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Maladies Pulmonaires Rares

CPAnet
Chronic Pulmonary Aspergillosis Network

# Aspergillose chronique pulmonaire en 2019

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TENON
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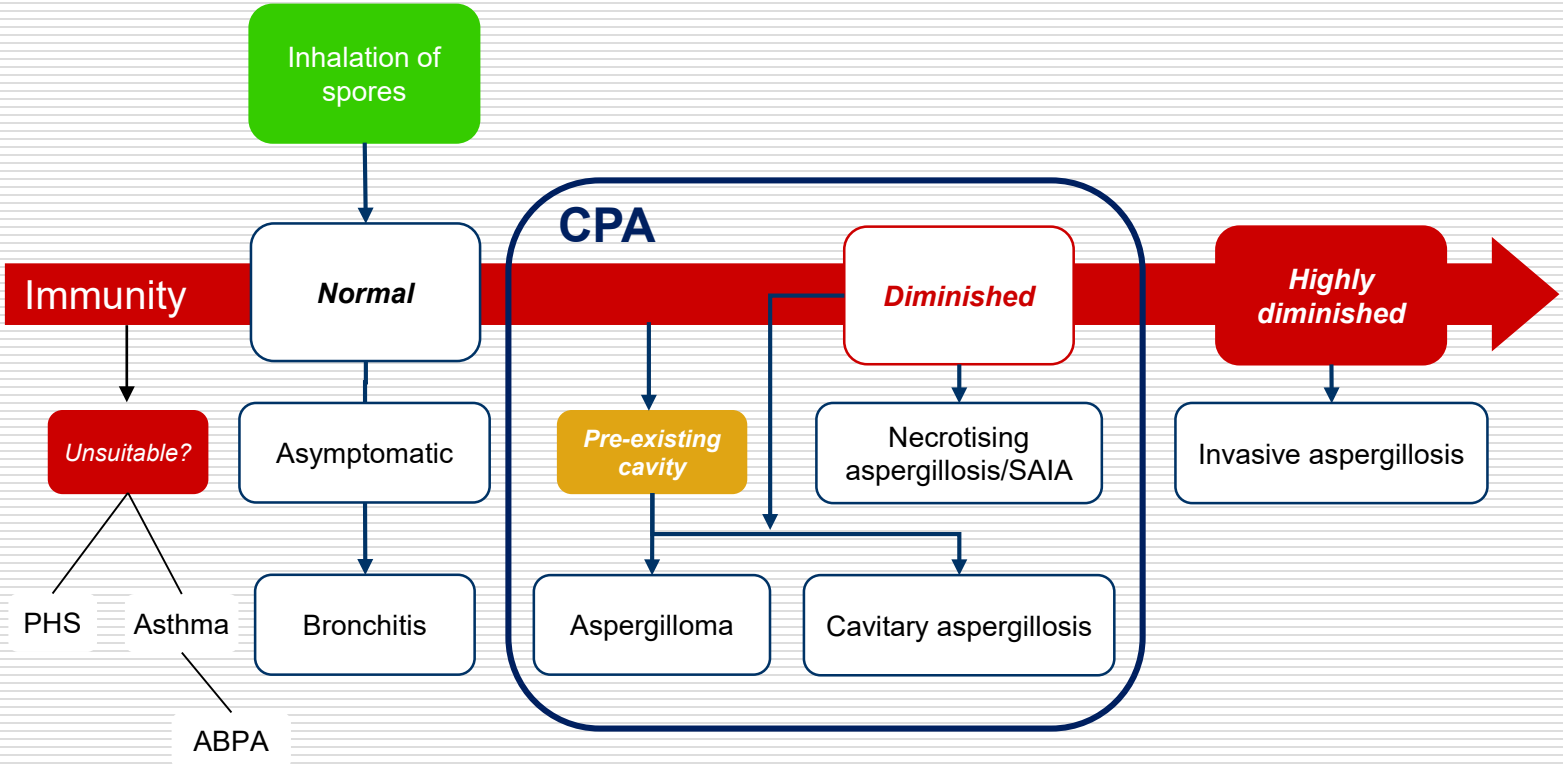
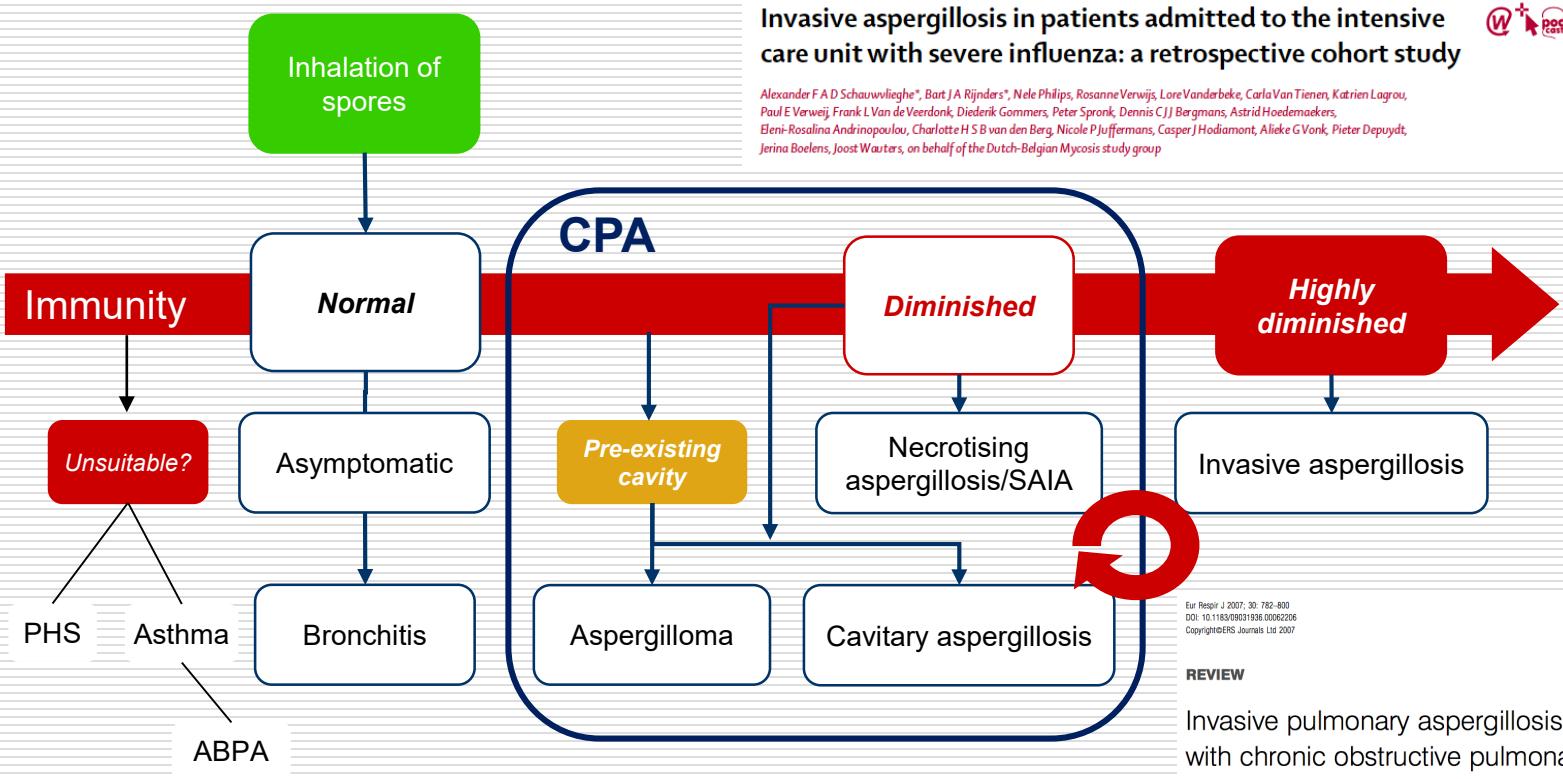
# Aspergillosis diseases in human



# Aspergillosis diseases in human




Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study

Alexander F A D Schauwvlieghe*, Bart J A Rijnders*, Nele Philips, Rosanne Verwijs, Lore Vanderbeke, Carla Van Tienen, Katrien Lagrou, Paul E Verweij, Frank L Van de Veerdonk, Diederik Gommers, Peter Spronk, Dennis C J J Bergmans, Astrid Hoedemaekers, Eleni-Rosalina Andrinopoulou, Charlotte H S B van den Berg, Nicole P Juffermans, Casper J Hodiamont, Alieke G Vonk, Pieter Depuydt, Jerina Boelens, Joost Wauters, on behalf of the Dutch-Belgian Mycosis study group

Eur Respir J 2007; 30: 782–800
DOI: 10.1183/09031936.00062206


REVIEW

Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease

P. Bulpa*, A. Dive* and Y. Sibille#

*Bulpa P, Eur Respir J 2007; Schauwvlieghe A, Lancet Respir Med 2018*

# Epidemiology of aspergillosis diseases

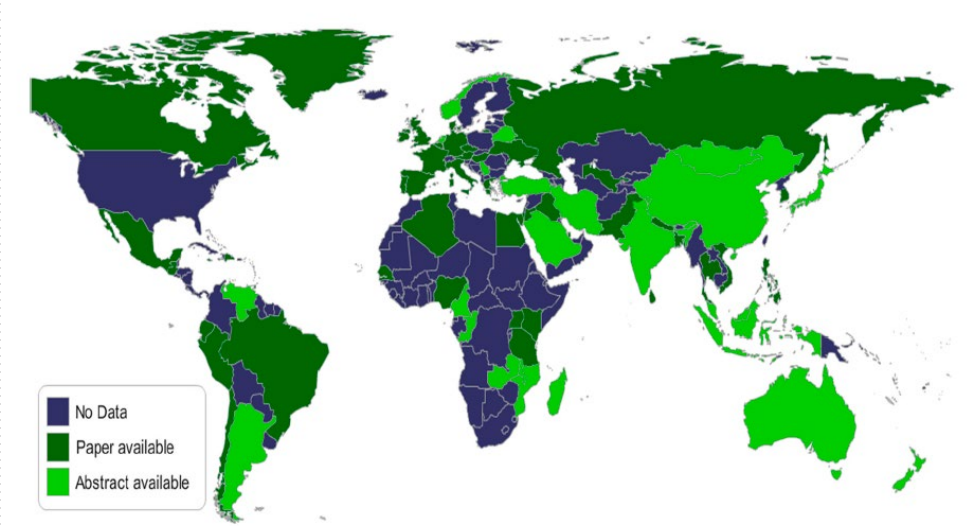
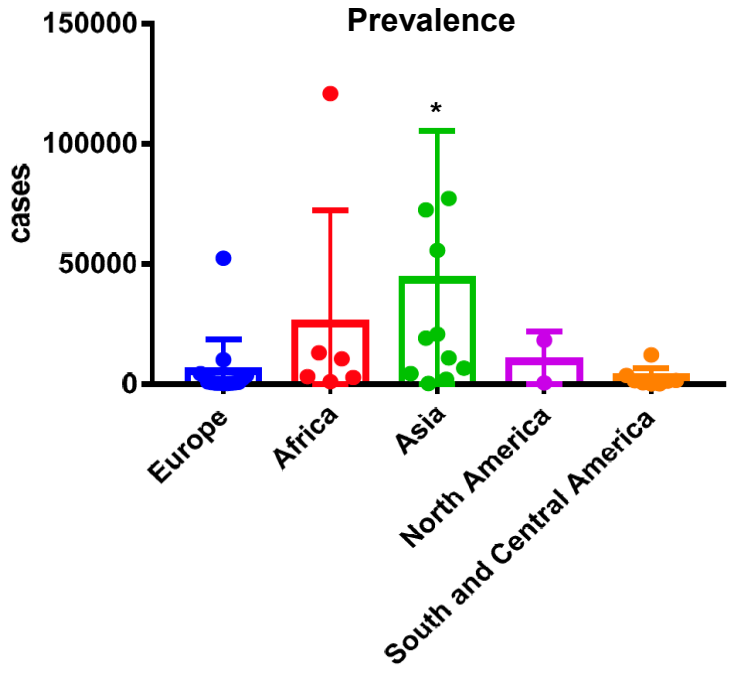



**Figure 1.** A map showing completed country estimates of fungal diseases by August 2017.




*Bongomin F, J Fungi 2017, 3:57*

# Epidemiology of aspergillosis diseases

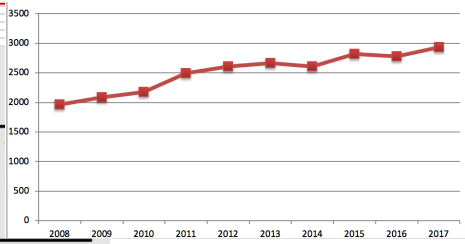




**Table 1** Burden of serious fungal infections in France.
*Poids épidémiologique des infections fongiques graves en France.*

| Infection | Number of infections per underlying disorder per year | | | | | Rate/100K | |
|---|---|---|---|---|---|---|---|
| | None/other | HIV/AIDS | Respiratory | Cancer/Tx | ICU | | |
| ABPA | — | — | 95,331 | — | — | 145 | 95,331 |
| SAFS | — | — | 124,678 | | | 189 | 124,678 |
| Chronic pulmonary aspergillosis | — | — | 3450 | — | — | 5.24 | 3450 |
| Invasive aspergillosis | 151 | 17 | 97 | 800 | 120 | 1.8 | 1185 |
| Mucormycosis | 10 | — | — | 69 | — | 0.12 | 79 |
| *Pneumocystis* pneumonia | 61 | 449 | 4 | 144 | — | 1 | 658 |
| Candidaemia | 533 | 28 | 85 | 1134 | 590 | 3.6 | 2370 |
| *Candida* peritonitis | 249 | — | — | — | 237 | 0.74 | 486 |
| Oesophageal candidiasis | — | 9075 | — | ? | — | 13.8 | 9075 |
| Recurrent vaginal candidiasis (4 ×/year +) | 730,690 | — | — | — | — | 2220[a] | 730,690 |
| Cryptococcosis | 32 | 76 | 2 | 21 | — | 0.2 | 131 |
| Total burden estimated | 731,726 | 9645 | 223,647 | 2168 | 947 | | 968,143 |

[a] Rate for adult females only.



Gangneux JP, J Mycol 2016, 26:385

# Chronic pulmonary aspergillosis care

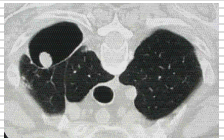
## Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management

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*

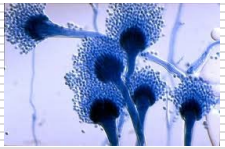
# Chronic pulmonary aspergillosis diagnosis

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*

# 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)*<br>*CCPA (n=9)* | *CNPA (n=19)*<br>*CCPA (n=22)* |
| **Lung disease** | **78%** | **95%** | **100%** | **92%** |
| COPD | 76% | 14% | 42% (FEV1/VC=49%) | 44% |
| Tuberculosis/mycobacteriosis | 20% | 93% | 54% | 27% |
| Bronchiectasis | - | - | - | 15% |
| Sarcoidosis | - | - | 17% | - |
| **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*

# CPA diagnosis, radiological domain

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

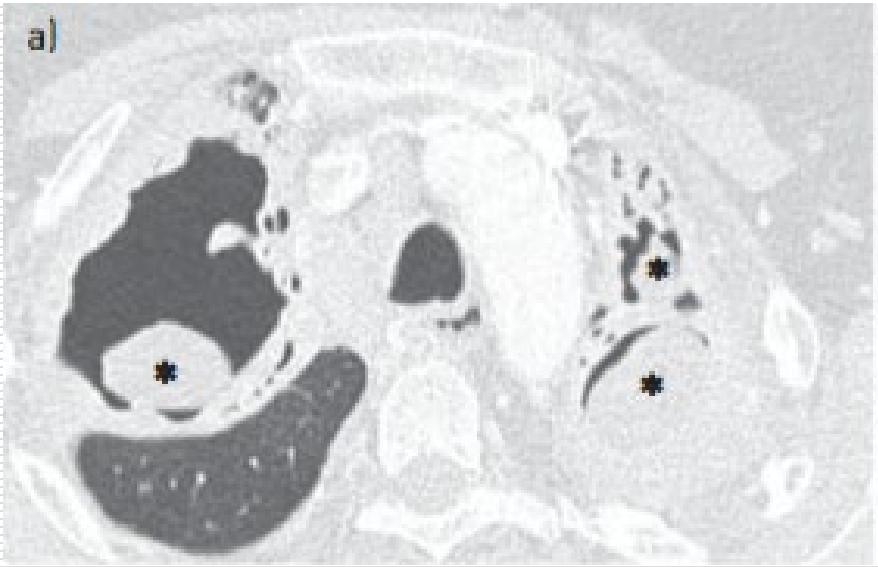
| Population | Intention | Intervention | SoR | QoE | Ref. | Comment |
|---|---|---|---|---|---|---|
| **Any features of cavitation, fungal ball, pleural thickening and/or upper lobe fibrosis** | Raise suspicion of CPA for physicians | Radiological report must mention possible CPA | A | II | [10, 11, 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] | |

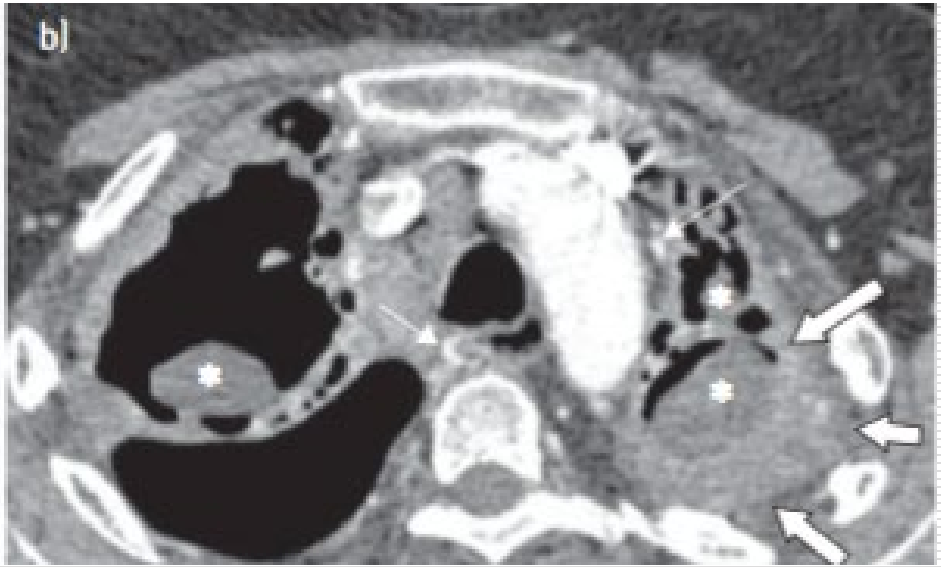
SoR: strength of recommendation; QoE: quality of evidence; CT: computed tomography; PET: positron emission tomography.

*Denning D, Eur Respir Dis 2016, 47:45*

# CPA diagnosis, radiological domain

**…related to aspergillus infection**



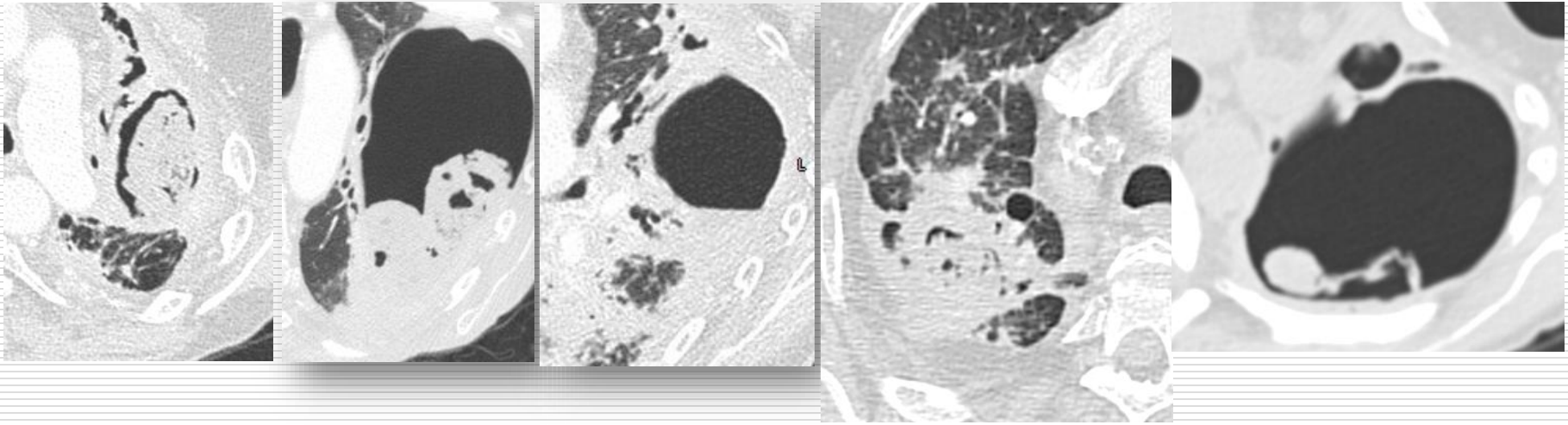






*Denning D, Eur Respir Dis 2016, 47:45*

# CPA diagnosis, radiological domain

**…related to aspergillus infection**

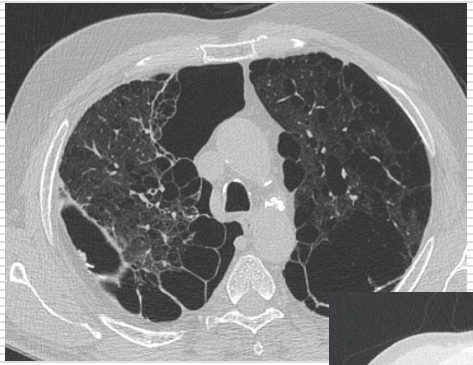




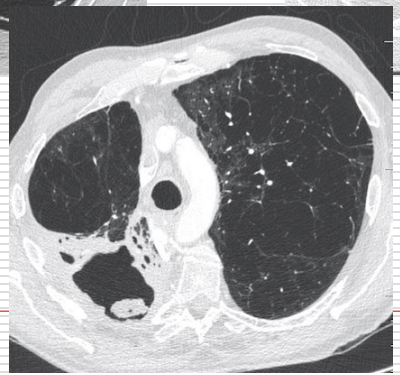
*Franois Laurent, by courtesy*

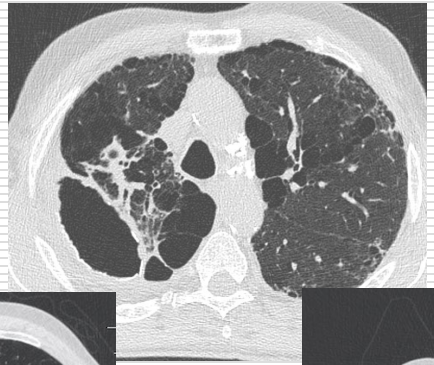
# CPA diagnosis, radiological domain

**…related to aspergillus infection**

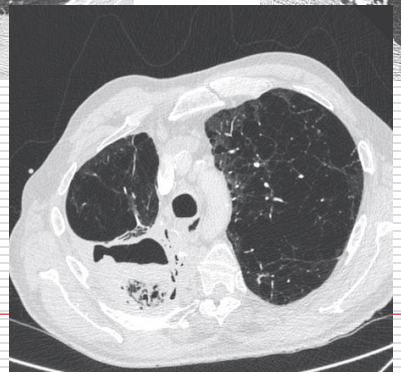


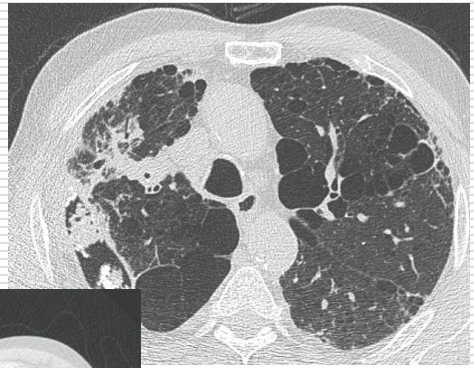
2010





2016





2017



*Franois Laurent, by courtesy*

# Chronic pulmonary aspergillosis

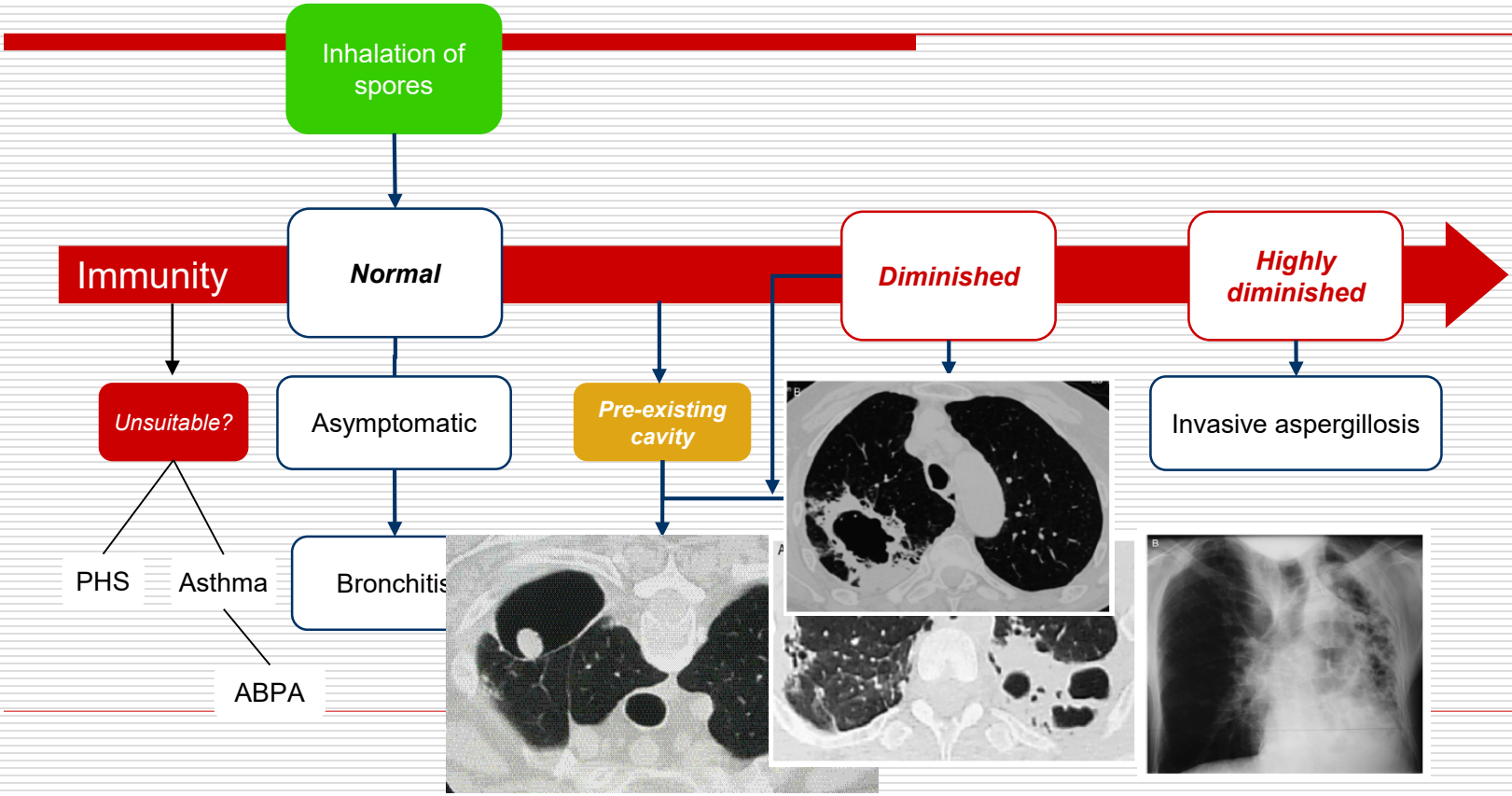
losis

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,*

# Chronic pulmonary aspergillosis



# Chronic pulmonary aspergillosis

**Table 4**

**Radiological characteristics by chronic pulmonary Aspergillosis type.**

| | Total (n = 69) | SA (n = 41) |
|---|---|---|
| Nodule | 58 (84.1%) | 41 (100%) |
| Cavity | 65 (94.2%) | 41 (100%) |
| Consolidation | 3 (4.3%) | 0 (0%) |
| Infiltration | 2 (2.9%) | 0 (0%) |
| Pleural thickening | 2 (2.9%) | 0 (0%) |
| Solitary | 56 (81.2%) | 41 (100%) |

All data are presented as number (%).

AN = Aspergillosis nodule, CCPA = chronic cavitary pulmonary aspergillosis, SA = simple aspergilloma, SAIA = semi-invasive aspergillosis.

*Hou X, Medicine 2017, 87:e8315*

# Chronic pulmonary aspergillosis

**Table 4**

**Radiological characteristics by chronic pulmonary Aspergillosis type.**

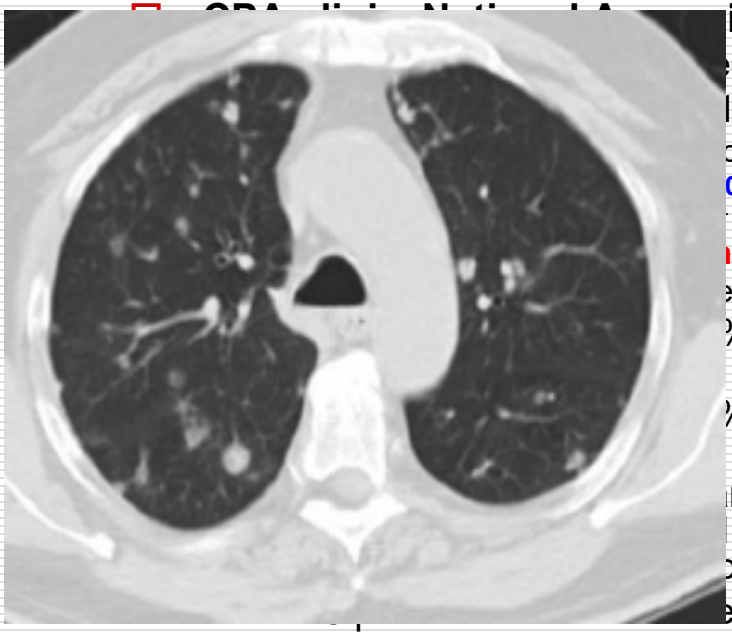
| | Total (n=69) | CCPA (n=10) | SAIA (n=15) | AN (n=3) | SA (n=41) |
|---|---|---|---|---|---|
| Nodule | 58 (84.1%) | 7 (70%) | 7 (46.7%) | 3 (100%) | 41 (100%) |
| Cavity | 65 (94.2%) | 10 (100%) | 14 (93.3%) | 0 (0%) | 41 (100%) |
| Consolidation | 3 (4.3%) | 0 (0%) | 3 (20%) | 0 (0%) | 0 (0%) |
| Infiltration | 2 (2.9%) | 2 (20%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Pleural thickening | 2 (2.9%) | 0 (0%) | 2 (%13.3) | 0 (0%) | 0 (0%) |
| Solitary | 56 (81.2%) | 5 (50%) | 7 (46.7%) | 3 (100%) | 41 (100%) |

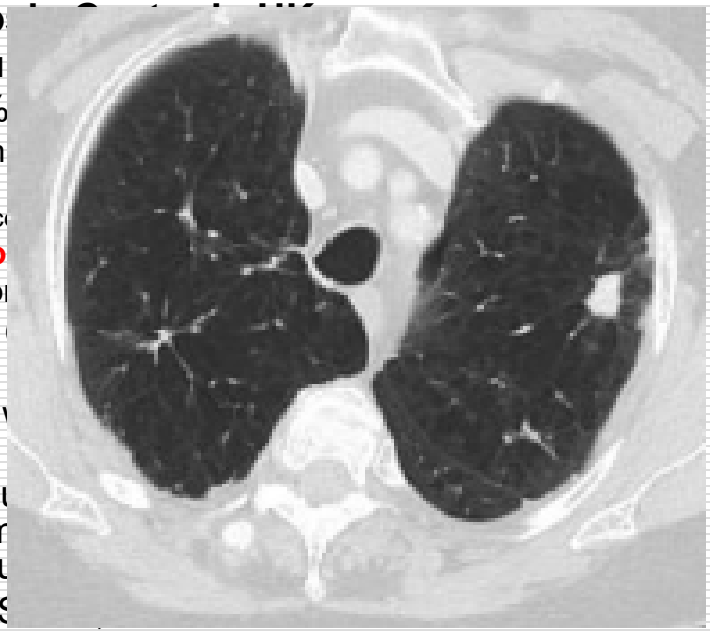
All data are presented as number (%).

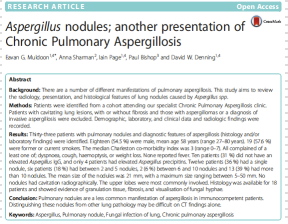
AN=Aspergillosis nodule, CCPA=chronic cavitary pulmonary aspergillosis, SA=simple aspergilloma, SAIA=semi-invasive aspergillosis.

*Hou X, Medicine 2017, 87:e8315*

# Aspergillus nodule(s)







*Aspergillus* nodules; another presentation of Chronic Pulmonary Aspergillosis

Ewan G. Muldoon[1,4*], Anna Sharman[2], Iain Page[2,4], Paul Bishop[3] and David W. Denning[1,4]

**Abstract**

**Background:** There are a number of different manifestations of pulmonary aspergillosis. This study aims to review the radiology, presentation, and histological features of lung nodules caused by Aspergillus spp.

**Methods:** Patients were identified from a cohort attending our specialist Chronic Pulmonary Aspergillosis clinic. Patients with cavitating lung lesions, with or without fibrosis and those with aspergillomas or a diagnosis of invasive aspergillosis were excluded. Demographic, laboratory, and clinical data and radiologic findings were recorded.

**Results:** Thirty-three patients with pulmonary nodules and diagnostic features of aspergillosis (histology and/or laboratory findings) were identified. Eighteen (54.5 %) were male, mean age 58 years (range 27–80 years). 19 (57.6 %) were former or current smokers. The median Charleston co-morbidity index was 3 (range 0–7). All complained of a least one of; dyspnoea, cough, haemoptysis, or weight loss. None reported fever. Ten patients (31 %) did not have an elevated *Aspergillus* IgG, and only 4 patients had elevated *Aspergillus* precipitins. Twelve patients (36 %) had a single nodule, six patients (18 %) had between 2 and 5 nodules, 2 (6 %) between 6 and 10 nodules and 13 (39 %) had more than 10 nodules. The mean size of the nodules was 21 mm, with a maximum size ranging between 5–50 mm. No nodules had cavitation radiographically. The upper lobes were most commonly involved. Histology was available for 18 patients and showed evidence of granulation tissue, fibrosis, and visualisation of fungal hyphae.

**Conclusion:** Pulmonary nodules are a less common manifestation of aspergillosis in immunocompetent patients. Distinguishing these nodules from other lung pathology may be difficult on CT findings alone.

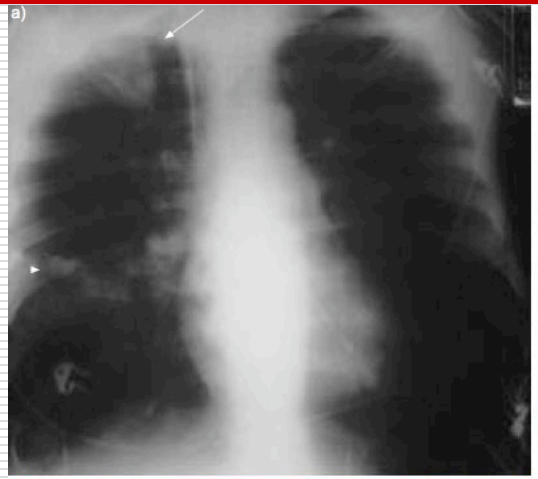
**Keywords:** Aspergillus, Pulmonary nodule, Fungal infection of lung, Chronic pulmonary aspergillosis

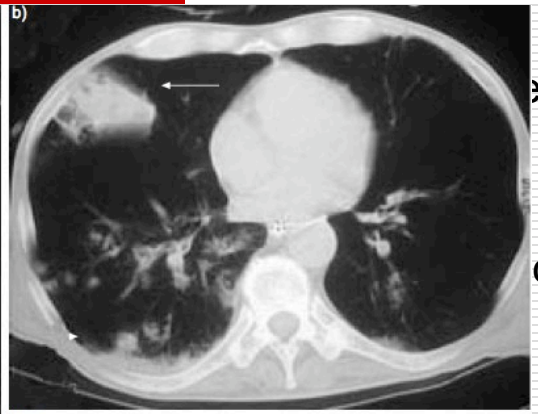


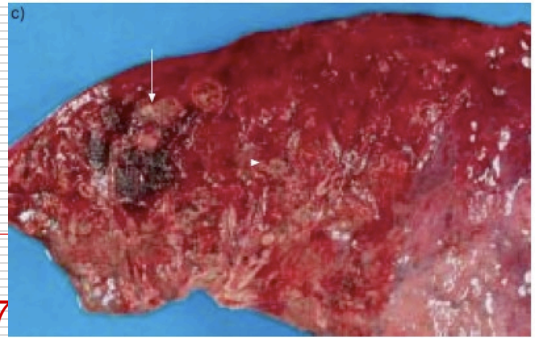
*Denning D, BMC Pulmonary Medicine 2016, 16:123*

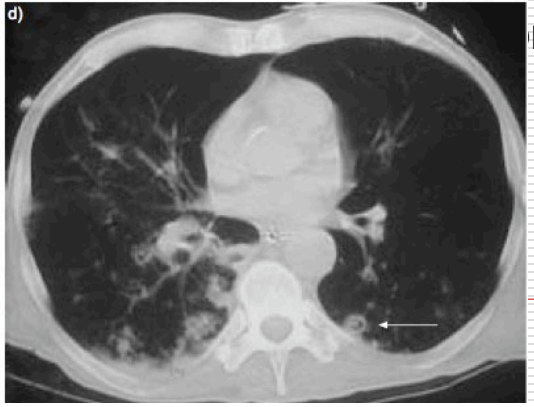
# Invasive aspergillosis in COPD/ICU

- ntional
- ct at
- n, 88%



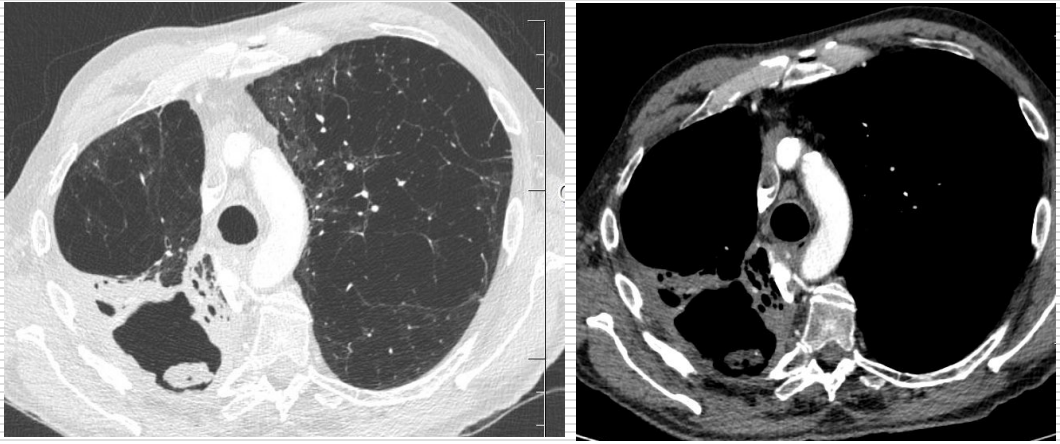



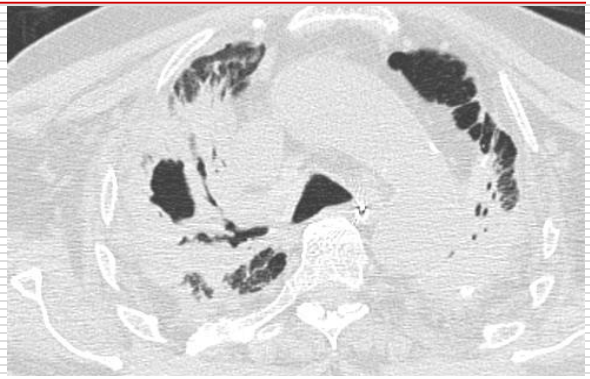

*Bulpa P, Eur Respir J 2007*

# CPA diagnosis, radiological domain

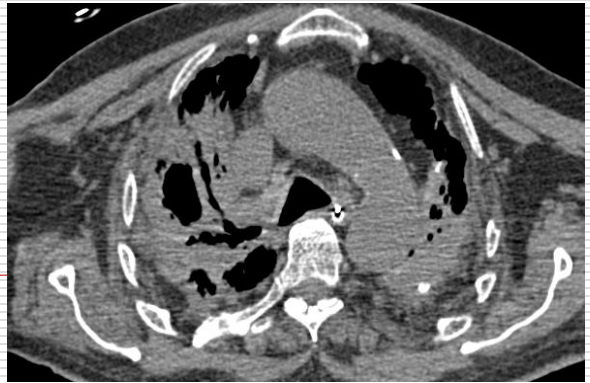
**…related to uderlying disease**



*Chronic obstructive pulmonary disease - COPD*



*Sarcoidosis*



*Denning D, Eur Respir Dis 2016, 47:45*

# CPA in sarcoidosis

ORIGINAL ARTICLE
SARCOIDOSIS AND ASPERGILLOSIS

## Chronic pulmonary aspergillosis complicating sarcoidosis

Yurdagül Uzunhan[1,2], Hilario Nunes[1,2], Florence Jeny[1,2], Maxime Lacroix[1,3], Sophie Brun[4], Pierre-Yves Brillet[1,3], Emmanuel Martinod[5], Marie-France Carette[6], Diane Bouvry[1,2], Caroline Charlier[7,8], Fanny Lanternier[7,8], Carole Planès[1,2], Abdellatif Tazi[9], Olivier Lortholary[7,8], Robert P. Baughman[10] and Dominique Valeyre[1,2]

TABLE 1 Characteristics of patients after fibrocystic lung sarcoidosis diagnosis with and without cavitary pulmonary aspergillosis paired according to the date of stage 4 diagnosis (difference <5 yea

2% of sarcoidosis

| | Cases | Controls | p-value |
|---|---|---|---|
| **Subjects n** | 64 | 64 | |
| **Male** | 43 (67.1%) | 32 (50%) | 0.07 |
| **SS or AC** | 21 (32.8%) | 21 (32.8%) | 1 |
| **Age years at stage 4** | 43±13.5 | 41.8±9.5 | 0.66 |
| **Smoking NS/ES (mean pack-years)** | 43 (67.1%)/22 (34.3%) (5.5) | 37 (57.8%)/27 (42.1%) (5.7) | 0.36 |
| **Diabetes mellitus** | 7 (10.9%) | 6 (9.3%) | 1 |
| **Pneumothorax** | 8 (12.5%) | 5 (7.8%) | 0.56 |
| **High-risk occupational exposure** | 24 (37.5%) | 11 (17.1%) | 0.01 |
| **PFT at stage 4 diagnosis** | | | |
| $FEV_1$ % predicted | 58.7±18.8 | 61.4±22.2 | 0.58 |
| FVC % predicted | 62.2±18.6 | 69.6±22.8 | 0.06 |
| $D_{LCO}$ % predicted | 50.7±16.7 | 53.3±17.0 | 0.35 |
| CPI | 45.5±14.8 | 39.7±16.2 | 0.07 |
| **Treatment for sarcoidosis at stage 4 diagnosis** | 53 (82.8%) | 58 (90.6%) | 0.29 |
| CTS ⩽10 mg per day | 13 (20.3%) | 15 (23.4%) | 0.83 |
| CTS >10 mg per day | 32 (50%) | 33 (51.5%) | 1 |
| Immunosuppressive drugs | 8 (12.5%) | 10 (15.6%) | 0.79 |



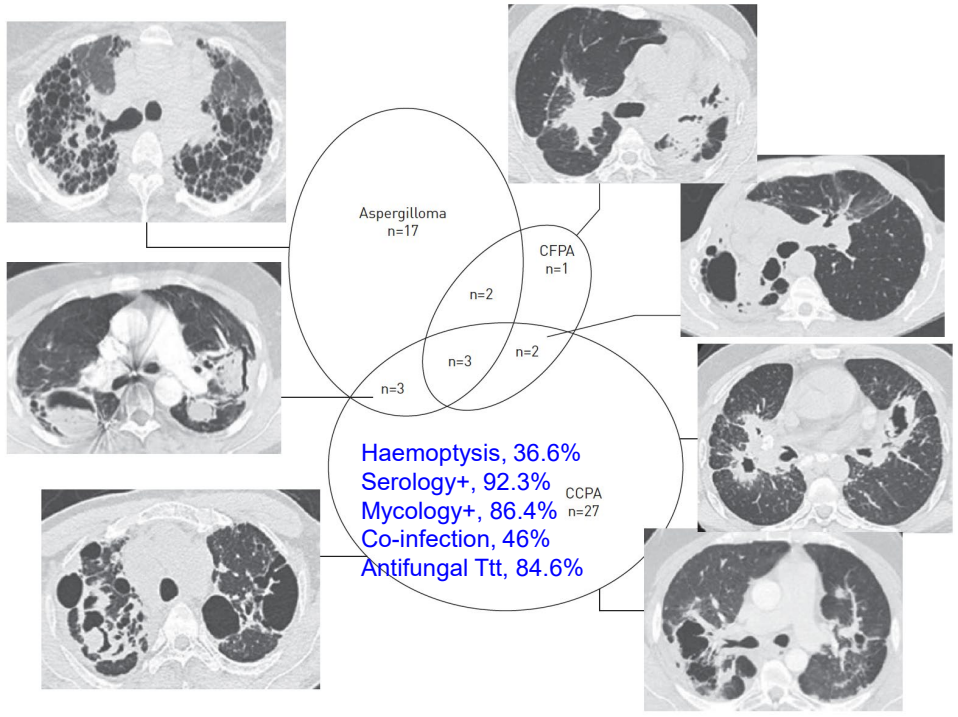
*Uzunhan Y, Eur Respir J 2017, 49*

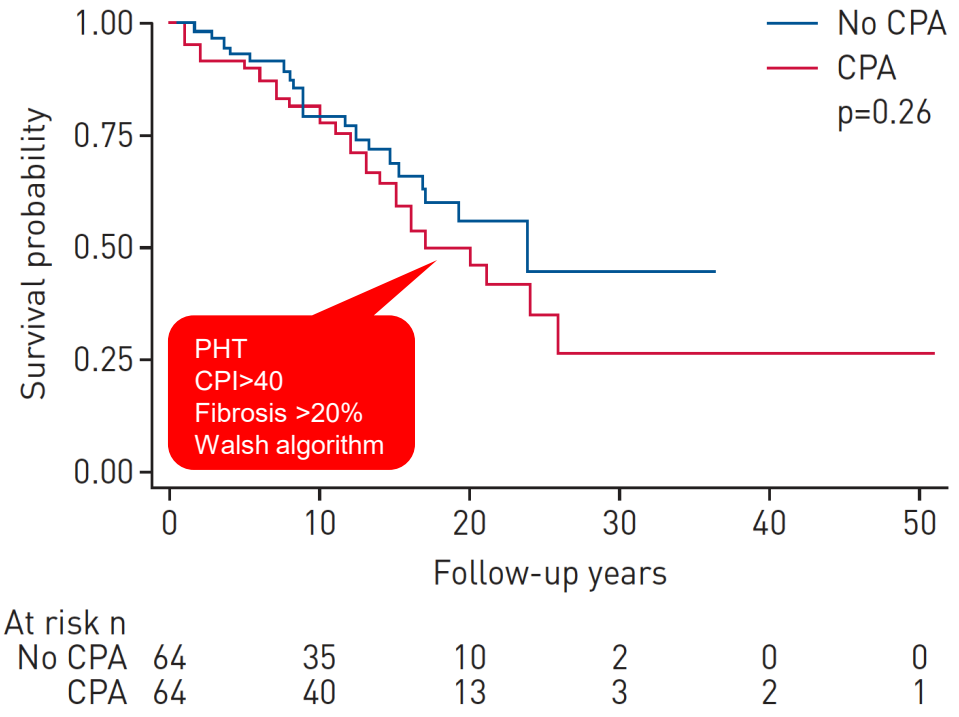
ORIGINAL ARTICLE
SARCOIDOSIS AND ASPERGILLOSIS

**Chronic pulmonary aspergillosis complicating sarcoidosis**

Yurdagül Uzunhan[1,2], Hilario Nunes[1,2], Florence Jeny[1,2], Maxime Lacroix[1,3], Sophie Brun[4], Pierre-Yves Brillet[1,3], Emmanuel Martinod[5], Marie-France Carette[6], Diane Bouvry[1,2], Caroline Charlier[7,8], Fanny Lanternier[7,8], Carole Planès[1,2], Abdellatif Tazi[9], Olivier Lortholary[7,8], Robert P. Baughman[10] and Dominique Valeyre[1,2]

# CPA in sarcoidosis




*Uzunhan Y, Eur Respir J 2017, 49:1*

ORIGINAL ARTICLE
INFECTION AND TUBERCULOSIS

CrossMark

Chronic pulmonary aspergillosis commonly complicates treated pulmonary tuberculosis with residual cavitation

Iain D. Page[1,2], Rosemary Byanyima[3], Sharath Hosmane[4], Nathan Onyachi[5], Cyprian Opira[6], Malcolm Richardson[1,7], Richard Sawyer[4], Anna Sharman[4] and David W. Denning[1,2]

# CPA in tuberculosis

**Uganda, 2-yr prospective cohort**

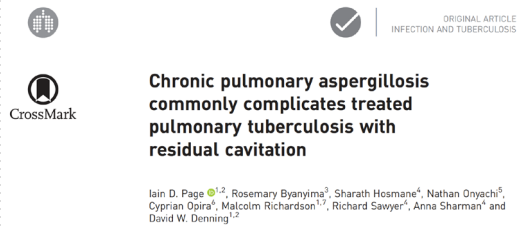
*284 re-survey on 398 treated TB; 50% HIV+*

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*



ORIGINAL ARTICLE
INFECTION AND TUBERCULOSIS

CrossMark

**Chronic pulmonary aspergillosis commonly complicates treated pulmonary tuberculosis with residual cavitation**

Iain D. Page[1,2], Rosemary Byanyima[3], Sharath Hosmane[4], Nathan Onyachi[5], Cyprian Opira[6], Malcolm Richardson[1,7], 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, serological domain

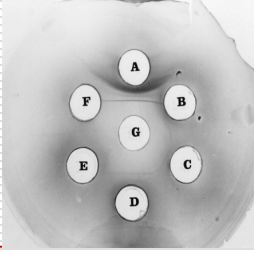



TABLE 6 Antibody diagnosis of chronic pulmonary aspergillosis (CPA)

| 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; 55:1738

# CPA diagnosis, mycological domain

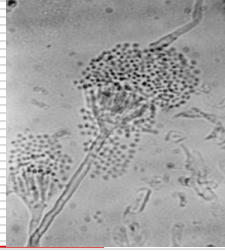
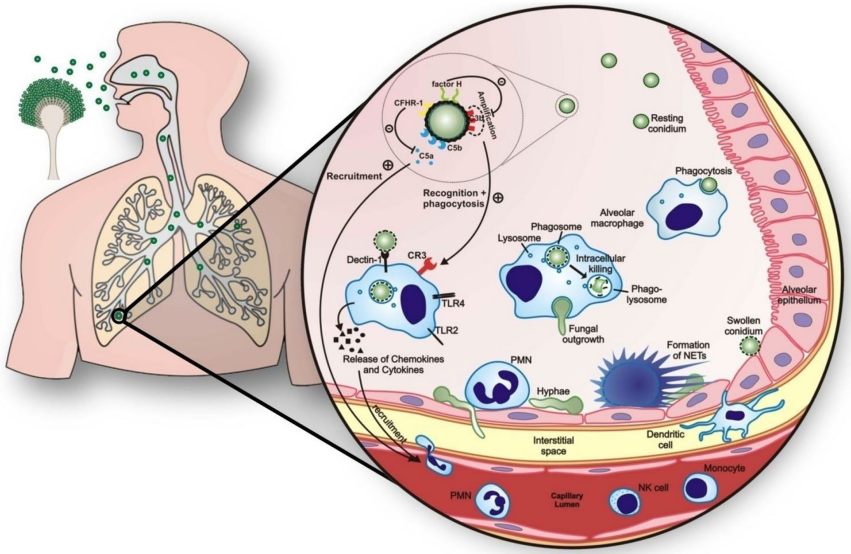


TABLE 4 Key tests on respiratory samples for patients with cavitary or nodular pulmonary infiltrate in non-immunocompromised patients

| 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/mycological domain

- 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*

# CPA diagnosis, serological/mycological domain

**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

# 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]

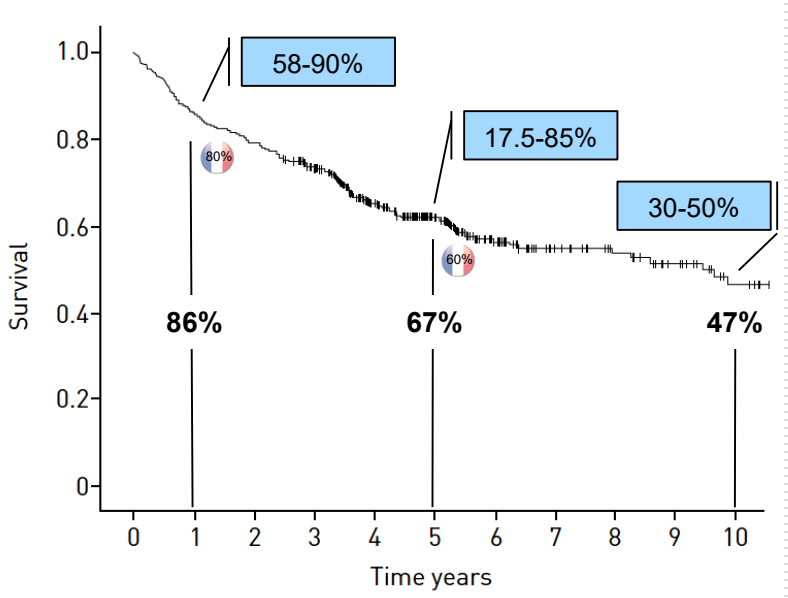
**Affiliations**: [1]The National Aspergillosis Centre, University Hospital of South Manchester, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [2]Dept of Medical Statistics, University Hospital of South Manchester, The University of Manchester, Manchester Academic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

ORIGINAL ARTICLE
RESPIRATORY INFECTIONS

# CPA prognosis

**Predictors of mortality in chronic pulmonary aspergillosis**

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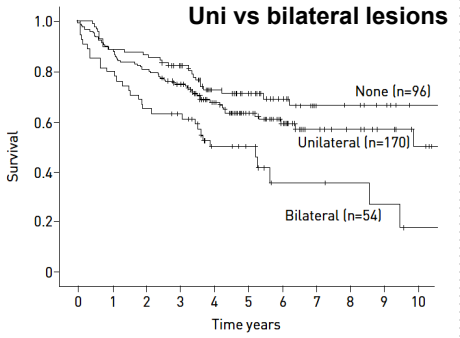
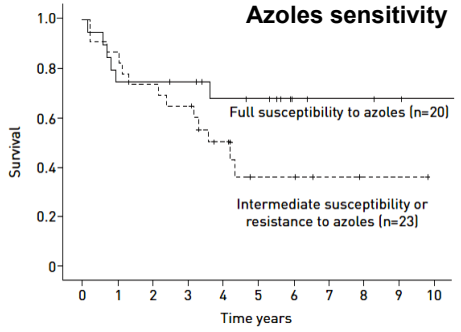
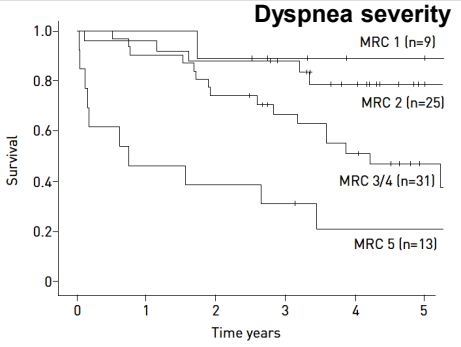



| Characteristics | HR, 95% IC, p value |
|---|---|
| Previous NTM | 2.07 [1.22-3.052], 0.007 |
| Previous COPD | 1.57 [1.05-2.36], 0.029 |
| Age | 1.05 [1.03-1.07], 0.001 |
| Activity score (≈MRC) | 1.02 [1.02-1.03], 0.007 |
| Albumin (g/L) (≈BMI) | 0.92 [0.87-0.96], 0.001 |

*Among age, sex, underlying disease, disease extension, albumin, CRP, activity*



*Lowes D, Eur Respir J 2017, 49:1*

# Therapeutic strategy

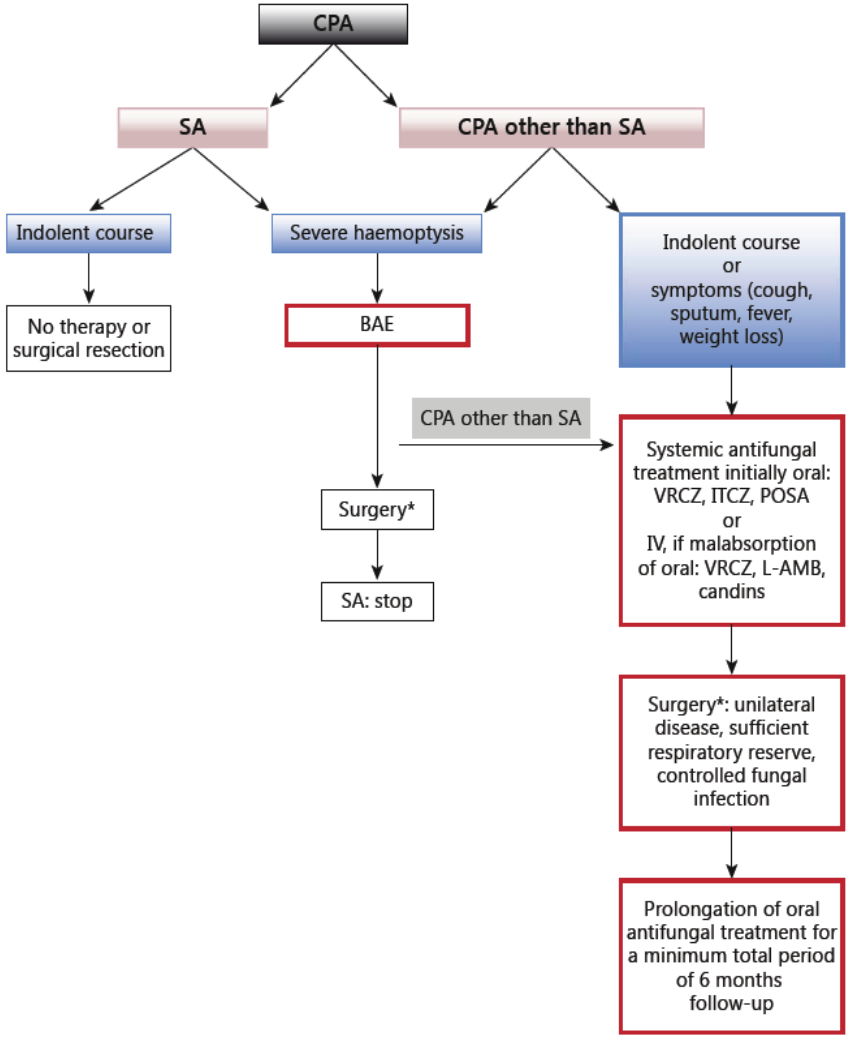
- Three main objectives
  - To limit further destruction of lung tissue
  - To prevent life-threatening haemoptysis
  - To improve quality of life



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

# Therapeutic strategy

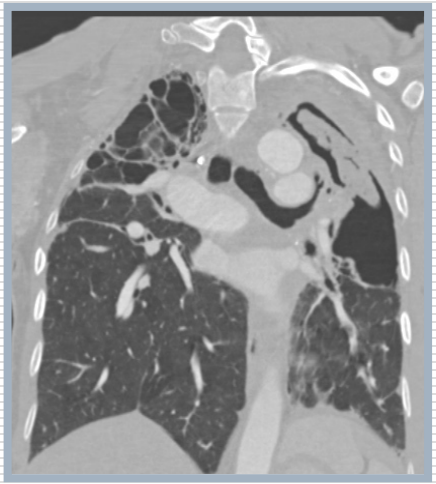
- Treatment of underlying condition,
  - Specific treatments of underlying l
    - TB, sarcoidosis, COPD
    - Difficulties: corticosteroids, pharmac
  - Specific treatment of comorbidities
  - Respiratory rehabilitation and re-n
- Treatment of haemoptysis by end
- Treatment of aspergillosis
  - Curative treatment = surgery; **exc**
    - eradicate aspergillosis
    - avoid relapse?
  - Palliative antifungic (systemic) trea




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

# Endovascular treatment

- 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
    - false arteriovenous aneuvrysm = pulmonary vaso-occlusion





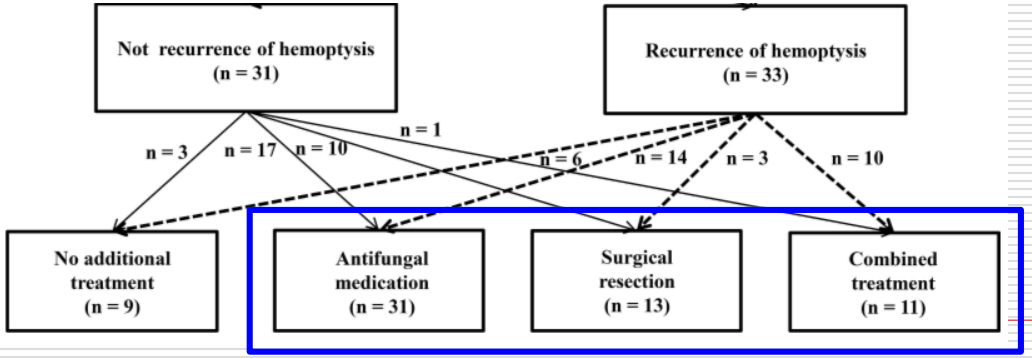
*Khalil A, AJR 2007; Shin B, PLoS One 2016, 11:0168373*

# Endovascular treatment

15%

**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 |



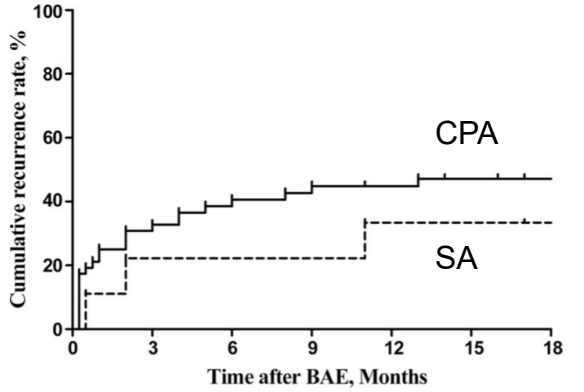




Fig 2. Cumulative recurrence rates following BAE in patients with CPA (solid line) and patients with SA (dotted line) (*P* = 0.061, log-rank test). BAE, bronchial artery embolization; CPA, chronic pulmonary aspergillosis.

*Shin B, PLoS One 2016, 11:0168373*

# Surgical treatment

- Avoid haemoptysis and loco-regional extension,
- Permanent cure, improve survival
- No randomised study
- etc.

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. |



*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*

# 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

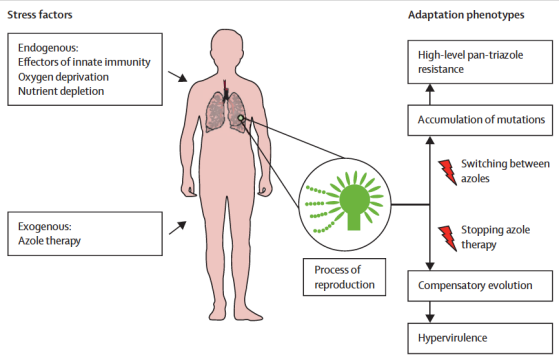
**Table 5 Surgical risk assessment**

| 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)



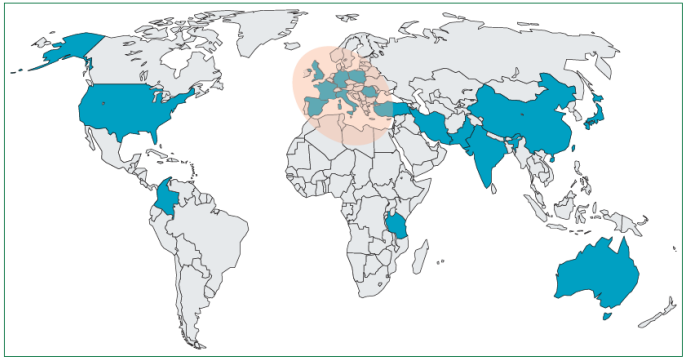
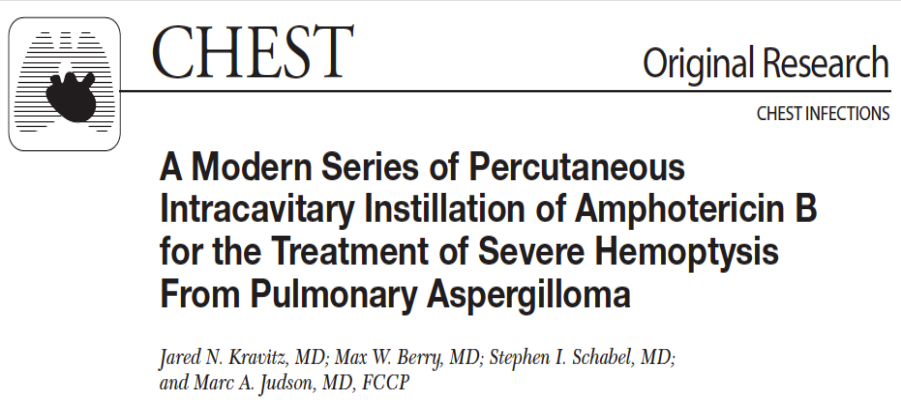



*Figure 1:* **Countries reporting azole-resistant isolates of *Aspergillus fumigatus* with either $TR_{34}$/L98H or $TR_{46}$/Y121F/T289A modifications**
Countries where mechanistic resistance is found are shown in blue. The region of highest burden of resistance is marked by the shaded oval (adapted from Verweij et al[47]).

*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*

# Antifungal treatments local/nebulized



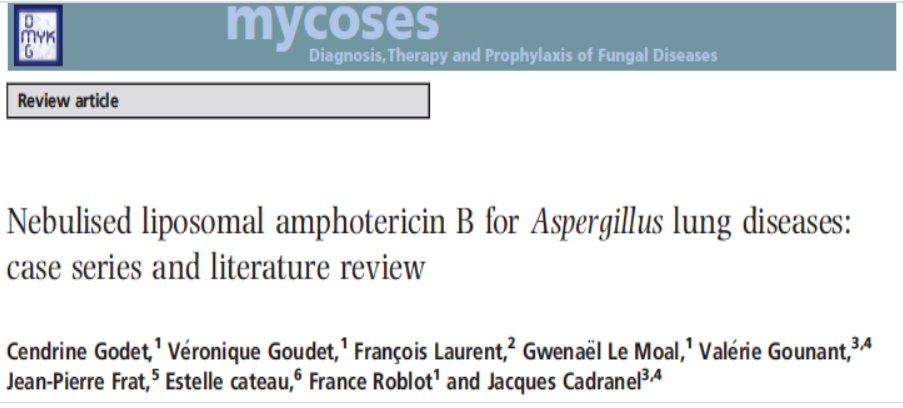
CHEST

Original Research

CHEST INFECTIONS

**A Modern Series of Percutaneous Intracavitary Instillation of Amphotericin B for the Treatment of Severe Hemoptysis From Pulmonary Aspergilloma**

*Jared N. Kravitz, MD; Max W. Berry, MD; Stephen I. Schabel, MD; and Marc A. Judson, MD, FCCP*



mycoses

Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Review article

Nebulised liposomal amphotericin B for *Aspergillus* lung diseases: case series and literature review

Cendrine Godet,[1] Véronique Goudet,[1] François Laurent,[2] Gwenaël Le Moal,[1] Valérie Gounant,[3,4] Jean-Pierre Frat,[5] Estelle cateau,[6] France Roblot[1] and Jacques Cadranel[3,4]

*Giron JM, Radiology 1993; Yamada H, Chest 1993; Giron J, J Radiol 1998; Ikemoto I, Intern Med 2000; Kravitz J, Chest 2013, 143:1414; Godet C, Mycosis 2015, 58:173*

# 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*

# Systemic antifungal treatments

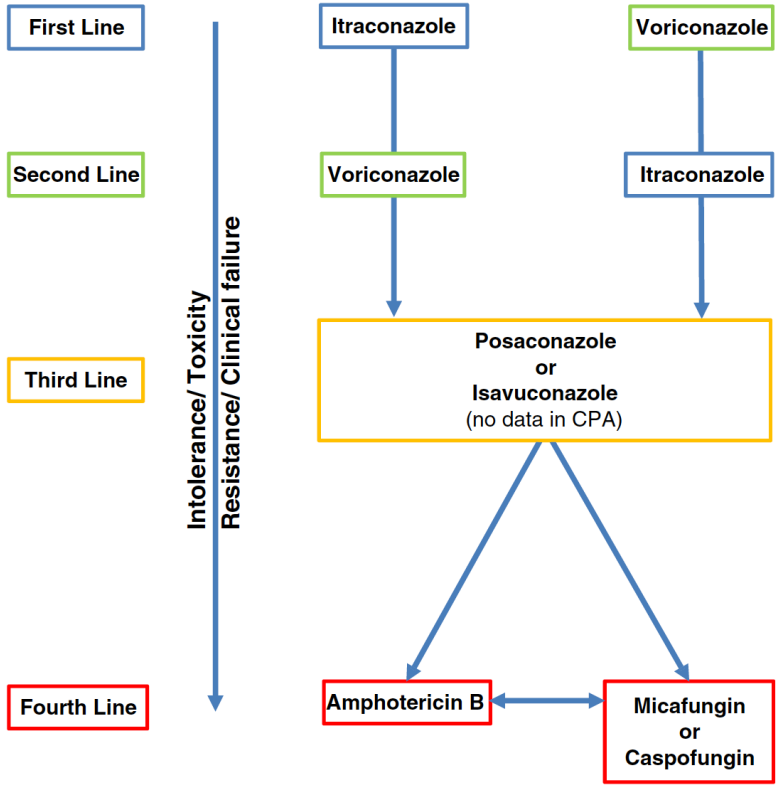
**Table 1.** Antifungal treatment of chronic pulmonary aspergillosis

| 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
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*

[ Original Research Chest Infections ]
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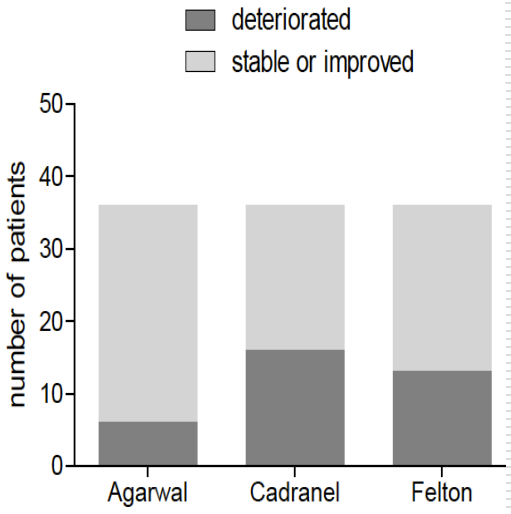
CT Imaging Assessment of Response to Treatment in Chronic Pulmonary Aspergillosis

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 Taper, MD; Marie France Carette, MD; Jean-Pierre Prat, 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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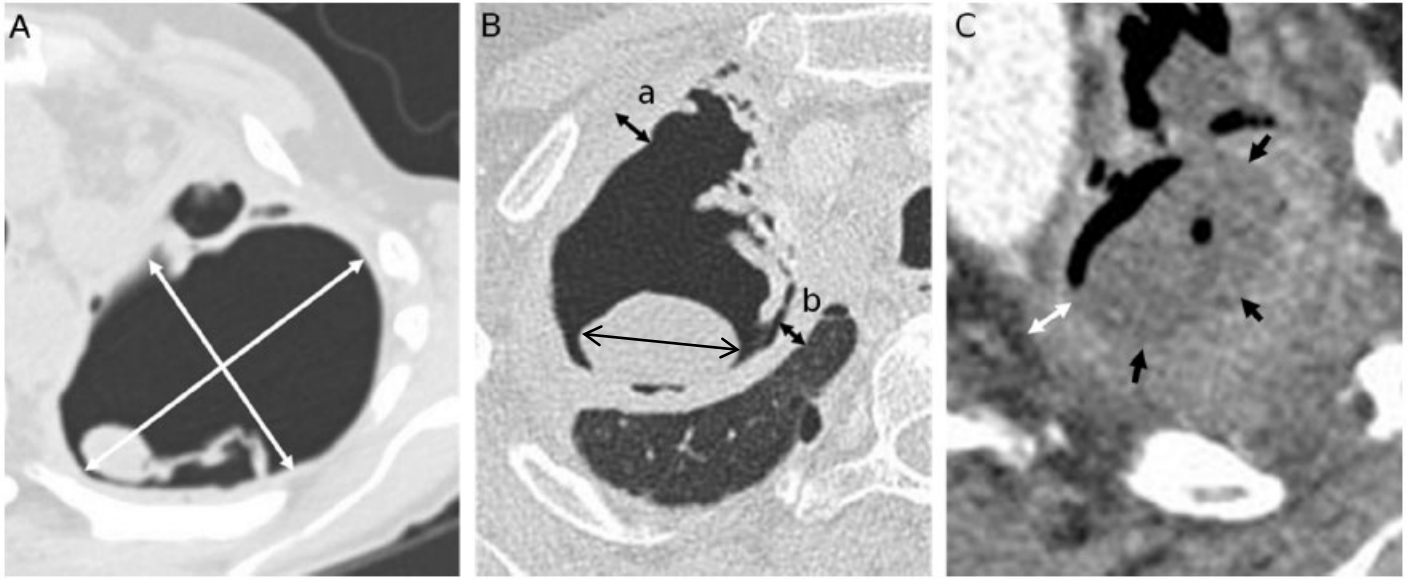
# Evaluation of systemic antifungal treatment



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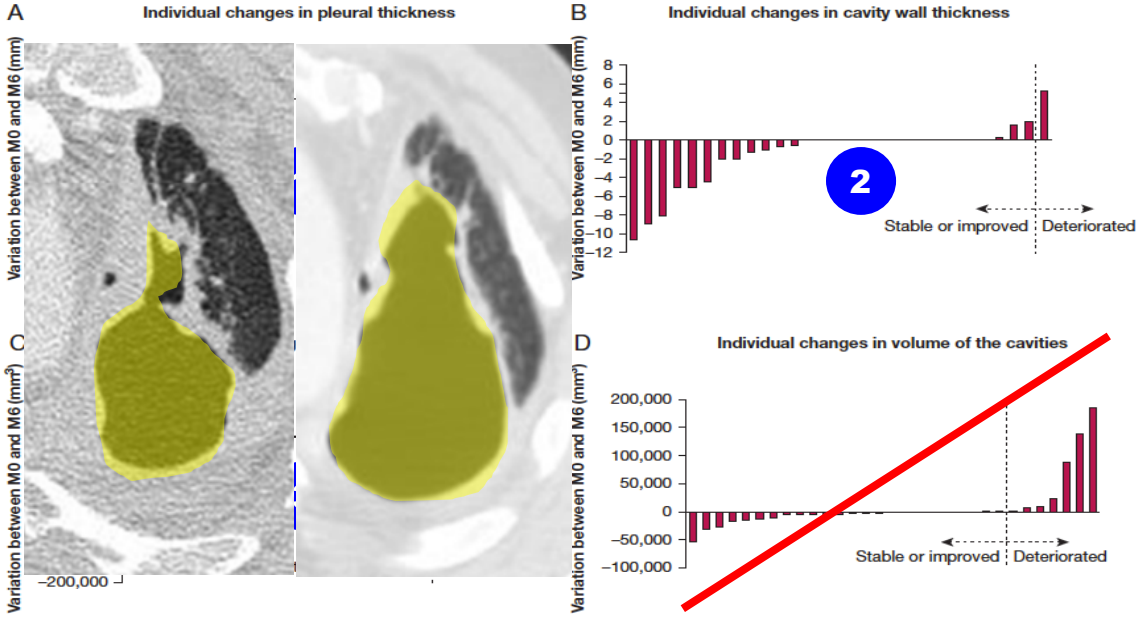
# Evaluation of systemic antifungal treatment






Godet C, Chest 2016, 150:139

- 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?

# 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

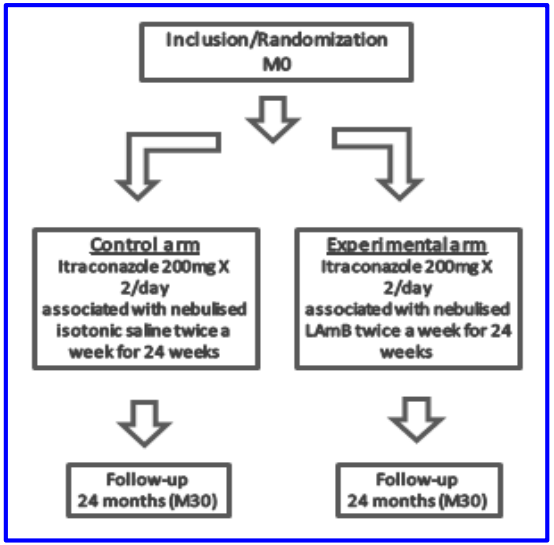
### Inclusion criteria

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*

CPAnet

Chronic Pulmonary Aspergillosis Network

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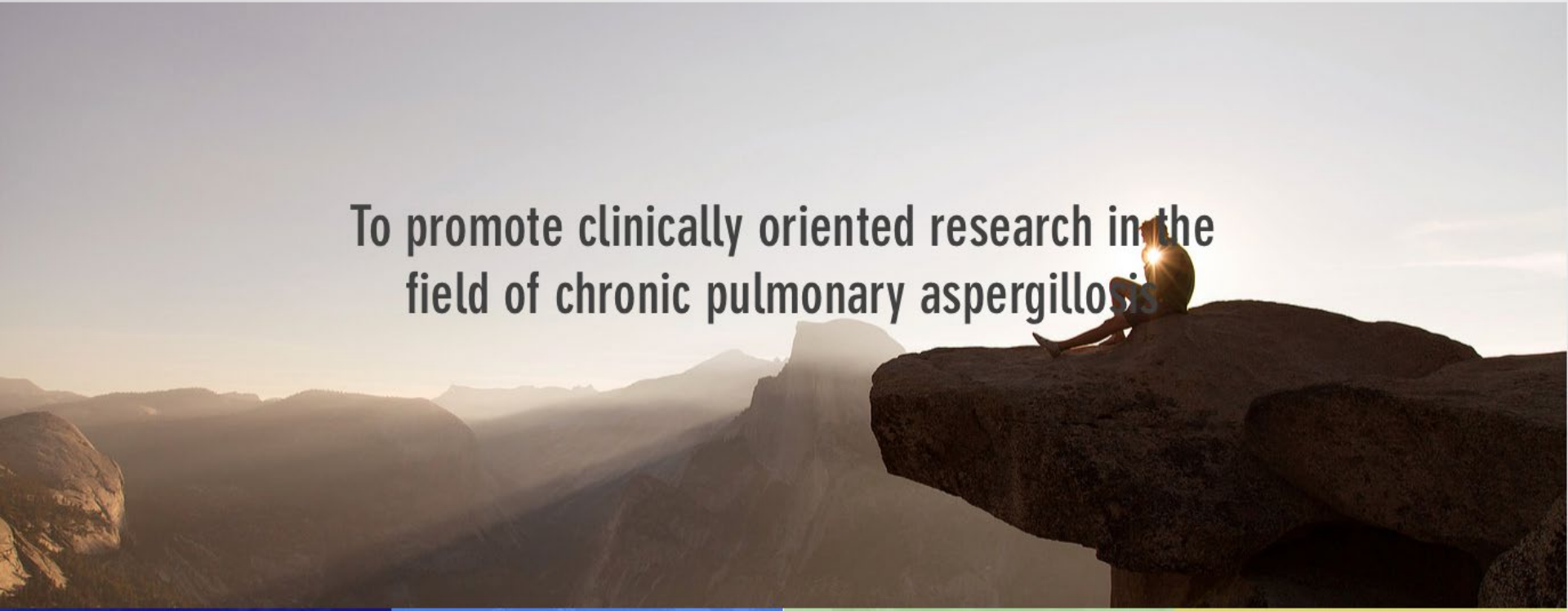


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