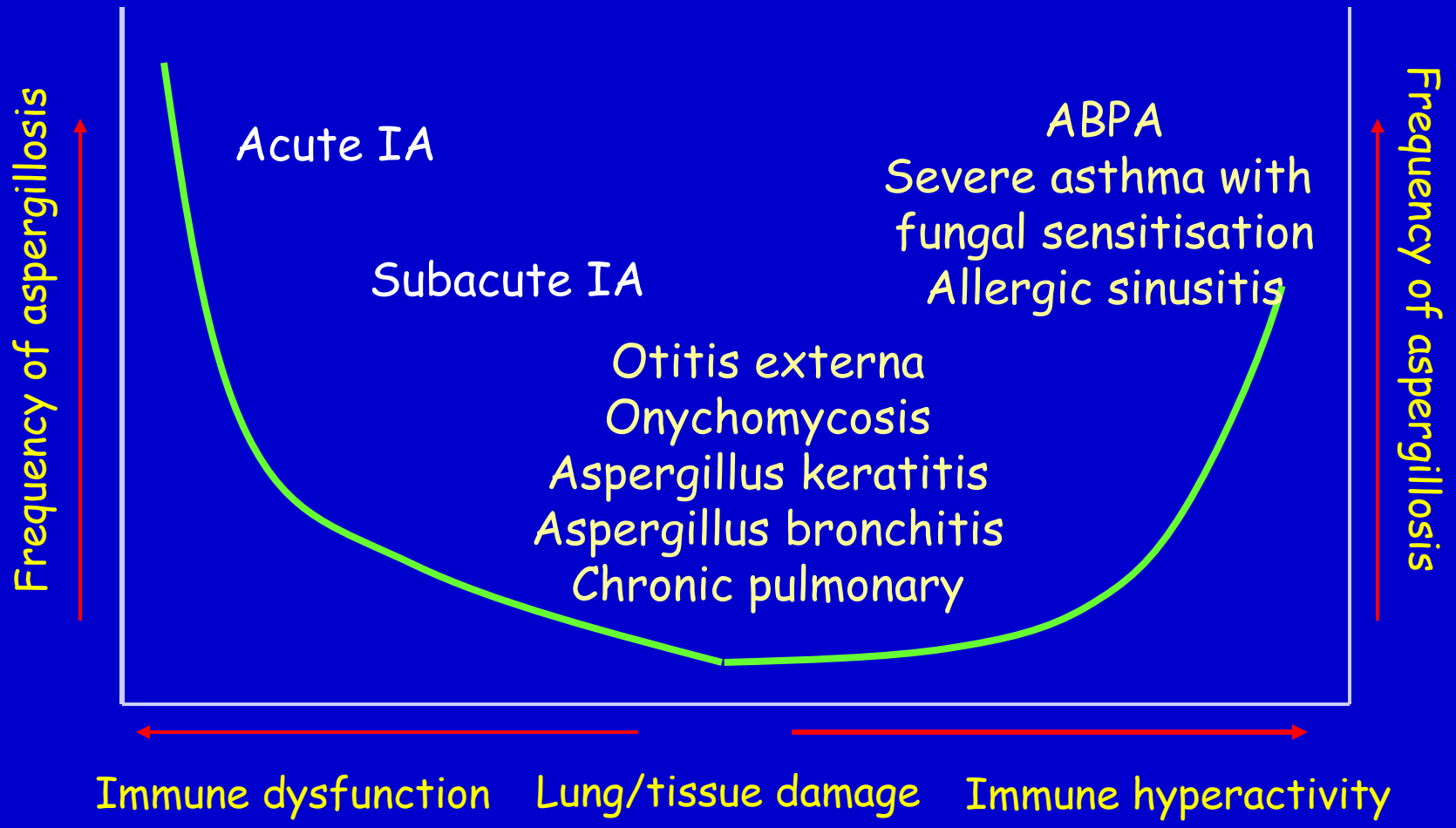
Single Admission

Mould allergens

Non-Mould allergens

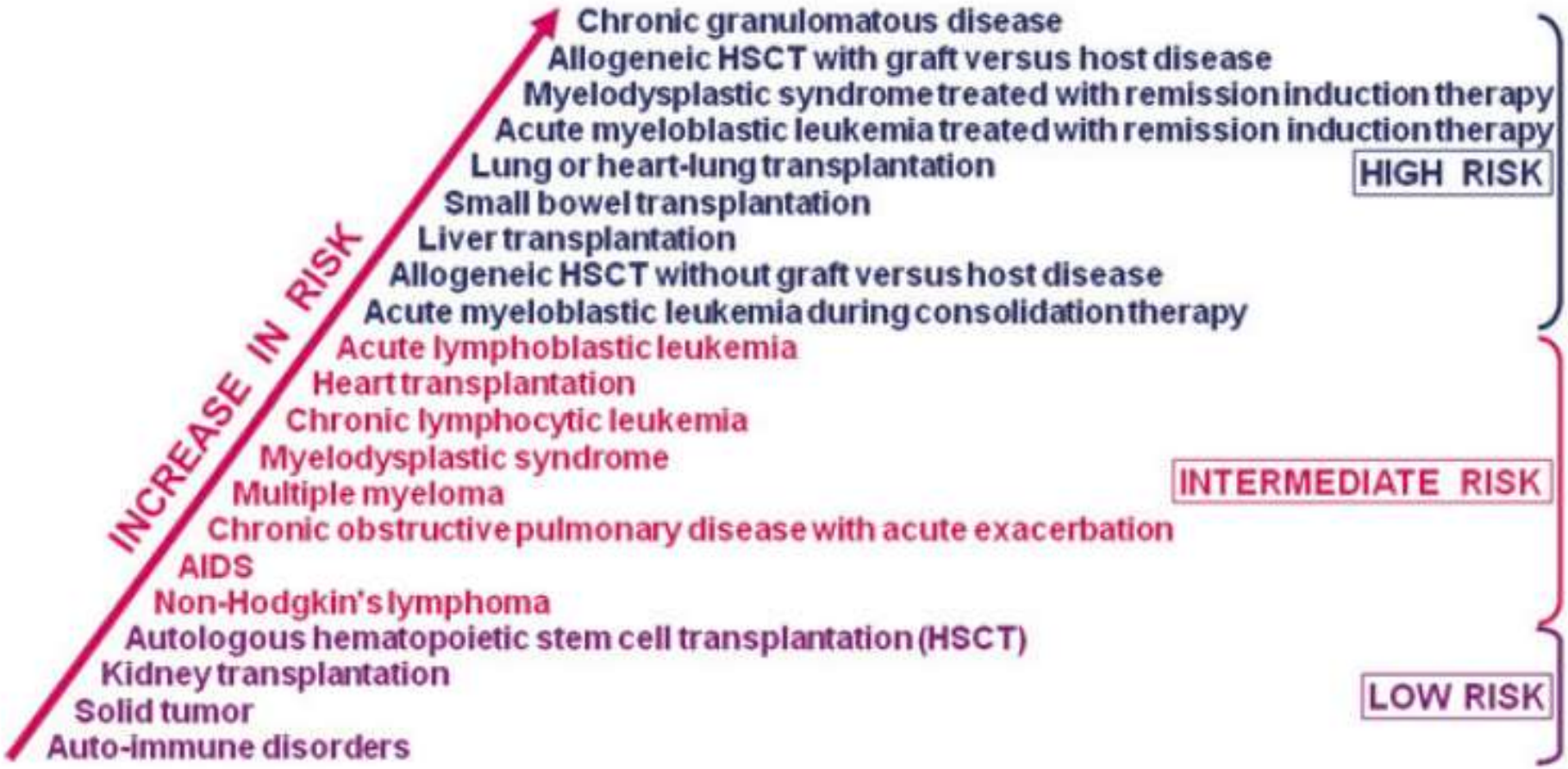
Interaction of *Aspergillus* with the host

A unique microbial-host interaction



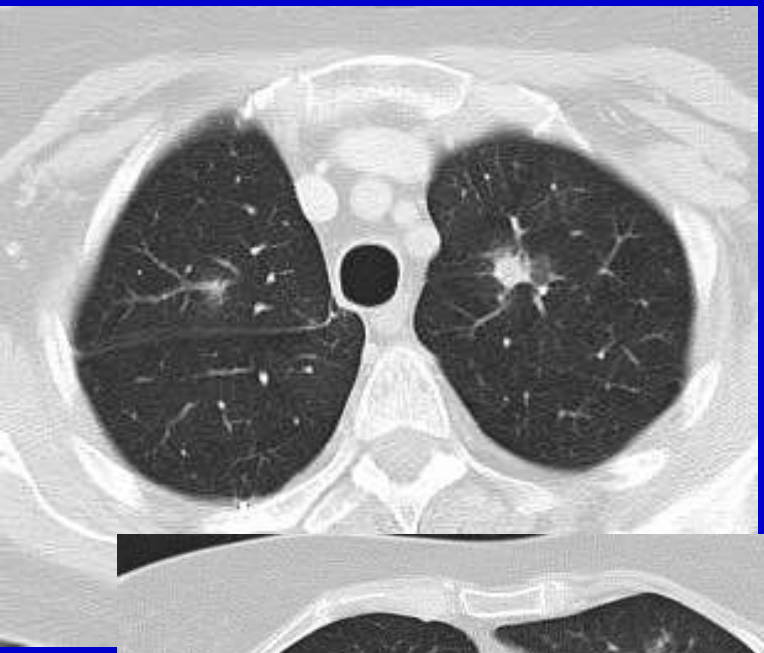
After Casadevall & Pirofski, Infect Immun 1999;67:3703

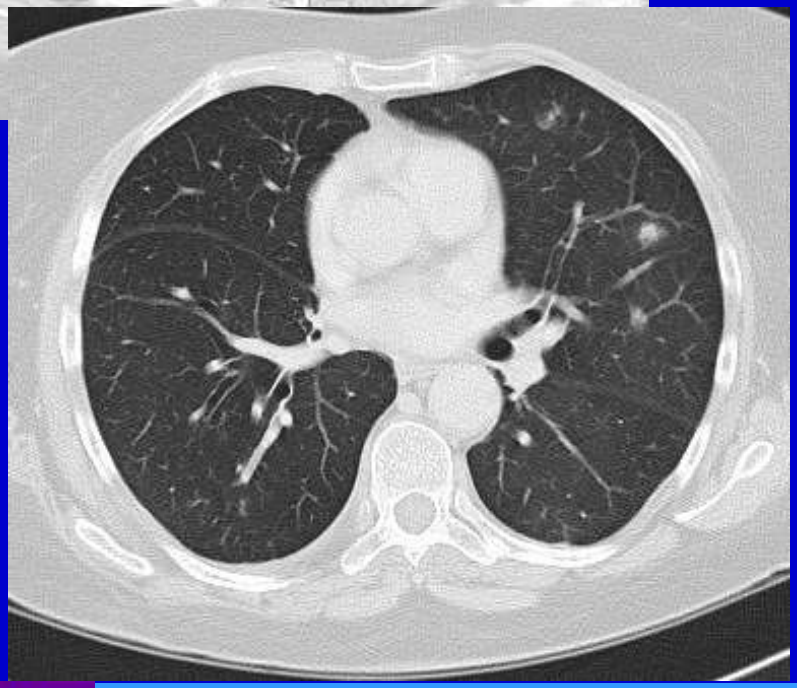
Risk groups and frequencies of invasive aspergillosis – different test performances

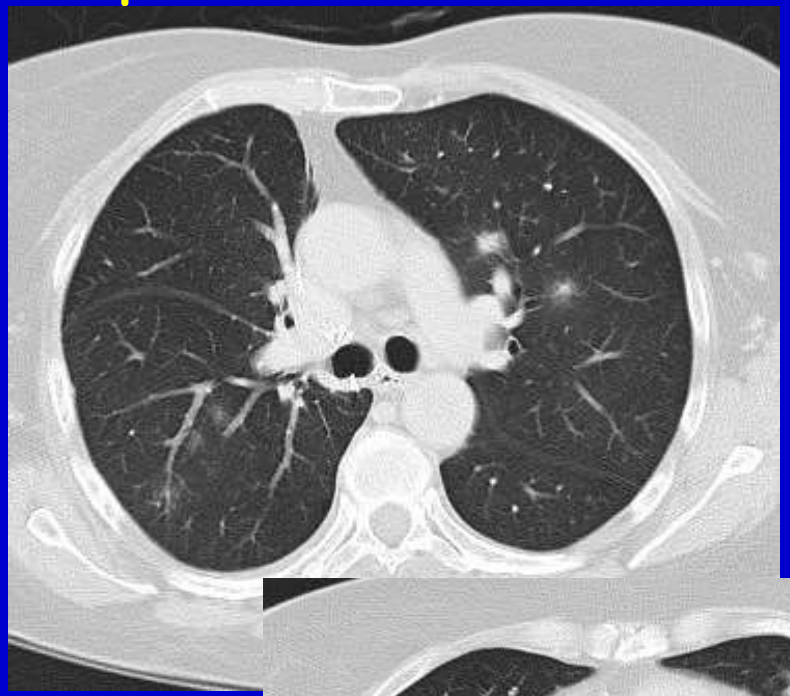


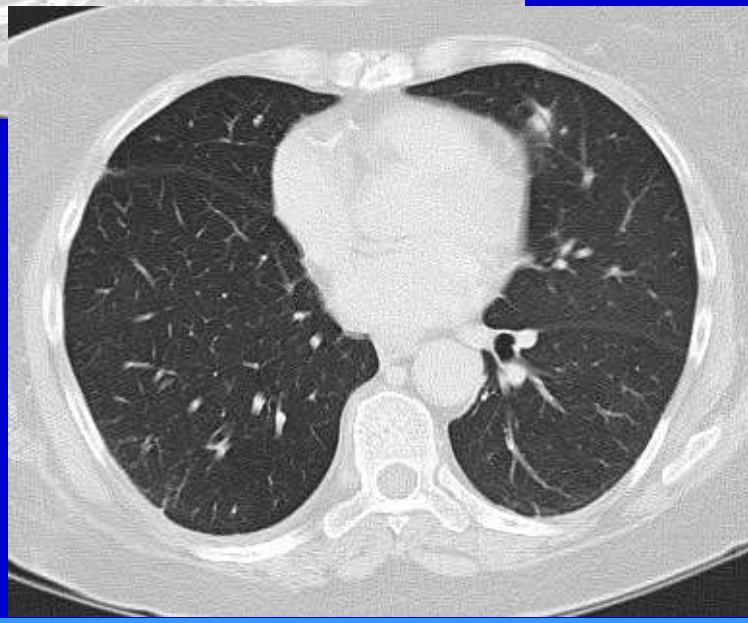
Herbrecht, Ann NY Acad Sci 2012;1271:23

CT scan showing nodules with halo – lung cancer and neutropenia









Examples of susceptibility tests

A

Susceptibility results for Aspergillus fumigatus complex

	MEC	MIC	MFC	RESULT
Itraconazole		1	1	Sensitive
Amphotericin		0.5		
Voriconazole		1		Sensitive
Posaconazole		0.125		Sensitive

Susceptibility results for Aspergillus fumigatus complex

B

	MEC	MIC	MFC	RESULT
Itraconazole		8	>8	Resistant
Amphotericin		4	4	
Voriconazole		8	>8	Resistant
Posaconazole		0.125	8	Sensitive
Terbinafine		4	>8	
Micafungin	2			

IA due to *fumigatus* sibling species

- *A. lentulus* - Fatal IA in heart transplant recipient in Zurich
- *A. lentulus* in mixed infection in COPD in Madrid
- *A. lentulus* in a renal transplant recipient in Buenos Aires
- *A. pseudofisheri* causing invasive otitis in Los Angeles
- *A. pseudofisheri* causing peritonitis in Saitama, Japan
- *A. pseudofisheri* in blood preceeding IPA in neutropenia in Estonia
- *A. calidoustus* & *A. novofumigatus* in leukaemia in Madrid, followed by *A. novofumigatus* and *A. viridinutans*

Zbinden A, Transpl ID 2012;14:E60; Alhambra A, Rev Iberoam Micol 2008;25:246; Montenegro G, J Med Microbiol 2009;58:391; Balajee SA, J Clin Microbiool 2005;43:5996; Jary H, J Clin Microbiol 2004;42:925; Palaez T, J Med Microbiol 2013;62:474

IA due to *terreus* sibling species - *alabamensis*

Isolate no.	Species	Geographic origin	Source	GenBank identification no. (*calM*, *enoA*, *benA*)	Yr of isolation
CBS15F8	*A. alabamensis*[a]	Argentina	Soil	EU147529, EU147622, EU147715	2006
CBS15F9	*A. alabamensis*[a]	Argentina	Soil	EU147530, EU147623, EU147716	2006
UAB1	*A. alabamensis*[a]	Alabama	Tracheal aspirate	EU147566, EU147659, EU147752	1996
UAB13	*A. alabamensis*[a]	Alabama	Sputum	EU147578, EU147671, EU147764	2000
UAB15	*A. alabamensis*[a]	Alabama	Sputum	EU147579, EU147672, EU147765	2000
UAB18	*A. alabamensis*[a]	Alabama	Sputum	EU147581, EU147674, EU147767	2000
UAB19	*A. terreus*	Alabama	BAL	EU147582, EU147675, EU147768	2000
UAB20	*A. alabamensis*[a]	Alabama	Wound	EU147583, EU147676, EU147769	2000
UAB21	*A. terreus*	Alabama	Sputum	EU147584, EU147677, EU147770	2000
UAB22	*A. alabamensis*[a]	Alabama	Tracheal aspirate	EU147585, EU147678, EU147771	2000
UAB23	*A. alabamensis*[a]	Alabama	Sputum	EU147586, EU147679, EU147772	2000
UAB22	*A. alabamensis*[a]	Alabama	Tracheal aspirate	EU147585, EU147678, EU147771	2000
UAB23	*A. alabamensis*[a]	Alabama	Sputum	EU147586, EU147679, EU147772	2000
UAB26	*A. terreus*	Alabama	Sputum	EU147587, EU147680, EU147773	2000
UAB28	*A. alabamensis*[a]	Alabama	BAL	EU147588, EU147681, EU147774	2000
UAB30	*A. alabamensis*[a]	Alabama	Sputum	EU147589, EU147682, EU147775	2001
UAB33	*A. alabamensis*[a]	Alabama	Foot tissue	EU147592, EU147685, EU147778	2001
UAB34	*A. terreus*	Alabama	Sputum	EU147593, EU147686, EU147779	2001
UAB37	*A. terreus*	Alabama	Tracheal aspirate	EU147594, EU147687, EU147780	2001
UAB38	*A. alabamensis*[a]	Alabama	Left ear	EU147595, EU147688, EU147781	2001

Baajee SA,Eucaryot Cell 2009;8:713

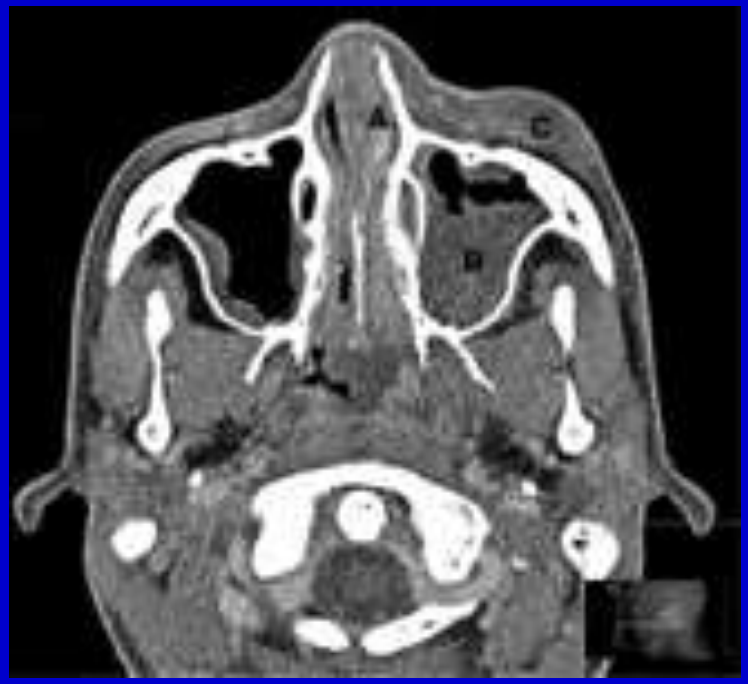
IA due to *terreus* sibling species – *alabamensis*

dissseminated IA in a dog

Burroughs E. Med Mycol Case Rep 2012;1:1

IA due to *niger* sibling species – *tubingensis*

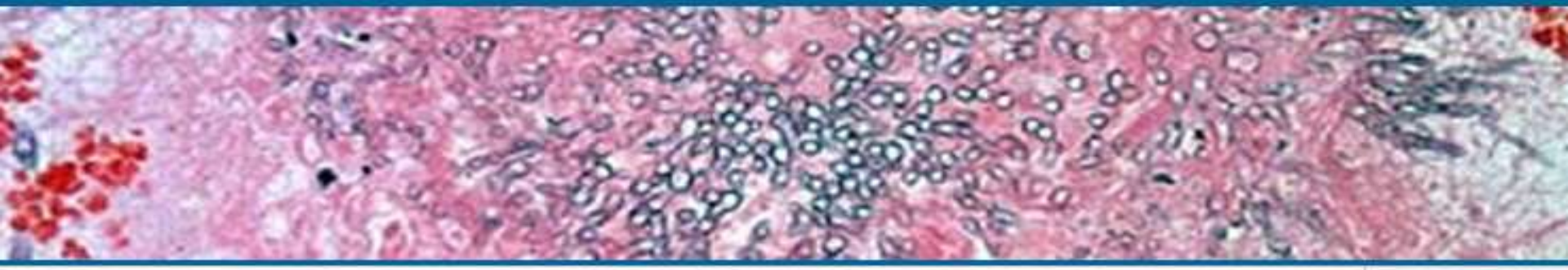
- Stem cell transplant recipient for PNH
- Tooth extraction
- Responded to 6 weeks L-AmB 5mg/Kg



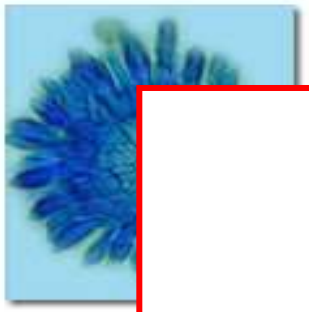
Bathoorn E. BMC Infect Dis 2013;13:59

Web www.aspergillus.org.uk

Patients | Scientific Information | Medical Information | Images | Educational Materials | Library



The Aspergillus Website



The **Aspergillus website** is a worldwide comprehensive resource providing a wide range of information about the **fungus Aspergillus** and the diseases - such as **Aspergillosis** that

WWW.aspergillus.org.uk

15 years and counting
Over 1M pages read monthly in >125 countries
Supported by the Fungal Infection Trust – 20 year anniversary in 2011

Aspergill
aspergillosis, ABPA, CPA and aspergilloma. Some asthma patients with very severe asthma may also be sensitised to fungi like aspergillus (SAFS). There is a section devoted to the needs of patients, friends and family suffering from the effects of Aspergillosis.
The UK's first National Aspergillosis Centre opened on May 1st 2009 - the opening meeting can be viewed. The centre is supported by the Regional Mycology Lab which also provides both air sampling and mould identification services for domestic and working environments.

Aspergillosis may affect patients whose immune system may be compromised - including those with **leukaemia, chemotherapy patients or those on steroids, transplant patients, cystic fibrosis, HIV or AIDS, chronic obstructive pulmonary disease (COPD), chronic granulomatous disease (CGD), severe asthma with fungal sensitivity (SAFS) and many others.**

Aspergillus does not solely affect humans; **birds and animals can also develop aspergillosis**, and some plant

search

Useful links

- Site upda
- What is a
- Register
- Passwor
- Aspergill
- Editorial

opular

- Patients
- Latest art
- Newslette
- Blog
- Patients
- Job adve
- RSS new

Headlines

A new database
discover any inter
other drugs a pati
2011-06-10
Patients website

The following species matched your search criteria:

50 asexual forms
5 sexual forms
12 previous names

Asexual forms

Aspergillus alabamensis	Aspergillus flavus var. oryzae	Aspergillus qizutongii
Aspergillus alliaceus	Aspergillus fumigatus	Aspergillus reptans
Aspergillus alutaceus	Aspergillus glaucus	Aspergillus restrictus
Aspergillus atroviolaceus	Aspergillus hollandicus	Aspergillus rubrobrunneus
Aspergillus beijingensis	Aspergillus janus	Aspergillus sejunctus
Aspergillus caesiellus	Aspergillus japonicus	Aspergillus spinosus
Aspergillus calidoustus	Aspergillus lentulus	Aspergillus sydowii
Aspergillus candidus	Aspergillus nidulans	Aspergillus tamarii
Aspergillus carneus	Aspergillus nidulans (Eidam)	Aspergillus tanneri
Aspergillus chevalieri	Aspergillus niger	Aspergillus terreus
Aspergillus clavatonanicus	Aspergillus niger var. awamorii	Aspergillus tetrazonus
Aspergillus clavatus	Aspergillus niveus	Aspergillus unguis
Aspergillus conicus	Aspergillus novoparasiticus	Aspergillus ustus
Aspergillus deflectus	Aspergillus ochraceopetaliformis	Aspergillus versicolor
Aspergillus fischerianus	Aspergillus ochraceus	Aspergillus viridinutans
Aspergillus flavipes	Aspergillus oryzae	Aspergillus wangduanlii
Aspergillus flavus	Aspergillus penicilloides	

Sexual forms

Emericella nidulans	Eurotium oryzae	Sartorya fumigata
Emericella unguis	Neosartorya spinosa	

Previous names

Aspergillus awamori	Aspergillus terreus var subfloccosus	Sterigmatocystis sydowii/Aspergillus tunetamus
Aspergillus flavus var. oryzae	Fennellia nivea	Sterigmatocystis unguis
Aspergillus oryzae	Neosartorya fischeri.	Sterigmatocystis ustus
Aspergillus ruber	Sterigmatocystis nidulans	Sterigmatocystis versicolor

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Images of aspergillosis and *Aspergillus*

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Species Images

(Please note there are multiple images associated with each species)

- *Aspergillus alliaceus*
- *Aspergillus calidoustus*
- *Aspergillus candidus*
- *Aspergillus chevalieri*
- *Aspergillus cretensis*
- *Aspergillus clavatus*
- *Aspergillus costaricaensis*
- *Aspergillus flavipes*
- *Aspergillus flavus*
- *Aspergillus flocculosus*
- *Aspergillus fumigatus* Fresen
- *Aspergillus glaucus*
- *Aspergillus ibericus*
- *Aspergillus lacticoffeatus*
- *Aspergillus lanosus*
- *Aspergillus lentulus*
- *Aspergillus neobridgeri*
- *Aspergillus niger* Tiegh. nom. cons
- *Aspergillus niveus*
- *Aspergillus ochraceus*
- *Aspergillus ochraceopetaliformis*
- *Aspergillus penicillioides*
- *Aspergillus persii*
- *Aspergillus piperis*
- *Aspergillus pseudoelegans*
- *Aspergillus pseudofisheri*
- *Aspergillus restrictus*
- *Aspergillus roseoglobulosus*
- *Aspergillus sclerotioniger*
- *Aspergillus steynii*
- *Aspergillus sydowii*
- *Aspergillus terreus* Thom
- *Aspergillus udagawae*
- *Aspergillus ustus*

Aspergillus amstelodami *(Eurotium amstelodami)*

Aspergillus alliaceus

Aspergillus calidoustus

Aspergillus candidus

Aspergillus chevalieri

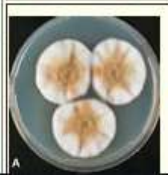
Aspergillus clavatus

Aspergillus costaricaensis

Aspergillus cretensis

Aspergillus flavipes

Aspergillus flavus



Aspergillus flocculosus

Aspergillus fumigatus Fresen

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LIFE LEADING INTERNATIONAL FUNGAL EDUCATION

English

WELCOME TO LIFE

AWARENESS. EDUCATION. SAVING LIVES

Over 300 million people are acutely or chronically infected by fungi, leading to death, long term illness, blindness, psychological problems and reduced work capacity. Many recent improvements in diagnostics and treatment have not reached treating clinicians in all countries, and access to appropriate diagnostics and simple antifungal agents is far from universal. This needs to change.

LIFE is a growing organisation. It is led by Professor David Denning who has been caring for patients with fungal infection for 25 years. He leads the National Aspergillosis Centre, UK (the first national clinical centre devoted to any fungal disease) and manages a clinical and laboratory research team.

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MEDICAL COMMUNITY

Providing medical professionals with the knowledge they need to recognise and treat fungal infections. LIFE believes knowledge about fungal infections, available diagnosis and treatments are key to improving patient outcomes.

This site provides you with current knowledge about fungal infections, fungi, diagnosis and treatment.

what the professionals say...

Fungal infections are particularly common in India, now increasing alarmingly. Better

Conclusions

Wide spectrum of aspergillosis – superficial, allergic, chronic and invasive.

Global burden of superficial and allergic aspergillosis much more common than chronic and invasive aspergillosis.

Many millions of people affected, some with major morbidity or death.

Wide variety of species involved, especially in fungal keratitis and onychomycosis.

Probably allergen cross-reactivity allows uncommon cryptic species to contribute to fungal allergy