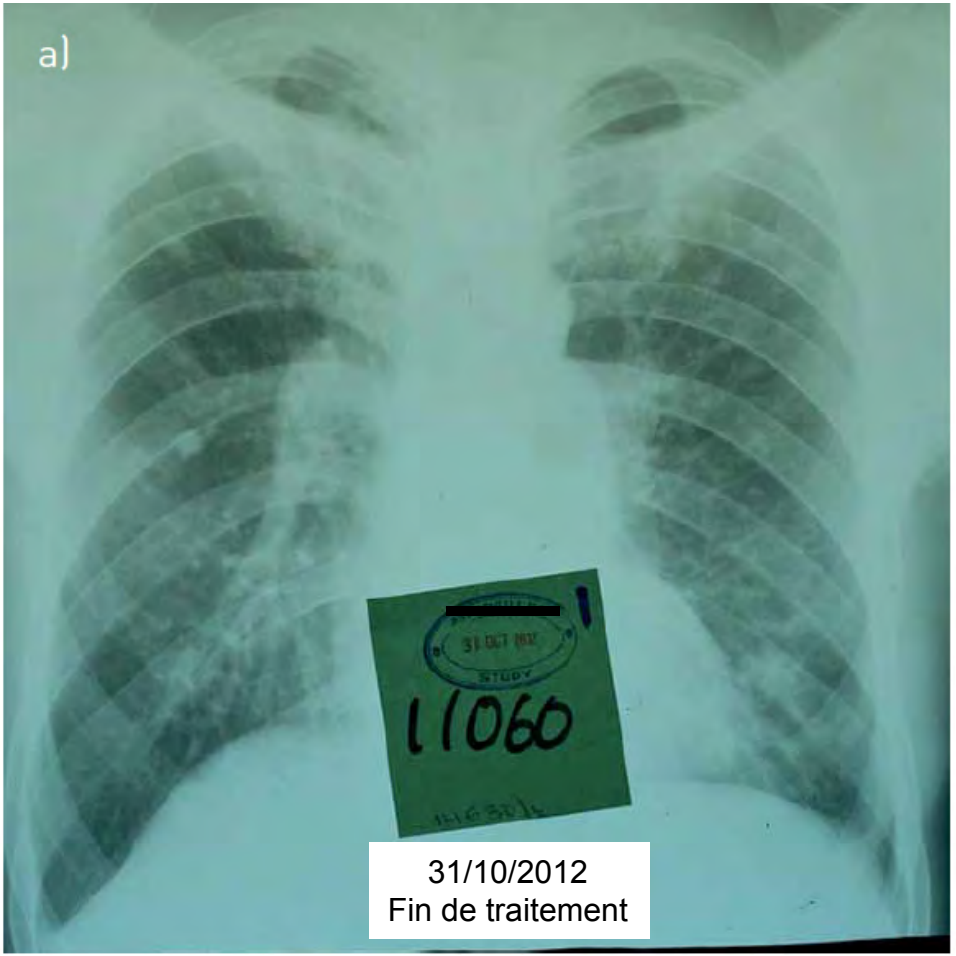
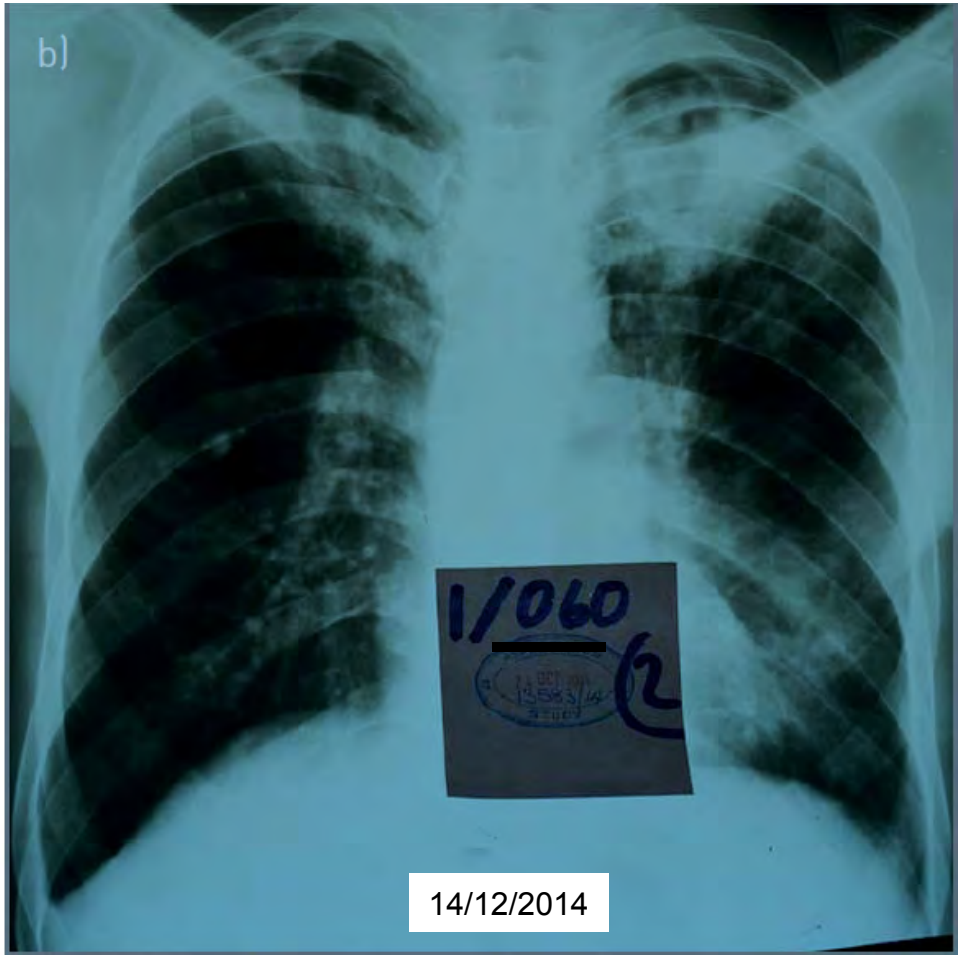
Cas clinique

- Ougandais de 36 ans en situation irrégulière
- Non fumeur, VIH négatif
- A été traité il y a 2 ans pour une tuberculose pulmonaire (programme de traitement, radiographies apportées)
- Ne prend aucun traitement
- Toux, expectoration purulente, hémoptysie de faible abondance, asthénie; 1,85 m/65 kg (BMI:17,5)


a)
[redacted]
11060
31/10/2012
Fin de traitement


b)
[redacted]
11060
14/12/2014

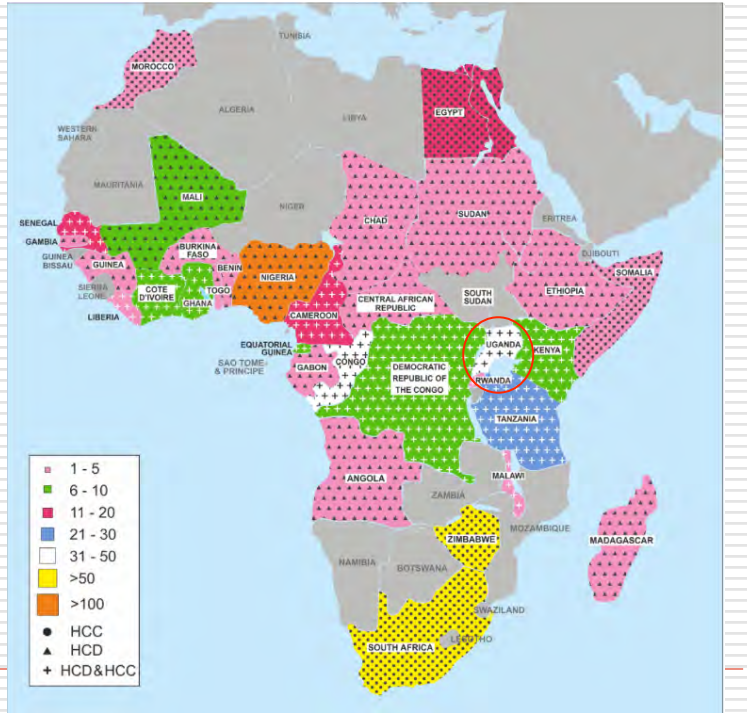
Quelles sont vos hypothèses ?

1. Séquelles de tuberculose
2. Cancer
3. Aspergillose pulmonaire chronique
4. Histoplasmose
5. Récidive de tuberculose

Quelles sont vos hypothèses ?

1. Séquelles de tuberculose
2. Infection bactérienne
3. Aspergillose pulmonaire chronique
4. Histoplasmose
5. Récidive de tuberculose

Histoplasmose en Afrique



Oladele et al, PLOS 2018

Quelle prise en charge proposez vous ?

1. Amoxycilline-acide clavulanique 1gx3 pendant 3 semaines et réévaluation
2. Sérologie aspergillaire
3. TDM thoracique injecté
4. ECBC pour recherches microbiologiques (BAAR, bactériologie, mycologie)
5. Reprise du traitement antituberculeux

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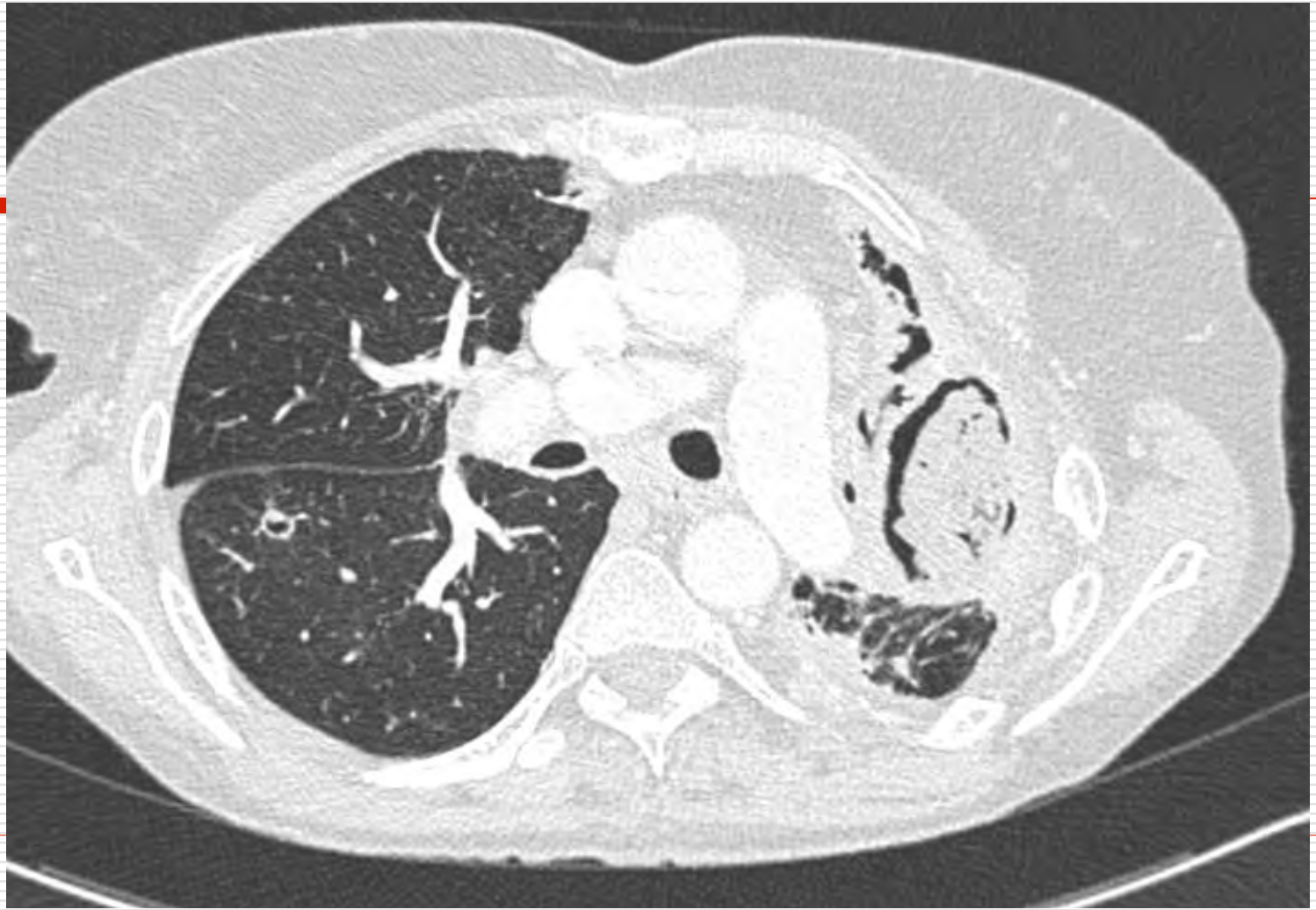
5. Reprise du traitement antituberculeux

Cas clinique

- Sérologie aspergillaire négative
- ECBC bactériologie et BAAR négatif
- ECBC présence de filaments aspergillaires au direct; type *A Flavus* en culture
- TDM thorax après 3 semaines d'antibiotique
- Amélioration de la toux et de l'expectoration, persistance des hémoptysies de faible abondance



Quelles sont vos commentaires ?

1. Il s'agit d'une aspergillose pulmonaire chronique
2. *Aspergillus Flavus* n'est pas pathogène
3. La négativité de la sérologie exclue une infection aspergillaire (il s'agit d'une colonisation)
4. Vous débutez un traitement par itraconazole
5. Le traitement antifungique va diminuer les hémoptysies

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Epidemiology of aspergillosis diseases

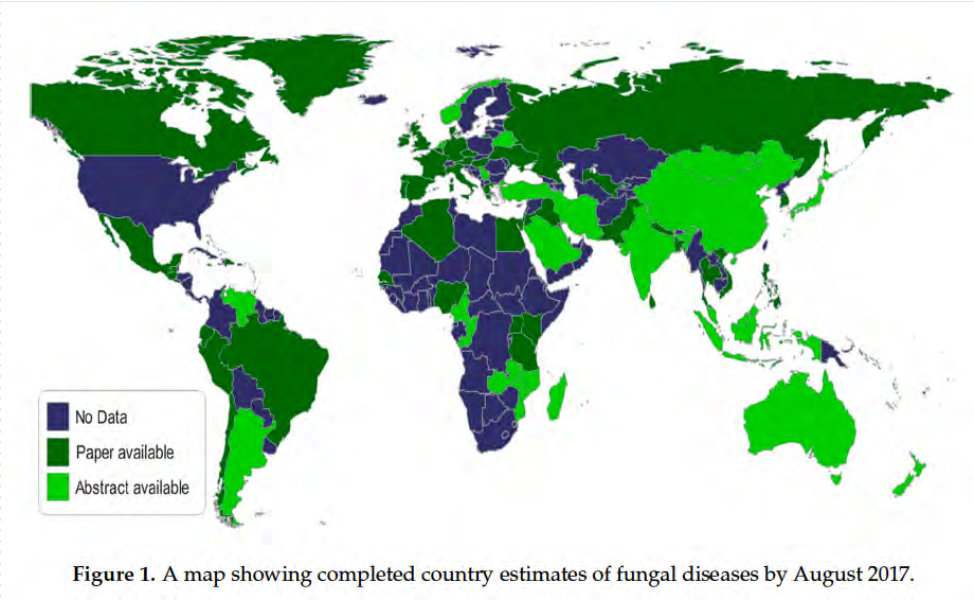
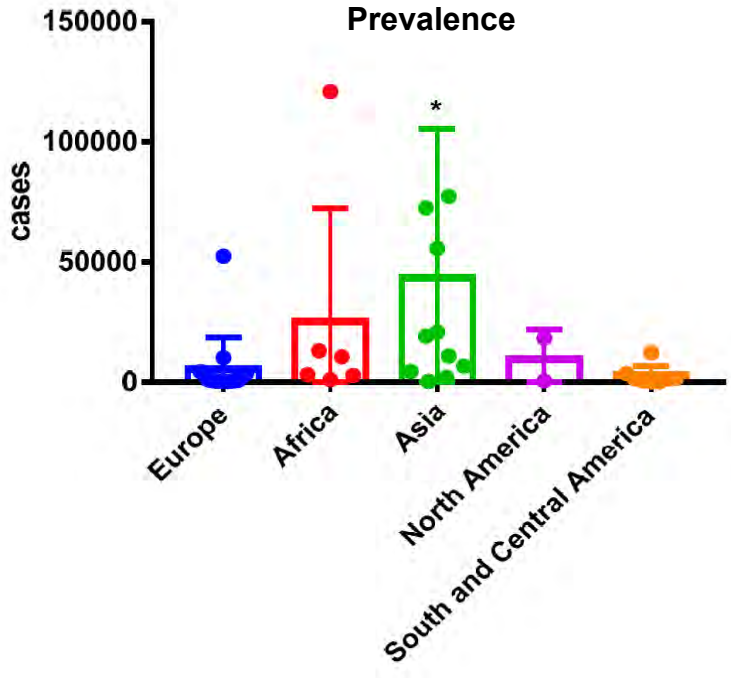


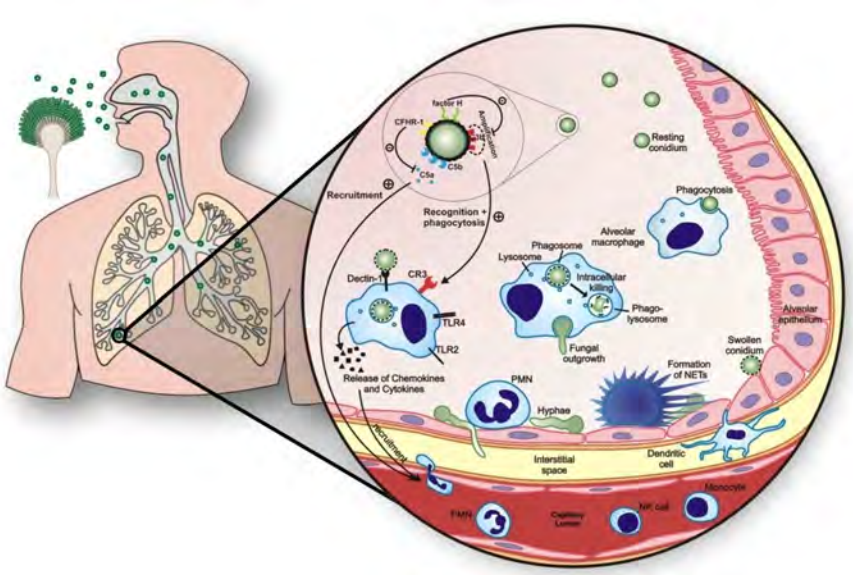
Figure 1. A map showing completed country estimates of fungal diseases by August 2017.



Bongomin F, J Fungi 2017, 3:57

Aspergillosis in human

- About 30 species pathogenic for humans
- *Aspergillus fumigatus* (AF) responsible for 90% of cases, then *A. flavus* and *A. niger*
- Small spores (2-5µm) ; rapid growth at 37C°in wet
- Pathogenicity factors related to *Af*, factors related to the host



Pitt JI et al, Regnum vegetabile 1993, 128:13

Aspergillosis in human

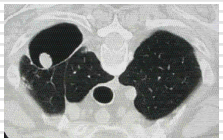
Table 2. Mycological findings in CPA case series

Study	Country	Year	Number of CPA cases	Number of isolates	*A. fumigatus* (proportion among positive cultures)	Other *Aspergillus* species
Agarwal *et al.*[18]	India	2013	31	13	13 (1.00)	
Cadranel *et al.*[12]	France	2012	41	41[b]	41 (1.00)	
Camara *et al.*[19]	France	2015	44	31	27 (0.87)	*A. niger* (1), *A. flavus* (1), more than 1 species (2)
Camuset *et al.*[20]	France	2007	24	21	20 (0.95)	*A. flavus* (1)
Chan *et al.*[21]	China	2016	29	25	17 (0.68)	*A. flavus* (2), *Aspergillus* spp. (4), more than 1 species (2)
Chawla *et al.*[10]	India	2013	22	22[b]	9 (0.41)	*A. flavus* (6), *A. niger* (1), *A. terreus* (1) and *A. versicolor* (1)
Cucchetto *et al.*[22]	Italy	2015	21	14	12 (0.86)	*A. niger* (2)
Hogan *et al.*[13]	UK	2011	42	7	7 (1.00)	
Felton *et al.*[14]	UK	2010	79	22	20 (0.91)	*A. flavus* (1), *A. nidulans* complex (1)
Hedayati *et al.*[11]	Iran	2015	33	16	10 (0.62)	NS
Kohno *et al.*[23]	Japan	2010	84	42	30 (0.71)	*A. niger* (4), *A. terreus* (1), undetermined species (7)
Benjelloun *et al.*[24]	Morocco	2015	81	9	9 (1.00)	
Lowes *et al.*[15]	UK	2017	392	48	43 (0.90)	*A. niger* complex (1), *A. terreus* (1), *A. nidulans* (1), *A. glaucus* (1), unspeciated isolate (1)
Ohara *et al.*[25]	Japan	2016	30	33[c]	19 (0.58)	*A. niger* (8), *A. flavus* (1), *A. terreus* (1), other *Aspergillus* species (4)
Shin *et al.*[26]	Republic of Korea	2014	168	19	NS	NS
Ohba *et al.*[27]	Japan	2012	42	75[c]	51 (0.48)	*A. niger* (56), *A. flavus* (12), unidentified (29)
Saito *et al.*[28]	Japan	2012	77	26	8 (0.31)	*A. flavus* (3), *A. niger* (1), undetermined (14)
Sambatakou *et al.*[29]	Greece	2006	36	36[b]	27 (0.75)	*A. niger* (1), *A. candidus* and *A. terreus* (1), *A. flavus* (1)
Koyama *et al.*[30]	Republic of Korea	2014	39	10	7 (0.7)	*A. niger* (3)
Shin *et al.*[31]	Republic of Korea	2016	55	30	NS	NS
Urabe *et al.*[32]	Japan	2017	30	6	NS	NS

Godet C, *J Antimicrob Chemoth* 2018, 73:280

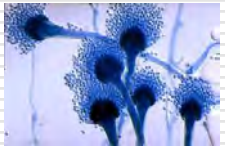
Chronic pulmonary aspergillosis diagnosis

Clinical context +



Radiological domain, by CT scan

and



Mycological domain, direct examination

or

Serological domain, IgG against *Af*

and

Exclude other diagnosis

Denning D, Eur Respir Dis 2016, 47:45

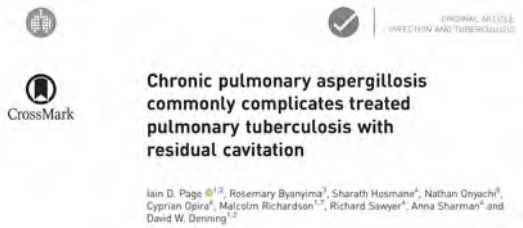
CPA risk factors – France 2018

Cas incidents APC	n=2 022	
Prévalence des pathologies pulmonaires associées, N (%)	1 an avant	5 ans avant
BPCO	796 (39.4)	888 (43.9)
Emphysème	372 (18.4)	449 (22.2)
DDB	294 (14.5)	354 (17.5)
Cancer bronchique	218 (10.8)	254 (12.6)
TB	38 (1.9)	59 (2.9)
Séquelles TB	86 (4.3)	104 (5.1)
NTM	51 (2.5)	59 (2.9)
Sarcoïdose	20 (1.0)	27 (1.3)
Fibrose	90 (4.5)	120 (5.9)

Cas incidents APC		n=2 022	
Prévalence des pathologies pulmonaires associées, N (%)		1 an avant	5 ans avant
Facteur favorisant	Pneumothorax	121 (6.0)	151 (7.5)
	Chirurgie thoracique	172 (8.5)	221 (10.9)
	Radiothérapie	33 (1.6)	57 (2.8)
Facteurs associés	Insuffisance respiratoire chronique	967 (47.8)	1044 (51.6)
	Diabète	287 (14.2)	316 (15.6)
	Malnutrition	795 (39.3)	894 (44.2)

± corticosteroids exposure, oral/inhaled

Maitre T, Journée du GREPI 2019


Chronic pulmonary aspergillosis commonly complicates treated pulmonary tuberculosis with residual cavitation

CPA in tuberculosis

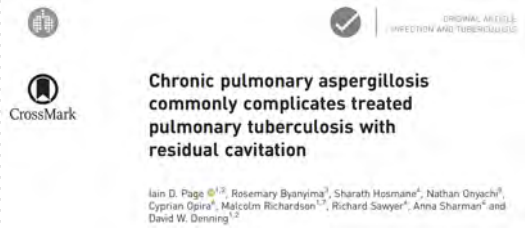
Uganda, 2-yr prospective cohort

284 re-survey on 398 treated TB; 50% HIV+

TABLE 4 Frequency of chronic pulmonary aspergillosis (CPA)

	All patients	HIV-positive	HIV-negative	p-value
Subjects	285	135	150	
CCPA	10 (3.5 (1.8–6.1))	2 (1.5 (0.3–4.7))	8 (5.3 (2.6–9.8))	0.108
CFPA	3 (1.1 (0.3–2.8))	1 (0.7 (0.1–3.4))	2 (1.3 (0.3–4.2))	1
Simple aspergilloma	1 (0.4 (0–1.6))	1 (0.7 (0.1–3.4))	0 (0 (0–1.7))	0.474
All definite CPA	14 (4.9 (2.8–7.9))	4 (3.0 (1–6.9))	10 (6.7 (3.5–11.5))	0.177
Seronegative fungal ball	2 (0.7 (0.1–2.2))	1 (0.7 (0.1–3.4))	1 (0.7 (0.1–3.1))	1
Probable CPA in non-CT group	2 (0.7 (0.1–2.2))	2 (1.5 (0.3–4.7))	0 (0 (0–1.7))	0.223
All definite and probable CPA	18 (6.3 (3.9–9.6))	7 (5.2 (2.3–9.9))	11 (7.3 (4–12.3))	0.478

Page I, Eur Respir J 2019, 53



Chronic pulmonary aspergillosis commonly complicates treated pulmonary tuberculosis with residual cavitation

Iain D. Page[1,2], Rosemary Byanyima[3], Sharath Hosmane[4], Nathan Onyachi[3], Cyprian Opira[3], Malcolm Richardson[1,2], Richard Sawyer[4], Anna Sharman[4] and David W. Denning[1,2]

CPA in tuberculosis

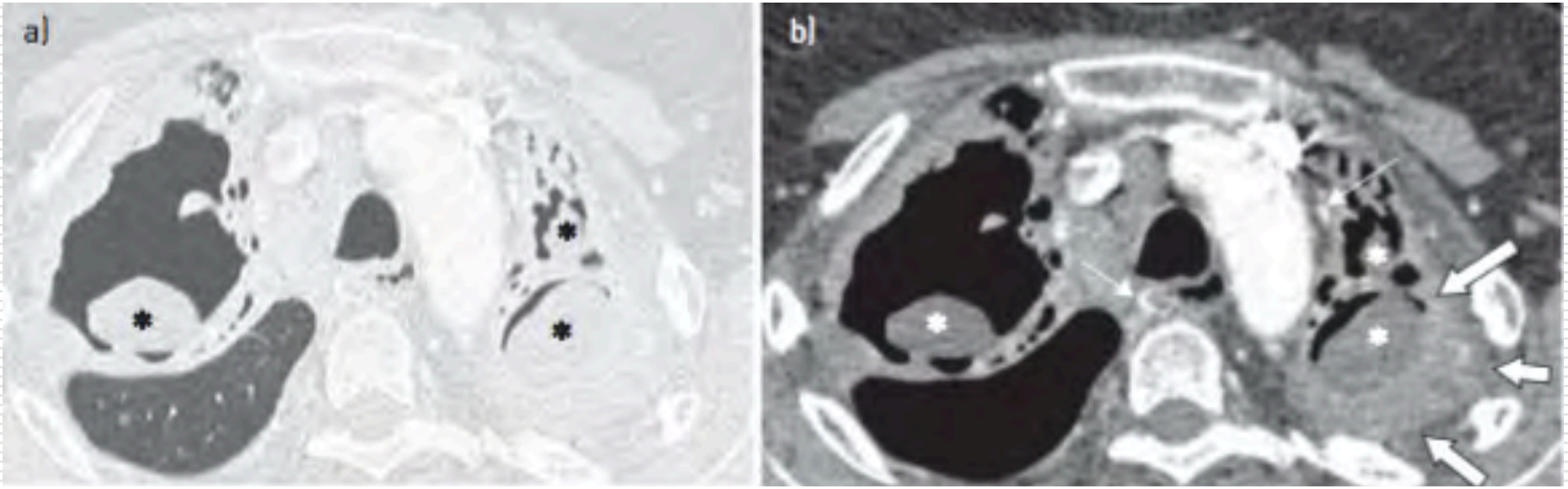
Uganda, 2-yr prospective cohort
284 re-survey on 398 treated TB; 50% HIV+

Author-defined CPA was present in 14 (4.9%, 95% CI 2.8–7.9%) resurvey patients. CPA was significantly more common in those with chest radiography cavitation (26% *versus* 0.8%; p<0.001), but possibly less frequent in HIV co-infected patients (3% *versus* 6.7%; p=0.177). The annual rate of new CPA development between surveys was 6.5% in those with chest radiography cavitation and 0.2% in those without (p<0.001). Absence of cavitation and pleural thickening on chest radiography had 100% negative predictive value for CPA. The combination of raised *Aspergillus*-specific IgG, chronic cough or haemoptysis and chest radiography cavitation had 85.7% sensitivity and 99.6% specificity for CPA diagnosis.

Page I, Eur Respir J 2019, 53

CPA diagnosis, radiological domain

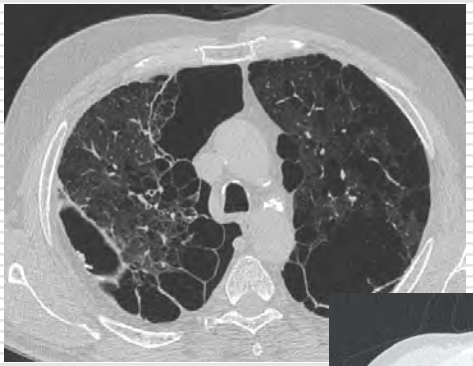
…related to aspergillus infection



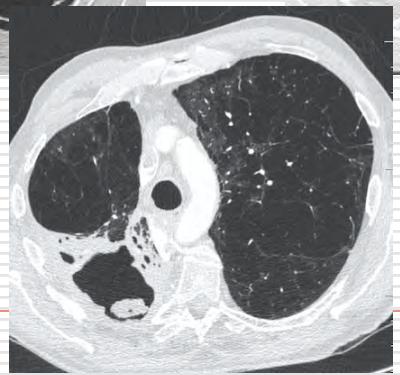
Denning D, Eur Respir Dis 2016, 47:45

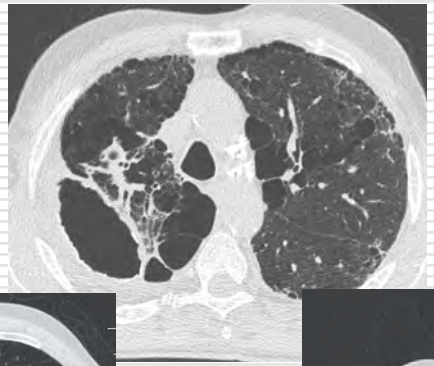
CPA diagnosis, radiological domain

…related to aspergillus infection

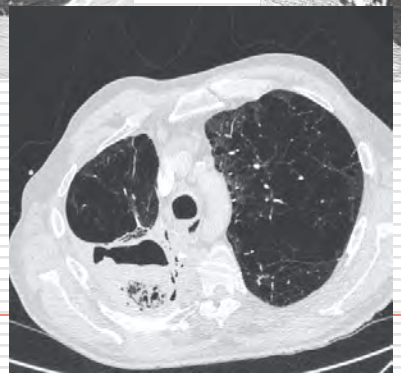


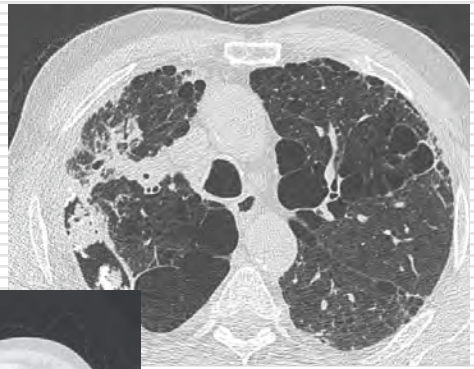
2010





2016



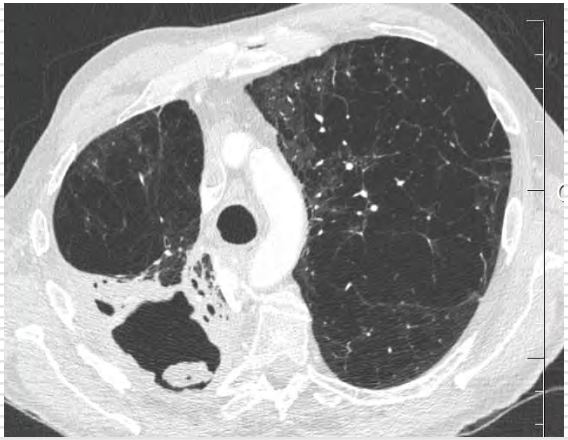


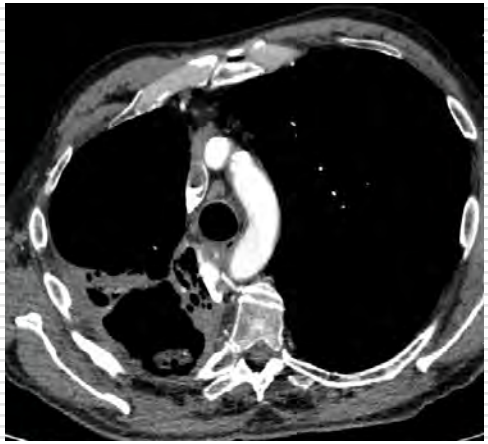
2017

Franois Laurent, by courtesy

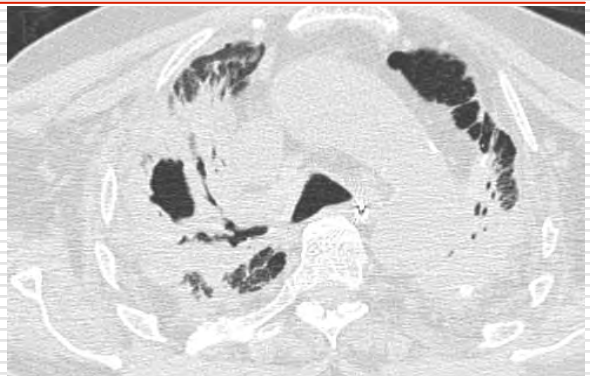
CPA diagnosis, radiological domain

…related to uderlying disease

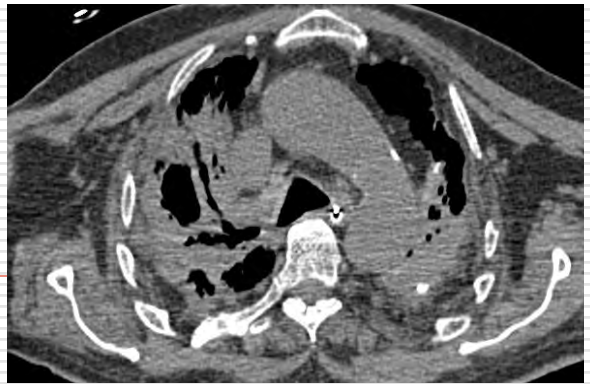




Chronic obstructive pulmonary disease - COPD



Sarcoidosis



Denning D, Eur Respir Dis 2016, 47:45

Chronic pulmonary aspergillosis

TABLE 3 Diagnostic criteria for different management of chronic pulmonary aspergillosis (CPA)

Term	Definition
Simple aspergilloma	Single pulmonary cavity containing a fungal ball, with serological or microbiological evidence implicating *Aspergillus* spp. in a non-immunocompromised patient with minor or no symptoms and no radiological progression over at least 3 months of observation.
CCPA	One or more pulmonary cavities (with either a thin or thick wall) possibly containing one or more aspergillomas or irregular intraluminal material, with serological or microbiological evidence implicating *Aspergillus* spp. with significant pulmonary and/or systemic symptoms and overt radiological progression (new cavities, increasing pericavitary infiltrates or increasing fibrosis) over at least 3 months of observation.
CFPA	Severe fibrotic destruction of at least two lobes of lung complicating CCPA leading to a major loss of lung function. Severe fibrotic destruction of one lobe with a cavity is simply referred to as CCPA affecting that lobe. Usually the fibrosis is manifest as consolidation, but large cavities with surrounding fibrosis may be seen.
***Aspergillus* nodule**	One or more nodules which may or may not cavitate are an unusual form of CPA. They may mimic tuberculoma, carcinoma of the lung, coccidioidomycosis and other diagnoses and can only be definitively diagnosed on histology. Tissue invasion is not demonstrated, although necrosis is frequent.
SAIA	Invasive aspergillosis, usually in mildly immunocompromised patients, occurring over 1–3 months, with variable radiological features including cavitation, nodules, progressive consolidation with "abscess formation". Biopsy shows hyphae in invading lung tissue and microbiological investigations reflect those in invasive aspergillosis, notably positive *Aspergillus* galactomannan antigen in blood (or respiratory fluids).

Denning D, Eur Respir J 2016, ...

CPA diagnosis, mycological domain

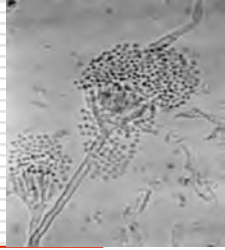
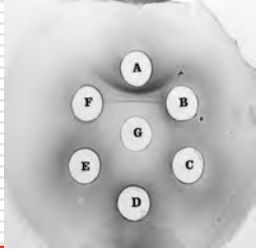


TABLE 4 Key tests on respiratory samples for patients with cavitary or nodular pulmonary infiltrate in non-immunocompromised patients

Test	Strength of recommendation	Quality of evidence
Direct microscopy for hyphae[#]	A	II
Fungal culture (sputum or BAL)[¶]	A	III
Histology	A	II
Fungal culture (transthoracic aspiration)	B	II
Aspergillus PCR (respiratory secretion)[+]	C	II
Bacterial culture (sputum or BAL)	C	IIt



CPA diagnosis, serological domain

TABLE 6 Antibody diagnosis of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE
Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients	Diagnosis or exclusion of CPA	*Aspergillus* IgG antibody	A	II
		Aspergillus precipitins	A	II
		Aspergillus IgM antibody	D	III
		Aspergillus IgA antibody	D	III
Intervention in context of asthma, ABPA or CF patients		*Aspergillus* IgE antibody	B	II

Urabe N, J Clin Microbiol 2017; 55:1736

CPA prognosis

ORIGINAL ARTICLE
RESPIRATORY INFECTIONS

Predictors of mortality in chronic pulmonary aspergillosis

David Lowes[1,3], Khaled Al-Shair[1,3], Pippa J. Newton[1], Julie Morris[2], Chris Harris[1], Riina Rautemaa-Richardson[1] and David W. Denning[1,2]

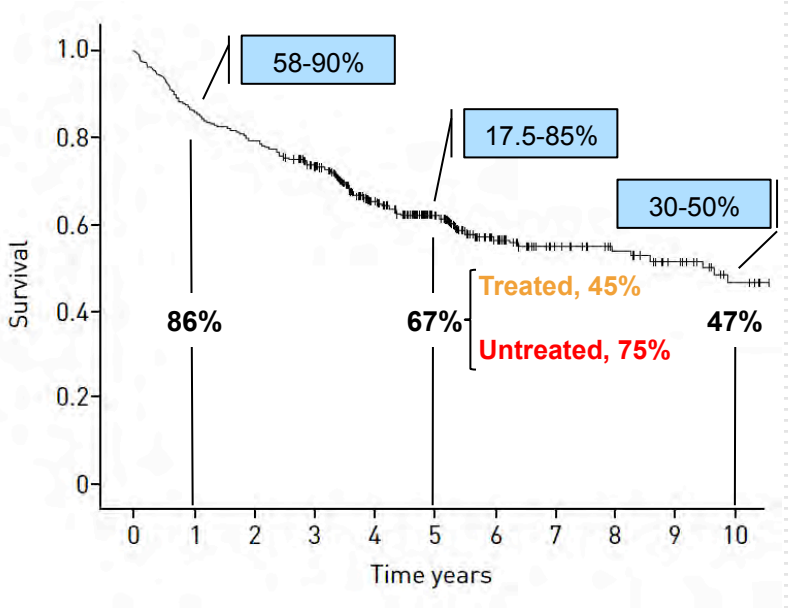
Affiliations: [1]The National Aspergillosis Centre, University Hospital of South Manchester, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [2]Dept of Medical Statistics, University Hospital of South Manchester, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [3]Both authors contributed equally.

Correspondence: David Denning, The National Aspergillosis Centre, University Hospital of South Manchester, Southmoor Road, Manchester, M23 9LT, UK. E-mail: ddenning@manchester.ac.uk

Underlying disease

TB	76 (21.0)
NTM	37 (10.2)
COPD	145 (40.1)
Asthma	73 (20.2)
ABPA	44 (12.2)
Pneumonia	79 (21.8)
Pneumothorax	52 (14.4)
Bronchiectasis	55 (15.2)
Sarcoidosis	22 (6.1)
Inflammatory arthritis	34 (9.4)
Thoracic surgery#	56 (15.4)
Lung cancer survivor	22 (5.7)
Other	25 (6.9)

CPA retrospective cohort 1992-2012 (n=387)



Lowes D, Eur Respir J 2017, 49:1

Cas clinique

Vous décidez de débuter un traitement par itraconazole

1. La dose initiale est de 200 mgx2/j
2. Il faut réaliser un dosage de la résiduelle vers le dixième jour
3. Il faut surveiller le bilan hépatique
4. La durée de traitement est d'environ 6 mois
5. Il y a de nombreuses interactions médicamenteuses

Cas clinique

Vous décidez de débuter un traitement par itraconazole

1. La dose initiale est de 200 mgx2/j

   dans notre expérience la majorité des malades reçoivent en général 200 ou 300 mg/j; possibilité de donner en 1 seule prise au milieu du repas

2. Il faut réaliser un dosage de la résiduelle vers le dixième jour
3. Il faut surveiller le bilan hépatique
4. La durée de traitement est d'environ 6 mois
5. Il y a de nombreuses interactions médicamenteuses

mycoses
Original article

Itraconazole in chronic cavitary pulmonary aspergillosis: a randomised controlled trial and systematic review of literature

Ritesh Agarwal,[1] Gella Vishwanath,[1] Ashutosh N. Aggarwal,[1] Mandeep Garg,[2] Dheeraj Gupta[1] and Arunaloke Chakrabarti[3]

[1]Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Department of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Chandigarh, India and [3]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Itraconazole treatment

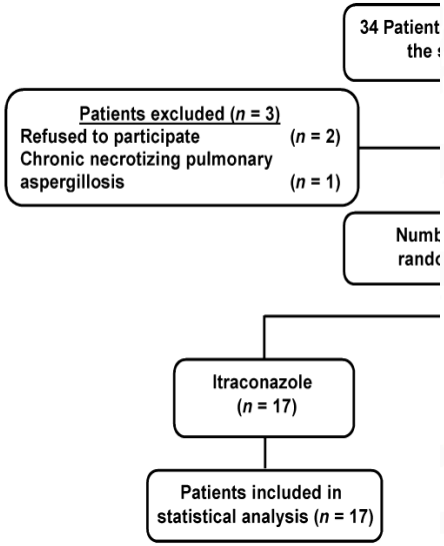


Table 2 Clinical outcomes of patients in both the groups after 6 months.

	Itraconazole (n = 17)	Control (n = 14)	P value
Overall response			
Improved	13 (76.5)	5 (35.7)	0.02
Failed	4 (33.5)	9 (64.3)	
Clinical response			
Improved	6 (35.2)	1 (7.1)	0.016
Stable	7 (41.2)	4 (28.6)	
Worsened	4 (23.6)	9 (64.3)	
Radiological response			
Present	4 (23.6)	0	0.01
Stable	9 (52.8)	5 (35.7)	
Progressive	4 (23.6)	9 (64.3)	

Agarwal R, Mycosis 2013, 56:559

Systemic antifungal treatments

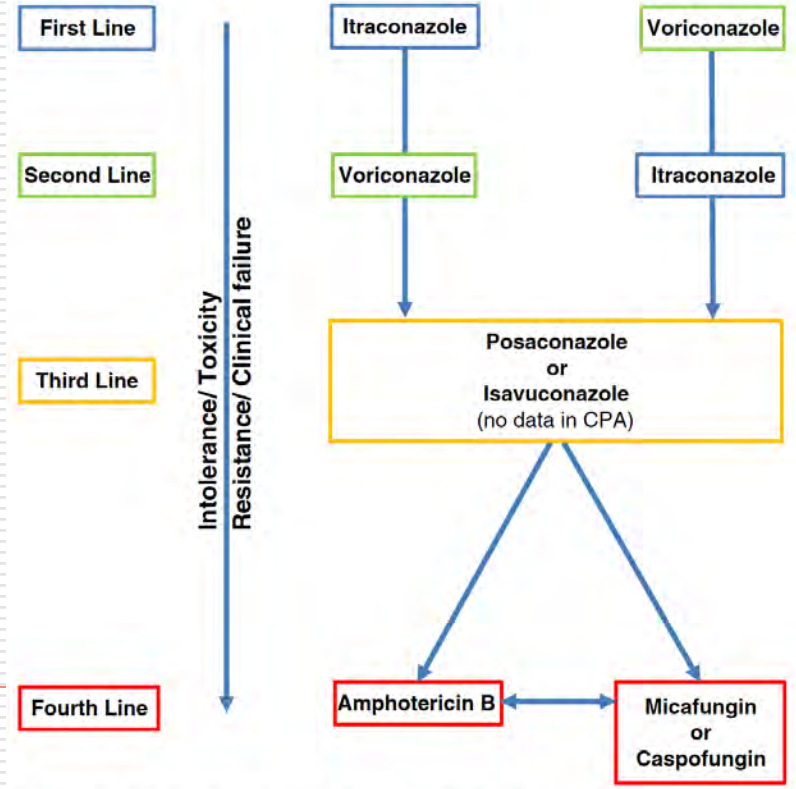
Table 1. Antifungal treatment of chronic pulmonary aspergillosis

Treatment algorithm[a]	Antifungal drug	Route	Dosage	Duration	Recommendation				Commentary
					ERS/ESCMID/ ECMM guideline[b]		IDSA guideline[b]		
					SoR	QoE	SoR	QoE	
First and second line	Itraconazole	p.o. (capsule, suspension)	200 mg b.i.d.	≥6 months	A	II	Strong	High	Adjust dosage with TDM
	Voriconazole	p.o. (tablets, suspension), i.v.	150–200 mg b.i.d.	≥6 months	A	II	Strong	High	Adjust dosage with TDM
Third line	Posaconazole	p.o. (suspension, tablet), i.v.	400 mg b.i.d. (suspension; 200 mg = 5 mL) 300 mg q.d. (tablet)	≥6 months (usually limited by high costs)	B	II	Strong, but third-line	Moderate	To enhance absorbtion, suspension should be taken together with a meal
	Isavuconazole	p.o., i.v.	Loading dose: 200 mg t.i.d. day 1 + 2; then 200 mg q.d. maintenance	≥6 months	–	–	–	–	*No data on efficacy and treatment duration so far
Fourth line	Amphotericin B – AmB deoxycholate – Liposomal-AmB	i.v.	0.7–1.0 mg/kg/day 3 mg/kg/day	3 weeks[c]	 C B	 III IIa	Weak	Low	Prefer liposomal-AmB (less toxic)
	Caspofungin	i.v.	50–70 mg q.d.	2–4 weeks[d]	C	IIa	Weak	Low	Lack of data; duration unclear
	Micafungin	i.v.	150 mg q.d.	2–4 weeks	B	II	Weak	Low	Lack of data; duration unclear

*Godet C, Laurent F, Philippe B, Cadranel J, Respiration 2014; Denning D, Eur Respir Dis 2016, 47:45; Alastruey-Izquierdo A, Cadranel J et al., Respiration 2018; *Bongomain F, Mycosis 2018*

Systemic antifungal treatments

Prolonged QT (IPP, isoptine, Tahor®); ECG, holter ECG
Drug interadtions +++ (CytP450)
Anorexia, nausea (diarrhea/constipation)
Hepatitis
Neuropathy (vorico > itra > posa)
Hypocorticism
Cardiac insuficiency (itra)
Dyschromatopsia; photosensitivity; cutaneous cancer (vorico)



Denning D, Eur Respir J 2016, 47:4;
Maghrabi F, Curr Fungal Infect Rep 2017, 11:242

Etude CPAAARI

Therapeutic efficacy comparison of a six-month treatment by itraconazole and nebulised AMBISOME® versus treatment by itraconazole alone in non- or mildly- immunocompromised patients with chronic pulmonary aspergillosis: a prospective, randomised, single blind study (single aspergilloma excluded)

Newsletter n°3 – Janvier 2019

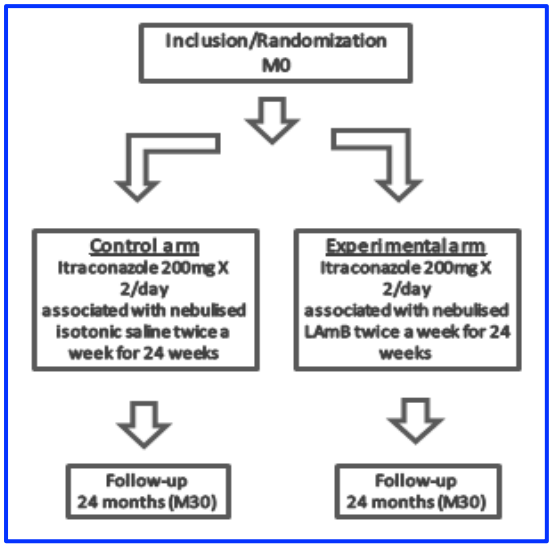
Inclusion criteria

All patients affected with **CPA "de novo" or in relapse** combining the following criteria are eligible:

1. Patient with CPA over at least 3 months of observation **documented by compatible thoracic CT-scan images**

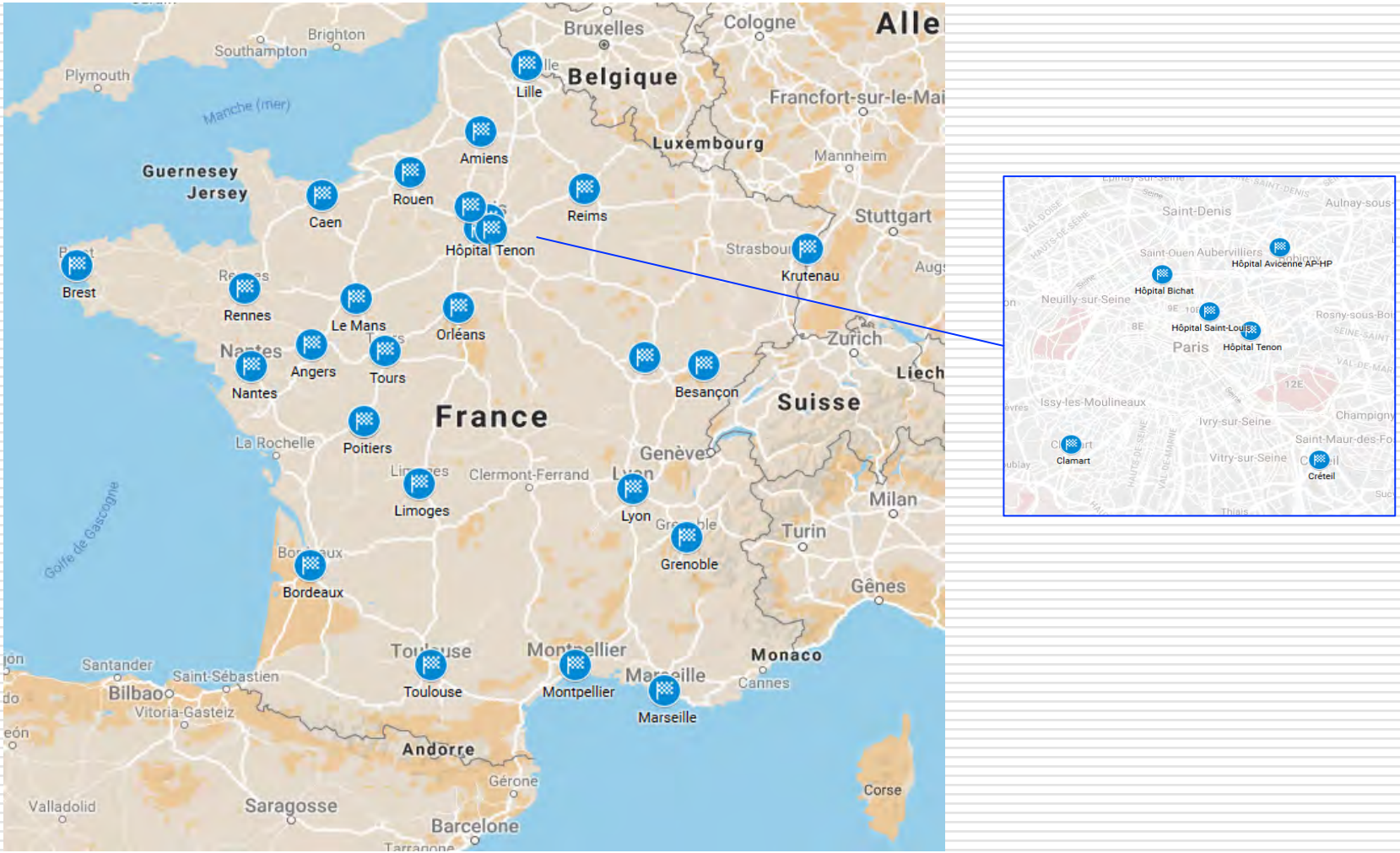
2. Associated with one other of the following criteria:
- anti-Aspergillus IgG and/or **precipitin antibodies**
- positive direct or culture examination of *Aspergillus* from bronchopulmonary samples
- revealing **aspergillar hyphae** on histological analysis

3. Free and informed consent signed



- Potential optimization of treatment duration;
- Primary outcome: stringent evaluation of therapeutic response defined as a composite criterion integrating both validated clinical parameters and **validated and standardized CT-scan objective parameters;**
- **The 24-month follow-up** after treatment discontinuation enabling to assess predictive factors of **relapse.**

Godet C, J Antimicrob Chemoth 2018, 73:280


Alle
Bruxelles
Cologne
Brighton
Southampton
Plymouth
Belgique
Lille
Francfort-sur-le-Mai
Manche (mer)
Luxembourg
Amiens
Mannheim
Guernesey
Jersey
Rouen
Caen
Reims
Stuttgart
Hôpital Tenon
Strasbour
Krutenau
Brest
Rennes
Le Mans
Orléans
Zurich
Nantes
Angers
Tours
Besançon
Liech
Suisse
France
La Rochelle
Poitiers
Genève
Clermont-Ferrand
Limoges
Lyon
Milan
Turin
Grenoble
Golfe de Gascogne
Bordeaux
Gênes
Monaco
Santander
Saint-Sébastien
Bilbao
Toulouse
Montpellier
Marseille
Cannes
Vitoria-Gasteiz
Andorre
Gérone
Corse
Valladolid
Saragosse
Barcelone
Saint-Denis
Aulnay-sous-
Saint-Ouen Aubervilliers
Hôpital Avicenne AP-HP
Hôpital Bichat
Neuilly-sur-Seine
Hôpital Saint-Louis
Hôpital Tenon
Paris
Rosny-sous-Bo
Issy-les-Moulineaux
Ivry-sur-Seine
Champigny
Saint-Maur-des-Fo
Clamart
Vitry-sur-Seine
Créteil

Cas clinique

Au deuxième mois de traitement le malade présente une hémoptysie extériorisée d'au moins 150 ml

1. Le scanner du thorax avec injection est "indispensable"
2. L'hémoptysie est de cause bronchique dans la majorité des cas
3. L'artériographie embolisation est le traitement de référence
4. Certains traitements médicaux peuvent être actifs
5. La chirurgie doit être envisagée à distance si possible

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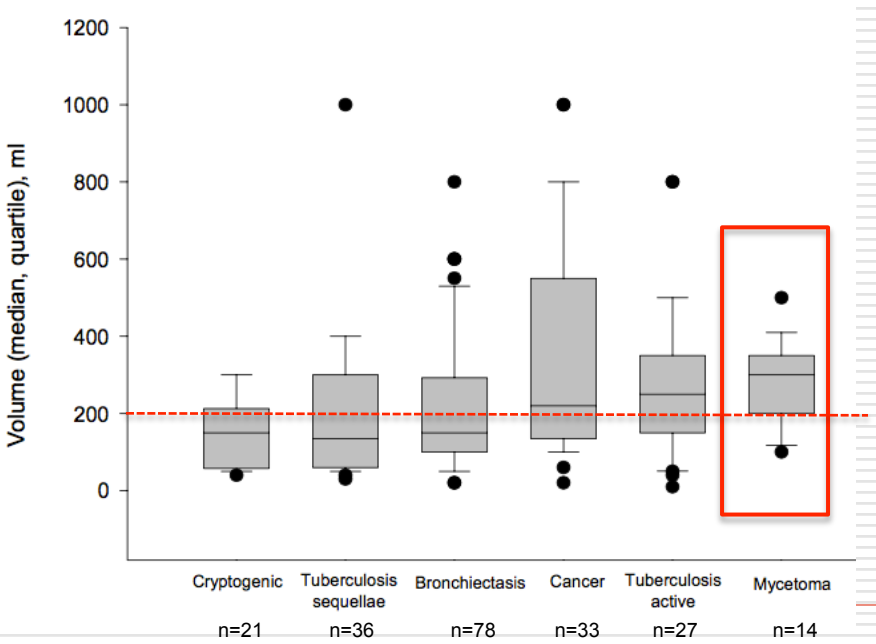
How to evaluate haemoptysis?

1999-2001, French retrospective cohort
230 consecutive patients referred for severe haemoptysis



Fartoukh M, Respiratory research 2007, 8:11

How to manage severe haemoptysis?

Massive/severe haemoptysis

≈ 200-300 ml/24h, CXR quadrants ≥2, need for mechanical ventilation?

Emergency room/ICU

Favorize coughing
Lateral decubitus position?

Oxygenation support
Volume resuscitation?

Stop aspirin, clopidrogel, anticoagulant
Broad spectrum antibiotics?

Systemic terlipressin infusion (1-2 mg qid)
Tranexamic acid infusion (500 mg tid)

Could compromise the use of BAE in the following 6 hours…

Sakr L, Respiration 2010, 80:38

How to manage severe haemoptysis?

Emergency room/ICU

Acute respiratory failure

Rigid tube intubation (airway clearance, bleeding tamponade, contralateral lung isolation)

Instillation of haemostatics

Bronchoscopic treatment

No acute respiratory failure

Admit to ICU for management

Localization of bleeding?

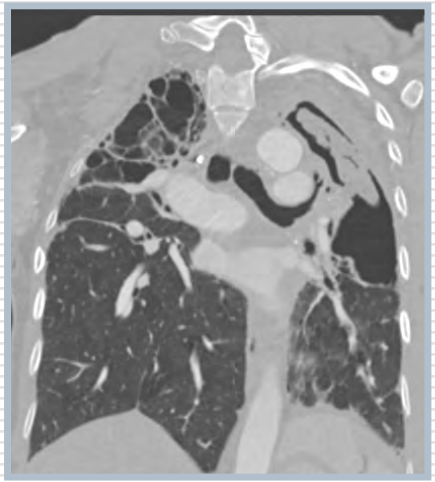
Mechanism of bleeding?

Treatment of bleeding?

Sakr L, Respiration 2010, 80:38

Major importance of injected CT-scan?

- Major systemic hypervascularisation
  - Bronchial and non-bronchial
  - Erosion of pulmonary blood vessels (arteries and veins)
- Importance of CT angiography
  - Etiological diagnosis
  - Localisation of bleeding associated with bronchoscopy
  - Mapping of vessels involved in hypervascularisation
  - Pin-pointing the mechanism
    - bronchial arterial hypervascularisation = **systemic arterial embolization 90%**
    - false arteriovenous aneuvrysm = pulmonary vaso-occlusion

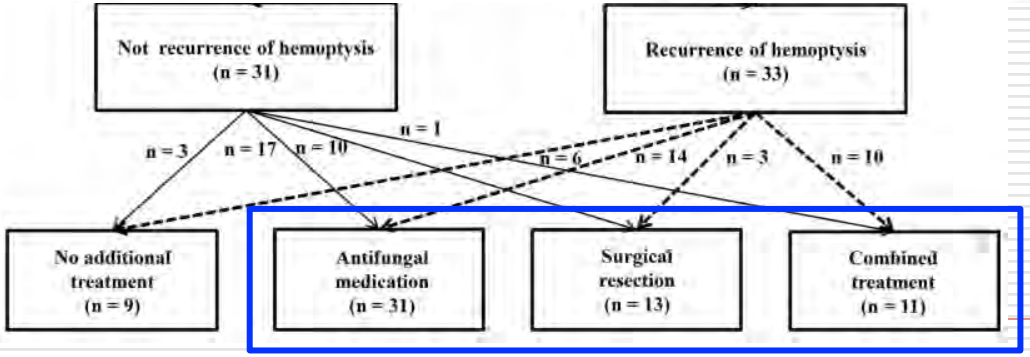


Khalil A, AJR 2007; Shin B, PLoS One 2016, 11:0168373

Endovascular treatment

Table 3. Clinical outcomes of the patients with pulmonary aspergillosis underwent bronchial arterial embolization for life-threatening hemoptysis.

		All patients (N = 64)	CPA (n = 55)	SA (n = 9)	*P* value
Outcomes of the first BAE					
	Immediate success	41 (64)	35 (64)	6 (67)	> 0.999
Additional treatments for pulmonary aspergillosis					
	No additional treatment	9 (14)	8 (15)	1 (11)	> 0.999
	Antifungal medication	31 (48)	31 (56)	0	0.002
	Surgical resection	24 (38)	16 (29)	8 (89)	0.001
Mortality		15 (23)	15 (27)	0	0.101



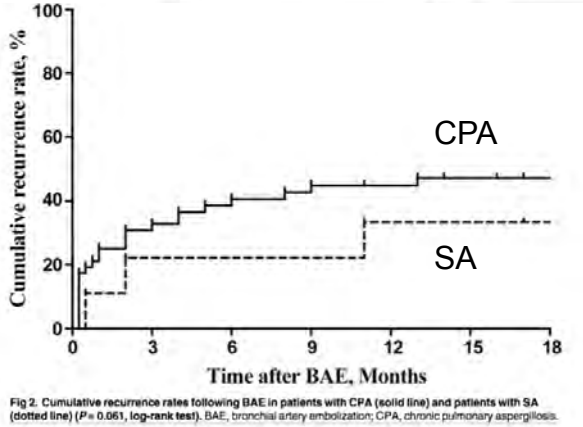


Fig 2. Cumulative recurrence rates following BAE in patients with CPA (solid line) and patients with SA (dotted line) ($P = 0.061$, log-rank test). BAE, bronchial artery embolization; CPA, chronic pulmonary aspergillosis.

Shin B, PLoS One 2016, 11:0168373

Surgical treatment

- Avoid haemoptysis and loco-regional extension,
- Permanent cure, improve survival
- No randomised study
- TABLE 11 Indications for and types of surgery for chronic pulmonary aspergillosis

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
Single/simple aspergilloma	Cure and prevention of life-threatening haemoptysis	Lobectomy or any other segmental resection	A	II	[9, 21, 124–131]	Risk/benefit assessment required. Patients should be seen in centres with experience of aspergillosis surgery.
		VATS	B	II	[129, 132]	May require conversion to thoracotomy.
CCPA refractory to medical management (including multi-azole resistance) with antifungal treatment and/or life-threatening haemoptysis	Improved control of disease, possibly cure	Careful risk assessment, followed by lobectomy or pneumectomy	A	II	[125, 127]	Prior embolisation as a temporising procedure.
		Thoracoplasty with simultaneous cavernostomy and muscle transposition flap	C/D	III	[133, 134]	Highly experienced surgical team required.

etc.

Godet C, Philippe B, Laurent F, Cadranel J Respiration 2014, 88:162

Surgical treatment

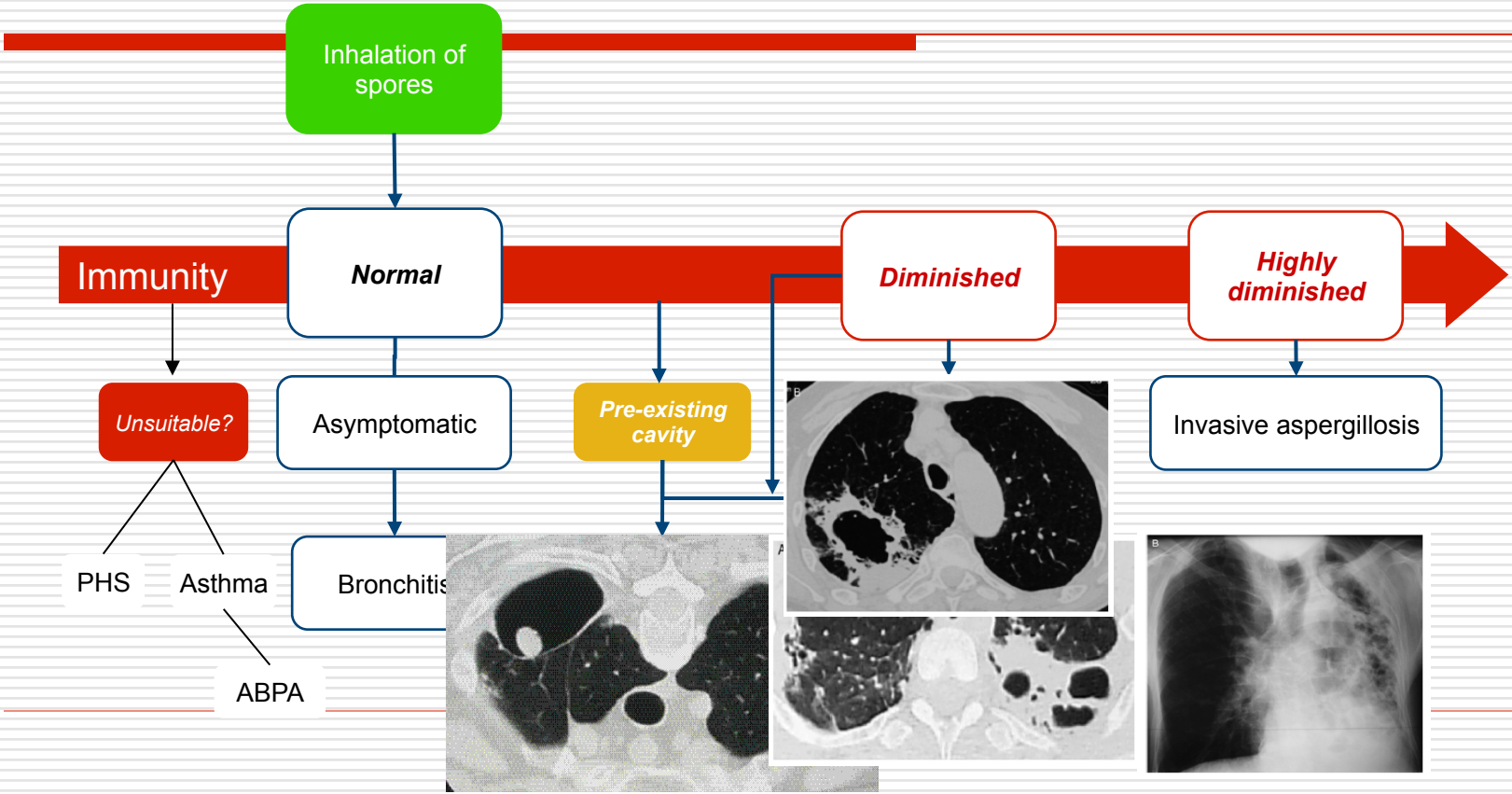
Table 4 Results of different studies concerning surgically treated cases of Aspergilloma

Author/year	Period	No. patients/No. operated	Operative mortality	Operative mortality in simple aspergilloma	Operative mortality in complex aspergilloma
Battaglini [13] 1985	1972-1983	15/15	13.3%	0	18.1%
Daly [21] 1986	1953–1984	53/53	22.6%	4.7%	34.3%
Shirakusa [11] 1989	1979–1987	24/35	0	0	0
Massard [6] 1992	1974–1991	63/63	9.5%	0	10.0%
Regnard [22] 2000	1977-1997	87/89	5.6%	0	6.2%
Akbari [9] 2005	1985-2003	60/65	3.3%	0	4.3%
Lejay [23] 2011	1998-2009	33/33	0	0	0
Chen [20] 2012	1975-2010	256/262	1.17%	0	1.9%
Current series	1996-2011	30/33	0	0	0

Farid D, J Cardiothor Surg 2013, 8:180; Sagan D, J Surg Res 2010; Lee JG, J Thorac Cardiovasc Surg 2009; Ohba H, Respir Medicine 2012

- Probablement sous estimée; diagnostic tardif
- Intérêt d'une surveillance radiologique et sérologique séquelles de tuberculose, sarcoidose, BPCO avec emphysème
- Facteurs de risque: dénutrition et corticothérapie inhalée
- Gravité potentielle des hémoptysie
- Stratégie de traitement multidisciplinaire, incluant la possibilité d'une chirurgie
- Comment choisir la bonne stratégie anti-fungique?

Chronic pulmonary aspergillosis



PanAfrican Medical Journal
Open Access
Case series

Les aspergillomes pulmonaires: à propos de 37 cas à Madagascar

Joëlson Lovaniaina Rakotoson[1,&], Notahiana Razafindramaro[1], Jocelyn Robert Rakotomizao[1], Hanta Marie Danielle Vololontiana[1], Radonirina Lazasoa Andrianasolo[1], Kiady Ravahatra[1], Michel Tiaray[1], Jobeline Rajaoarifetra[1], Hendriniaina Rakotoharivelo[1], Ange Christophe Félix Andrianarisoa[1]

CPA in Madagascar

Tableau 1: Les facteurs de risque présents chez 37 patients pris en charge pour aspergillose pulmonaire au Centre Hospitalier Universitaire d'Antananarivo, Madagascar

Facteurs de risque		Effectif	Pourcentage
Tuberculose		33	89,1
	TPM+	31	83,7
	TPM-	2	5,4
Autres atteintes pulmonaires		**9**	**24,3**
	Abcès	2	5,4
	BPCO	6	16,2
	DDB	1	2,7
Alcoolo-tabagisme		**18**	**48,6**
	Alcool	7	18,9
	Tabac	3	8,1
	Alcool et tabac	8	21,6
Immunodépression		**2**	**5,4**
	VIH	1	2,7
	Cancer	1	2,7
Exposition aux polluants		**12**	**32,4**
	professionnels	7	18,9
	domestiques	5	13,5

TPM+ : tuberculose pulmonaire à bacilloscopie positive, TPM- : tuberculose pulmonaire à bacilloscopie négative, BPCO : bronchopneumopathie chronique obstructive, DDB : dilatation des bronches

+ dénutrition, diabète
+ corticoides oraux, inhalés(?)

Systemic antifungal treatments

- Retrospective cohorts
  - small numbers of patients
  - aspergillus diseases poorly defined
  - itraconazole alone or in combination with Ampho. B; duration of treatment poorly defined
  - endpoints poorly defined
- Prospective studies
  - few studies, low statistical power
  - endpoints poorly defined
  - only one controlled study

Godet C, Laurent F, Philippe B, Cadranel J, Respiration 2014; Denning D, Eur Respir Dis 2016, 47:45; Alastruey-Izquierdo A, Cadranel J et al., Respiration 2018

CPA diagnosis, radiological domain

TABLE 7 Radiological diagnoses and follow-up of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
Any features of cavitation, fungal ball, pleural thickening and/or upper lobe fibrosis	Raise suspicion of CPA for physicians	Radiological report must mention possible CPA	A	II	[10, 11, 24, 25, 40, 55, 56]	CPA is often missed for years and patients mismanaged; microbiological testing required for confirmation
Suspicion of CPA on chest radiograph	Diagnosis or exclusion of CPA	CT scan (contrast)	A	II	[55]	High quality CT with vessel visualisation
		PET scan	D	III	[57, 58]	Expert radiology advice
Follow-up on or off therapy		CT (low dose)	B	III	[15, 55]	General need to minimise radiation exposure, especially multiple CT scans
		Chest radiograph	B	III		
		Initial follow-up at 3 or 6 months or with change of status	A	II	[15, 59]	

SoR: strength of recommendation; QoE: quality of evidence; CT: computed tomography; PET: positron emission tomography.

Denning D, Eur Respir Dis 2016, 47:45

Clinical context – underlying lung disease

	Underlying disease (n=237)	Patients (n=126)	Literature
Tuberculosis	21 (16.7%)	**20 (15.9%)**	**31 to 81%**
Non MTB	20 (15.9%)	**18 (14.3%)**	
COPD/emphysema	42 (33.3%)	**12 (9.5%)**	**42 to 56%**
Pneumothorax (± emphysema)	21 (16.7%)	**12 (9.5%)**	**12 to 17%**
ABPA (± asthma)	18 (14.3%)	**15 (11.9%)**	**12%**
Asthma (± hypersensitivy)	13 (10.3%)	3 (2.4%)	5.6 to 12%
Sarcoidosis	9 (7.1%)	**9 (7.1%)**	**12 to 17%**
Rheumatoid arthritis	5 (4%)	4 (3.2%)	2.4%
Lung cancer survivor	13 (10.3%)	12 (9.5%)	8 to 10%
Thoracic surgery	18 (14.3%)	6 (4.8%)	-
Pneumonia	28 (22.2%)	10 (7.9%)	9.2 to 12%
Others	19 (8.2%)	5 (3.2%)	-

Adapted from Smith NL, Eur Respir J 2010

Clinical context – comorbidities and steroids

	Saraceno (1997)	**Nam** (2010)	**Camuset** (2007)	**Vertigo** (2010)
Type of aspergillosis	*CNPA (n=59)*	*CPA (n=43)*	*CNPA (n=15)* *CCPA (n=9)*	*CNPA (n=19)* *CCPA (n=22)*
Comorbidities	**64%**	**40%**	**33%**	**41%**
Alcohol	17%	-	12.5%	10%
Diabetes	7%	12%	8%	5%
Malnutrition	**64%**	**35%**	-	**BMI = 17 (13-39)**
Corticosteroids	**42%**	**-**	**50%**	**37%**
Inhaled route	-	-	-	29%
Oral route	-	19%	-	15%

Saraceno J, Chest 1997; Camuset J, Chest 2007; Nam HS, Int J Infect Dis 2010; Cadranel J, for the VERTIGO group, CPLF 2010

Surgical treatment

Table 5 Surgical risk assessment

Lower risk
Risk of *Aspergillus* empyema
Intrapulmonary cavity
Solid lesion
Smooth-walled cavity
Single lesion or small, localised collection of several interrelated lesions
Risk of space infection
Localised lesion and lobectomy or segmental resection
Chest wall normal
Risk of overall poor outcome
Good pulmonary function
Young
Well nourished
No other significant comorbidities

Farid D, J Cardiothor Surg 2013, 8:180

Surgical treatment

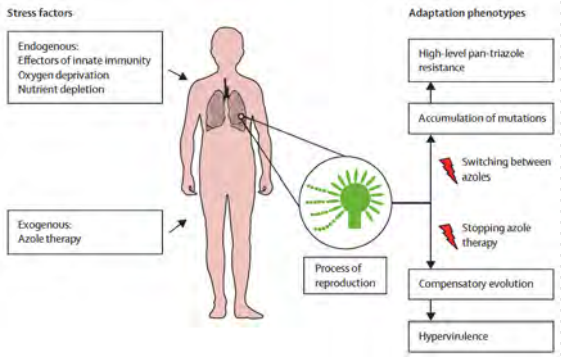
Table 5 Surgical risk assessment

Lower risk	Higher risk
Risk of *Aspergillus* empyema	**Peri-operative antifungal treatment?**
Intrapulmonary cavity	Pleural involvement including thickening
Solid lesion	Cavitary lesion with fungal ball or fluid level
Smooth-walled cavity	Irregular or bumpy cavity surface (indicating fungal growth on surface of cavity)
Single lesion or small, localised collection of several interrelated lesions	Extensive multicavity lesion
	Smear positive for Af at direct examination
	Prior radiotherapy to proposed surgical site
	Prior lobectomy or other thoracic surgery
Risk of space infection	
Localised lesion and lobectomy or segmental resection	Second lobectomy or pneumonectomy
Chest wall normal	Scoliosis or ankylosing spondylitis
	Other pleural/pulmonary disease preventing full lung mobilisation
	Immunosuppression
	Intrapleural spillage during surgery
Risk of overall poor outcome	Haemoptysis **Arterio-embolization**
Good pulmonary function	FEV1 <1.0. L/sec **Rehabilitation**
Young	Older (>70 years)
Well nourished	Thin, low BMI or reduced albumin **Renutrition**
No other significant comorbidities	Diabetes, other concurrent pulmonary infection (ie non-tuberculous mycobacterial or *Pseudomonas* infection) **Specific treatment**
	Other associated significant comorbidities **Specific treatment**

Farid D, J Cardiothor Surg 2013, 8:180

Antifungal treatments

- **Therapeutic classes**
  - Polyenes (IV, local?)
    - Amphotericin B deoxycholate
    - Liposomal amphotericin B
    - Amphotericin lipid complex
  - Echinocandins (IV)
    - Caspofungin
    - Micafungin
  - **Triazoles** (IV, oral)
    - Itraconazole
    - Voriconazole
    - Posaconazole
    - (Isavuconazole)



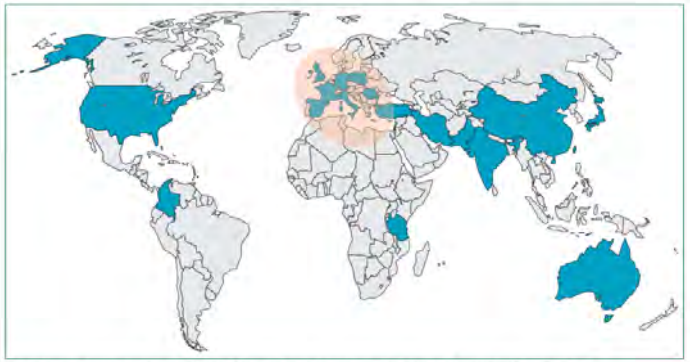
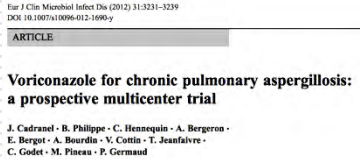


Figure 1: Countries reporting azole-resistant isolates of *Aspergillus fumigatus* with either TR$_{34}$/L98H or TR$_{46}$/Y121F/T289A modifications
Countries where mechanistic resistance is found are shown in blue. The region of highest burden of resistance is marked by the shaded oval (adapted from Verweij et al[4]).

Ullman AJ, Clin Microbiol Infect 2018, 24 supp1:e1; Verweij P, Lancet Infect Dis 2016, 16:e251; Perlin DS, Lancet Infect Dis 2017, 17:e383


Eur J Clin Microbiol Infect Dis (2012) 31:3231–3239
DOI 10.1007/s10096-012-1690-y

ARTICLE

Voriconazole for chronic pulmonary aspergillosis: a prospective multicenter trial

J. Cadranel · B. Philippe · C. Hennequin · A. Bergeron · E. Bergot · A. Bourdin · V. Cottin · T. Jeanfaivre · C. Godet · M. Pineau · P. Germaud

Systemic antifungal treatment, oral

- Prospective, non-comparative, multicentre study, **07/2005-12/2008**
- Diagnostic criteria:
  - clinical+CT+mycological+serology
    - CNPA, n=19
    - CCPA, n=22
- No pre-treated patients
  - severe haemoptysis
  - eligible for surgery
  - prior systemic treatment
- Voriconazole
  - 200 mg x 2/d, 6 months
  - >6 months and <12 months
- Endpoints
  - clinical, radiological and mycological
  - 3 months, 6 months, end of treatment
  - centralised review by panel
- Objectives
  - primary
    - CT improvement (>50%) + mycological eradication at 6 months > 30%
  - secondary
    - radiological efficiency
    - quality of life and safety
    - relapse at 6 months post EOT
    - survival

Cadranel J, Eur J Clin Microbiol Infect Dis 2012

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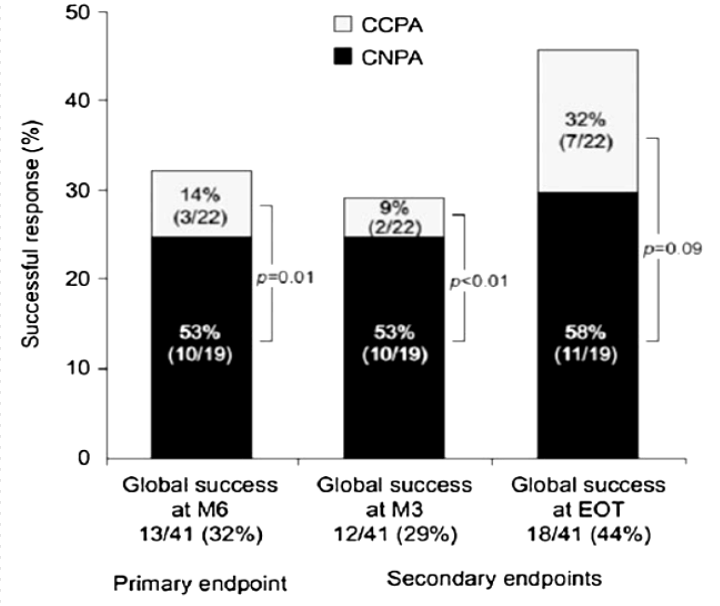
ARTICLE

Voriconazole for chronic pulmonary aspergillosis: a prospective multicenter trial

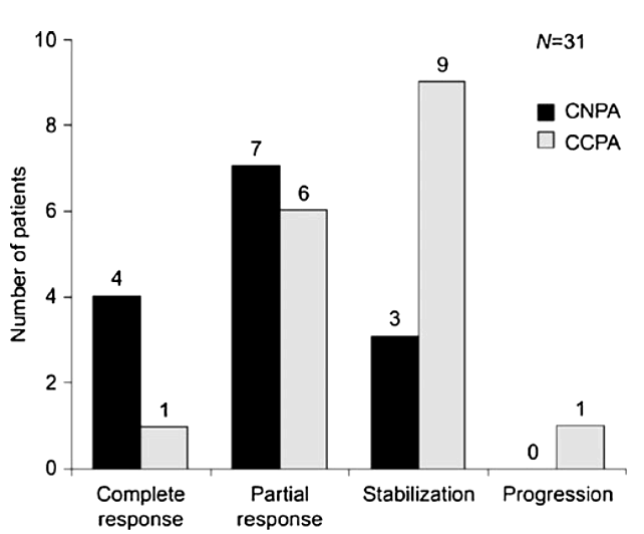
J. Cadranel · B. Philippe · C. Hennequin · A. Bergeron · E. Bergot · A. Bourdin · V. Cottin · T. Jeanfaivre · C. Godet · M. Pineau · P. Germaud

Systemic antifungal treatment, oral

Global success (treatment duration 8.3 months [1-13.5])



Radiological response



Cadranel J, Eur J Clin Microbiol Infect Dis 2012

Eur J Clin Microbiol Infect Dis (2012) 31:3231–3239
DOI 10.1007/s10096-012-1690-y
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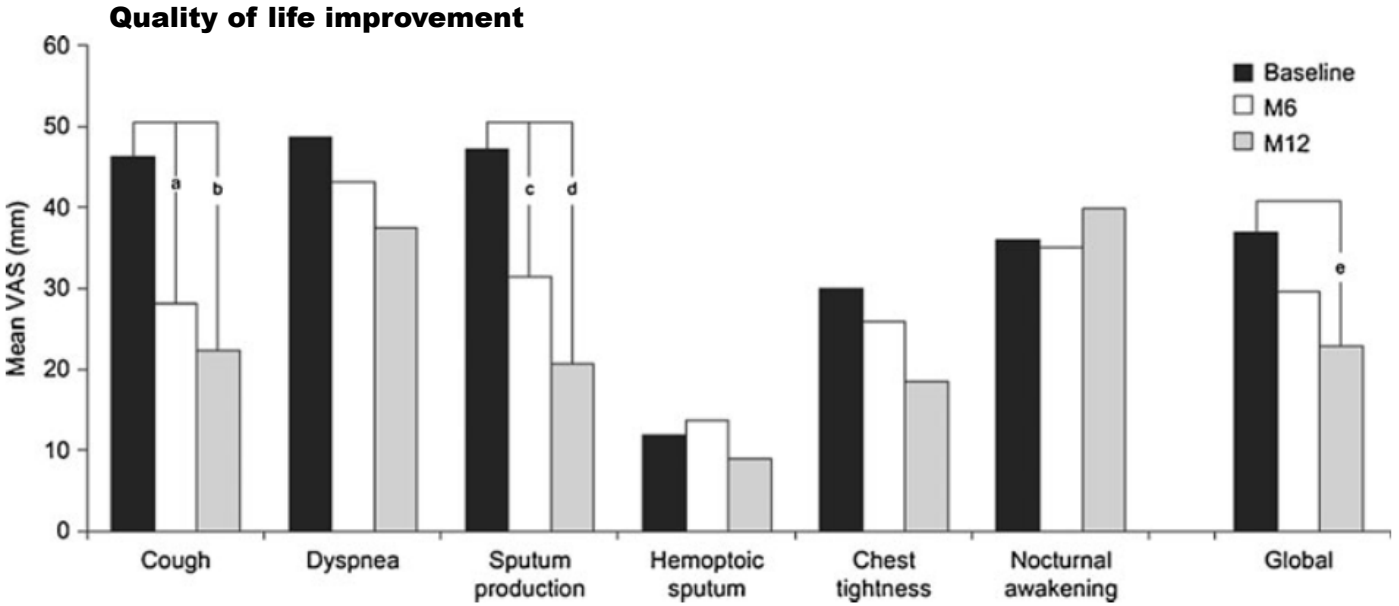
Systemic antifungal treatment, oral



Cadranel J, Eur J Clin Microbiol Infect Dis 2012

[Original Research Chest Infections]
CHEST

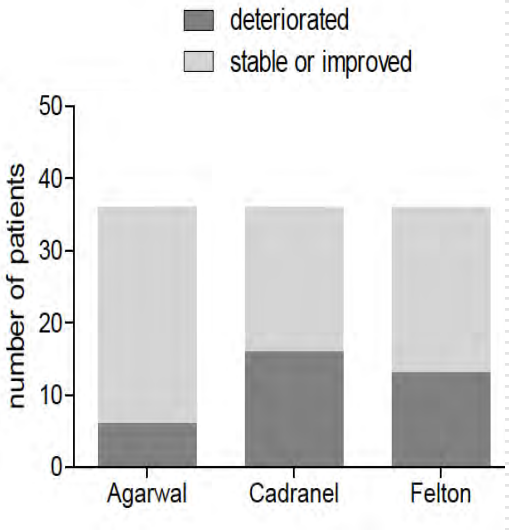
CT Imaging Assessment of Response to Treatment in Chronic Pulmonary Aspergillosis

Cendrine Godet, MD; François Laurent, MD, PhD; Anne Bergeron, MD, PhD; Pierre Ingrand, MD, PhD; Catherine Beigelman-Aubry, MD; Boubou Camara, MD; Vincent Cottin, MD, PhD; Patrick Germaud, MD; Bruno-Philippe, MD; Christophe Pison, MD, PhD; Cécile Tiper, MD; Marie France Carette, MD; Jean-Pierre Fiat, MD; Guillaume Béraud, MD, PhD; France Roblot, MD; and Jacques Cadranel, MD, PhD; for the ACHROSCAN Study Group

Evaluation of systemic antifungal treatment

e-Table 2–*Radiological criteria included in the definition of the response according to the different authors.*

Response to treatment	Cavity (size/number)	Fungus ball (size/number)	Pleural thickening	Pericavitary thickening	Pericavitary infiltrates
Improvement					
Agarwal *et al*	NE	↓	↓	NE	↓
Felton *et al*	↓	↓	↓	↓	NE
Cadranel *et al*	↓	↓	↓	NE	↓
Stability					
Agarwal *et al*	NE	–	–	NE	–
Felton *et al*	–	–	–	–	NE
Cadranel *et al*	–	–	–	NE	–
Deterioration					
Agarwal *et al*	NE	↑	↑	NE	↑
Felton *et al*	↑	↑	↑	↑	NE
Cadranel *et al*	↑	↑	↑	NE	↑



Godet C, Chest 2016, 150:139

[Original Research Chest Infections]

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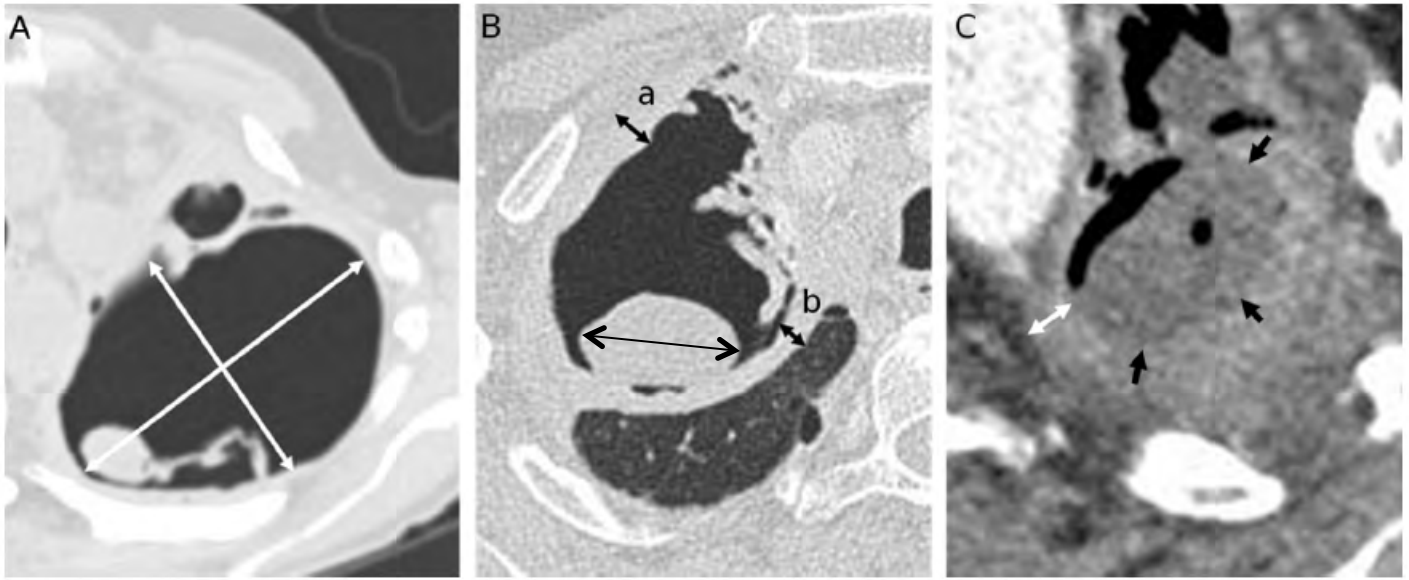
Evaluation of systemic antifungal treatment



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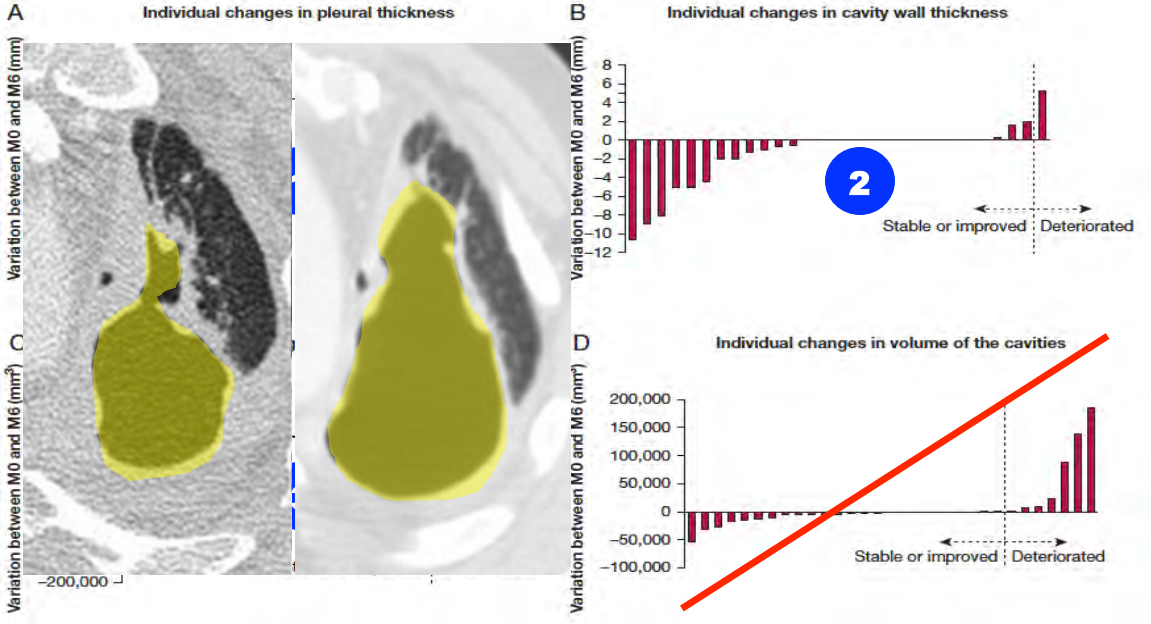
Evaluation of systemic antifungal treatment



Godet C, Chest 2016, 150:139

Therapeutic strategy

- Three main objectives
  - To limit further destruction of lung tissue
  - To prevent life-threatening haemoptysis
  - To improve quality of life

Godet C, Philippe B, Laurent F, Cadranel J Respiration 2014, 88:162

CPA diagnosis, mycological domain?

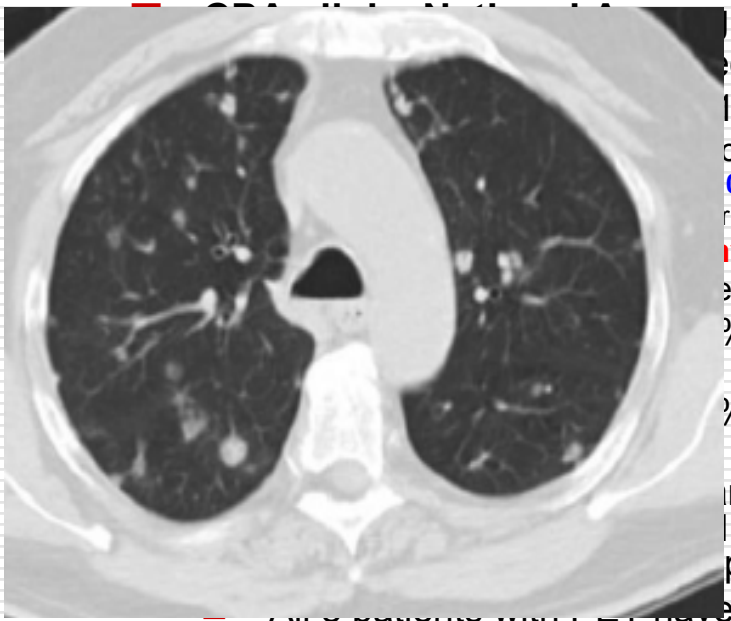
- Immunological diagnosis
  - Aspergillus galactomannan antigen in invasive aspergillosis
    - different techniques,
    - highly specific (> 90%), sensitivity 70% (interest of repeated samples); diagnostic value depends on the center
    - can be applied to LBA or products of secretion

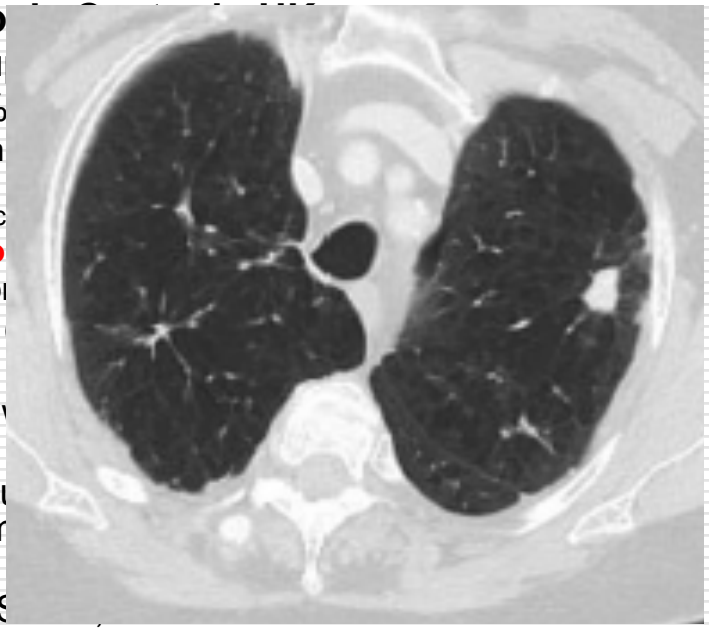
TABLE 5 Contribution of antigen to the diagnosis of chronic pulmonary aspergillosis (CPA)

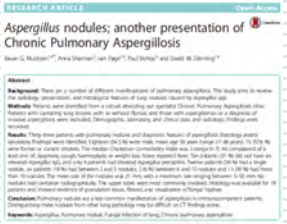
Population	Intention	Intervention	SoR	QoE
Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients	Diagnosis of exclusion of CPA	Antigen BAL	B	II
		Antigen (serum) Antigen (sputum)	C No data	II

Izumikawa K, Medical Mycology 2012, 50:811; Kono Y, Respir Med 2013, 107:1094; Shin B, J Infect 2014, 68:494

Aspergillus nodule(s)







Denning D, BMC Pulmonary Medicine 2016, 16:123

Chronic pulmonary aspergillosis care

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

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

Eur Respir J 2016, 47:45

Aspergillosis diseases in human