Managing chronic pulmonary aspergillosis infection

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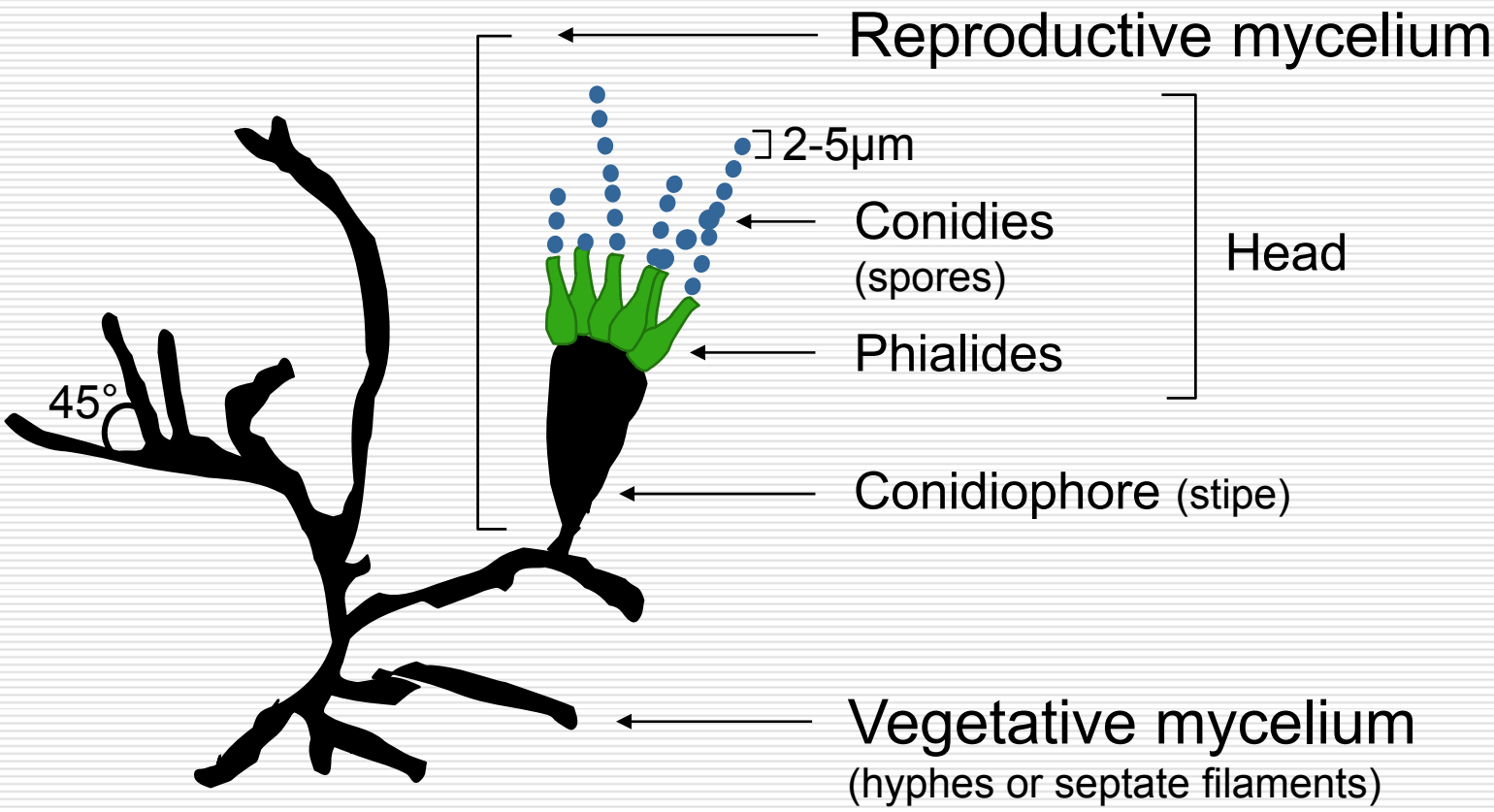
Conflict of interest statement : J Cadranel

- Principal investigator of the VERTIGO trial on behalf of Pfizer France
- Paid for talks on behalf of Pfizer
- Travel grants from Pfizer

Aspergillosis in human

Aspergillus fumigatus anatomy



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

Aspergillosis in human

Summary

- Fungi (*Ascomycetes*) of the order of *Plectomycetes*, the family of *Aspergillacea*
- Small percentage of the fungal flora (2%)
- About 30 species pathogenic for humans
- *Aspergillus fumigatus* (AF) responsible for 90% of cases, then *A. flavus* and *A. Niger*

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

Aspergillosis in human
Summary

- Cosmopolitan proliferating on decaying organic matter (plants, cereals, air conditioners ...)
- Found in 50% of urban habitats
- Permanent in the atmosphere
  - with renewed automno-winter and during demolition work
  - in the environment: 1-20 spores/m3
- Pathogenicity factors of *Aspergillus*, factors related to the host

Bull Soc Franç Mycol Med 1985,14:81; Bull Soc Franç Mycol Med 1982, 11:363; Clinical Allergy 1984, 14:354; Pathol Biol 1994, 42:706.

Aspergillosis in human

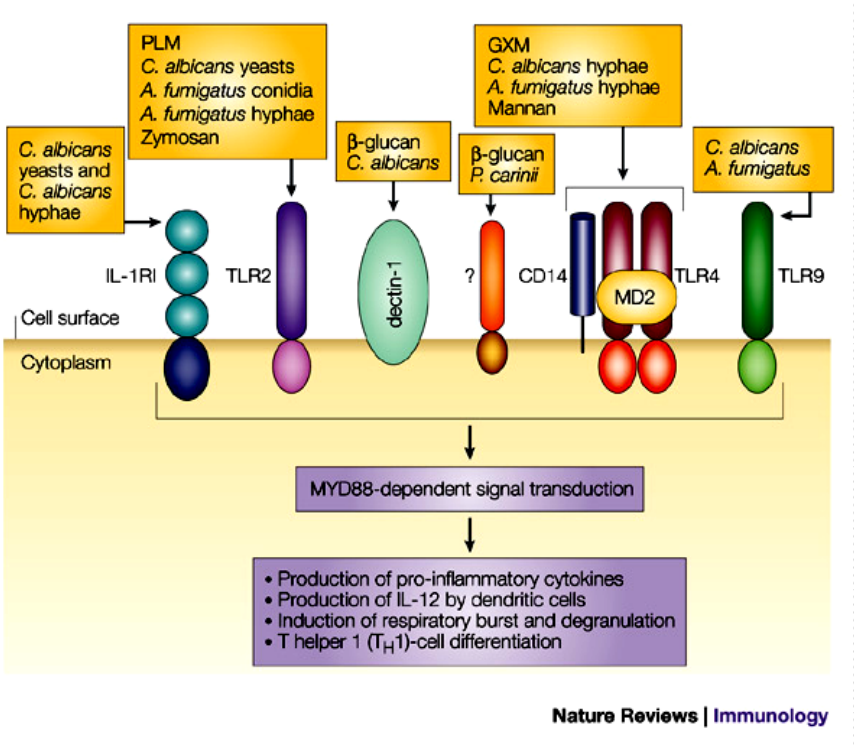
Pathogenicity factors of Aspergillus

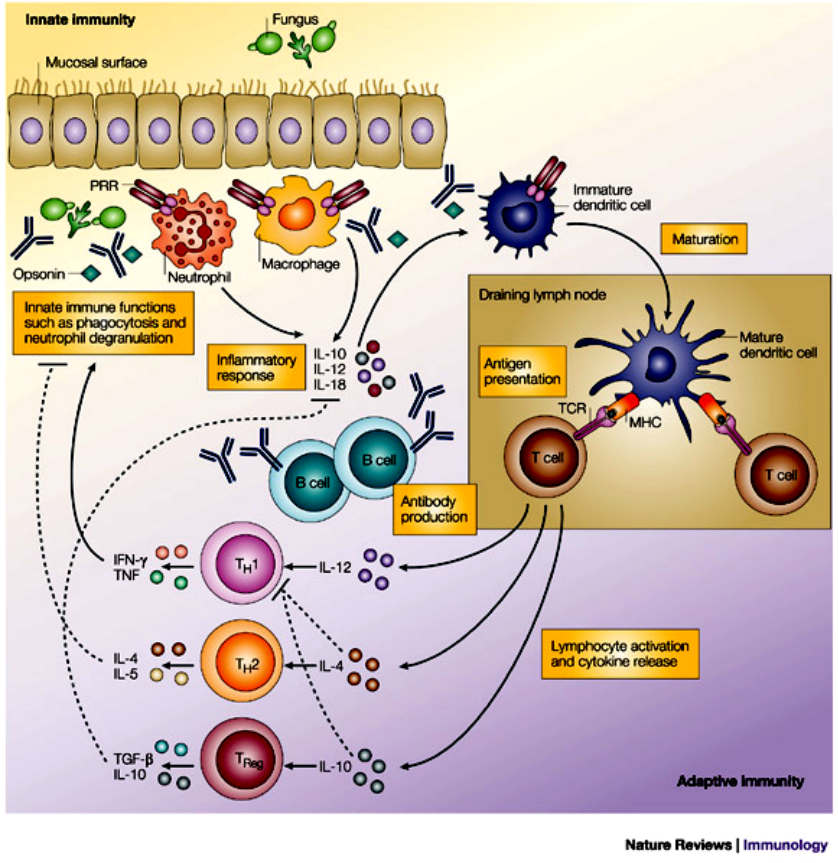
- Small spores (2-5µm): acute inhalation; growth at 37°C in wet
- Filament formation: embarrassment to phagocytosis
- Receptors to fibrinogen and laminin: adhesion to the matrix
- Production of proteases and toxins (fumigatoxine, fumagillin, haemolysin ...) responsible for shock, hemorrhage, necrosis and inhibition of cellular repair
- To exhaust host defenses (gliotoxin)

Infect Immun 1994, 62:2169; Biol Cell 1993, 77:201; Contrib Microbiol 1999,2:182; Clin Exp Allergy 2000, 30:476

Aspergillosis in human

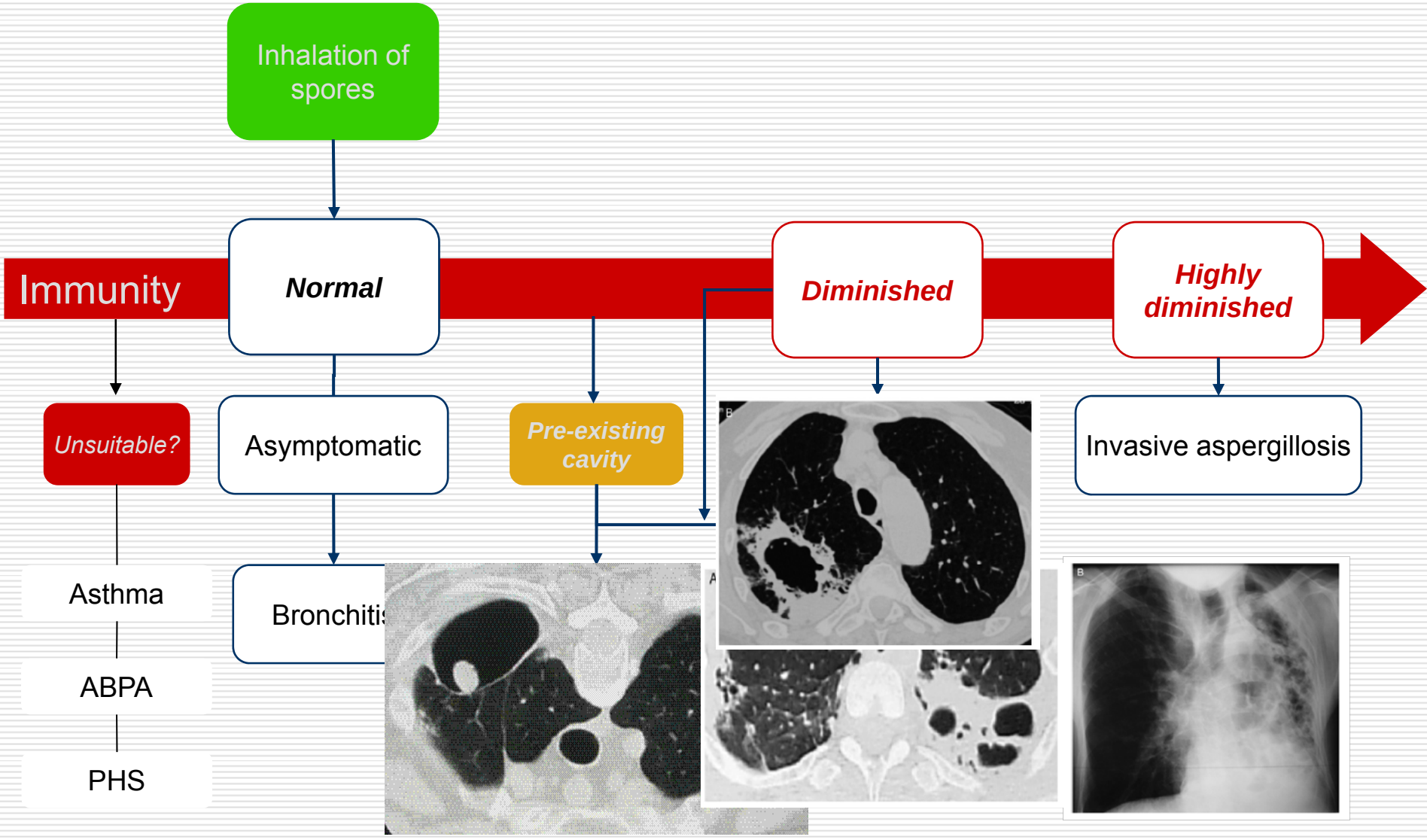
Pathogenicity factors related to the host





Nature Rev Immunol 2004, 4:11-24

Anatomical and clinical continuum



Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003

Pulmonary aspergillosis

Diagnostic methods

- Mycological diagnosis samples: sputum, fibroaspiration, BAL, biopsy ...
  - Direct examination:
    - size of the filaments, number and branching angle, aspect of the head
  - Cultures:
    - Sabouraud medium, several tubes, 37°C for at least 48 hours to 15 days, special media for identification
    - results even more valuable than:
      - sample obtained on "protected“ specimen
      - repeatidly positive on direct examination
      - growing rapidly in culture to the "bottom of the tube »
- Absence of other pathogens +++

Pulmonary aspergillosis

Diagnostic methods

- Biological and immunological diagnosis
  - antigenemia (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
  - PCR diagnosis?
  - specific IgE (RIA, ELISA):
    - indicator of an immediate hypersensitivity
    - interest of associated skin testing
  - specific IgG assay:
    - screening by indirect hemagglutination (> 1 / 160);
    - confirmed by immunoprecipitation (≥ 3 arcs catalase),
    - indicator tissue infection
    - interest of associated skin testing

Pulmonary aspergillus infection

Diagnostic methods: depending on the situation

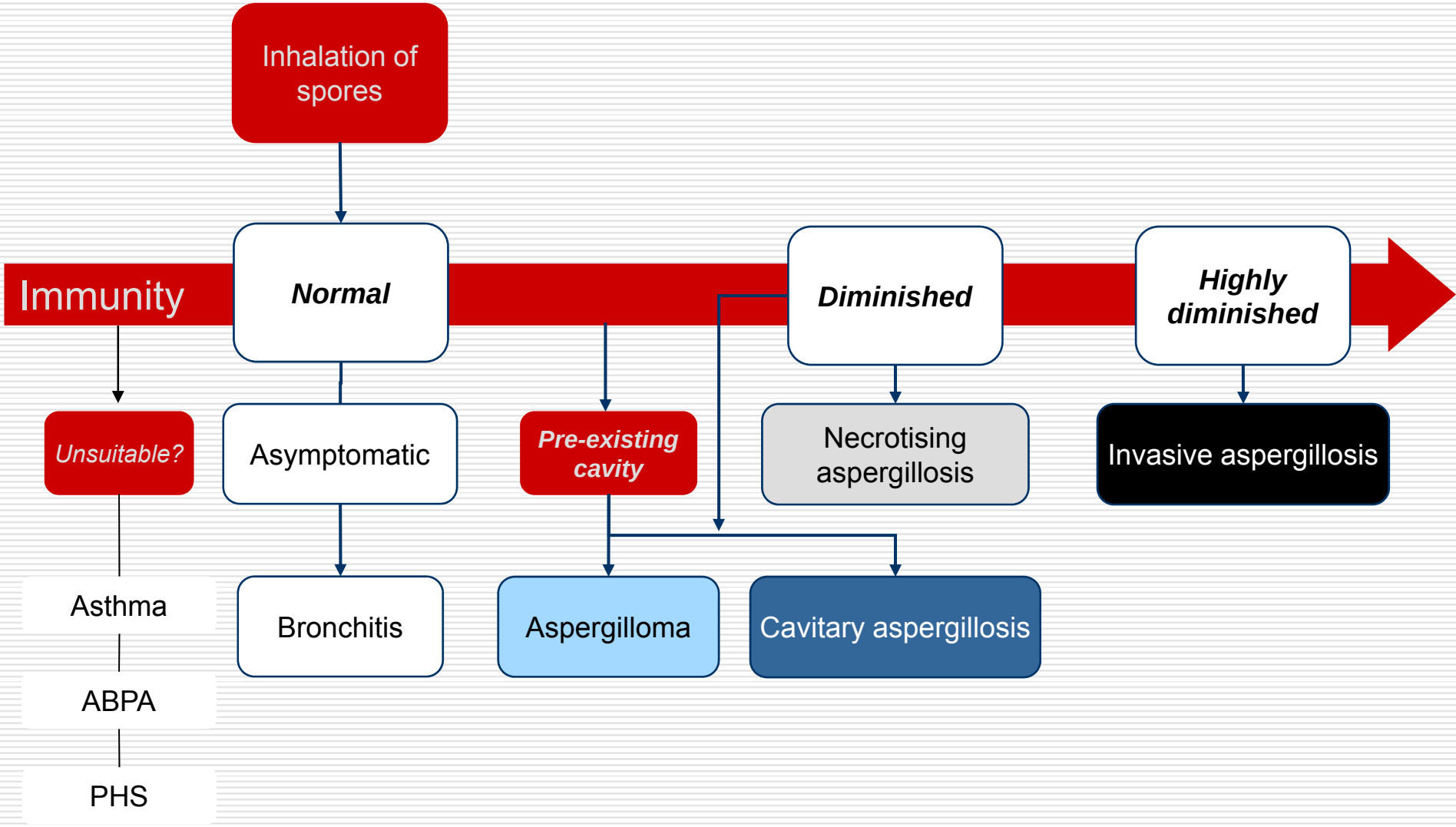
	Aspergilloma	CCPA	CNPA	Invasion
CT-scan				
- mycetoma	+++	++	+	-
- pneumonia	-	++	++	++
- necrosis	-	+	++	++
Direct exam	-	±	++	++
Culture	±	++	++	++
Antigenemia	-	-	±	++
IgG	++	+++	++	-

Chronic pulmonary aspergillosis

- Numerous clinical, radiological, anatomical and pathological entities
  - Simple pulmonary aspergilloma
  - Complex pulmonary aspergilloma
  - Chronic, fibrosing or pleural cavitary pulmonary aspergillosis
  - Semi-invasive pulmonary aspergillosis
  - Chronic necrotising pulmonary aspergillosis
  - Pseudomembranous tracheobronchitis caused by Asp.
  - Invasive pulmonary aspergillosis

Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003

Anatomical and clinical continuum



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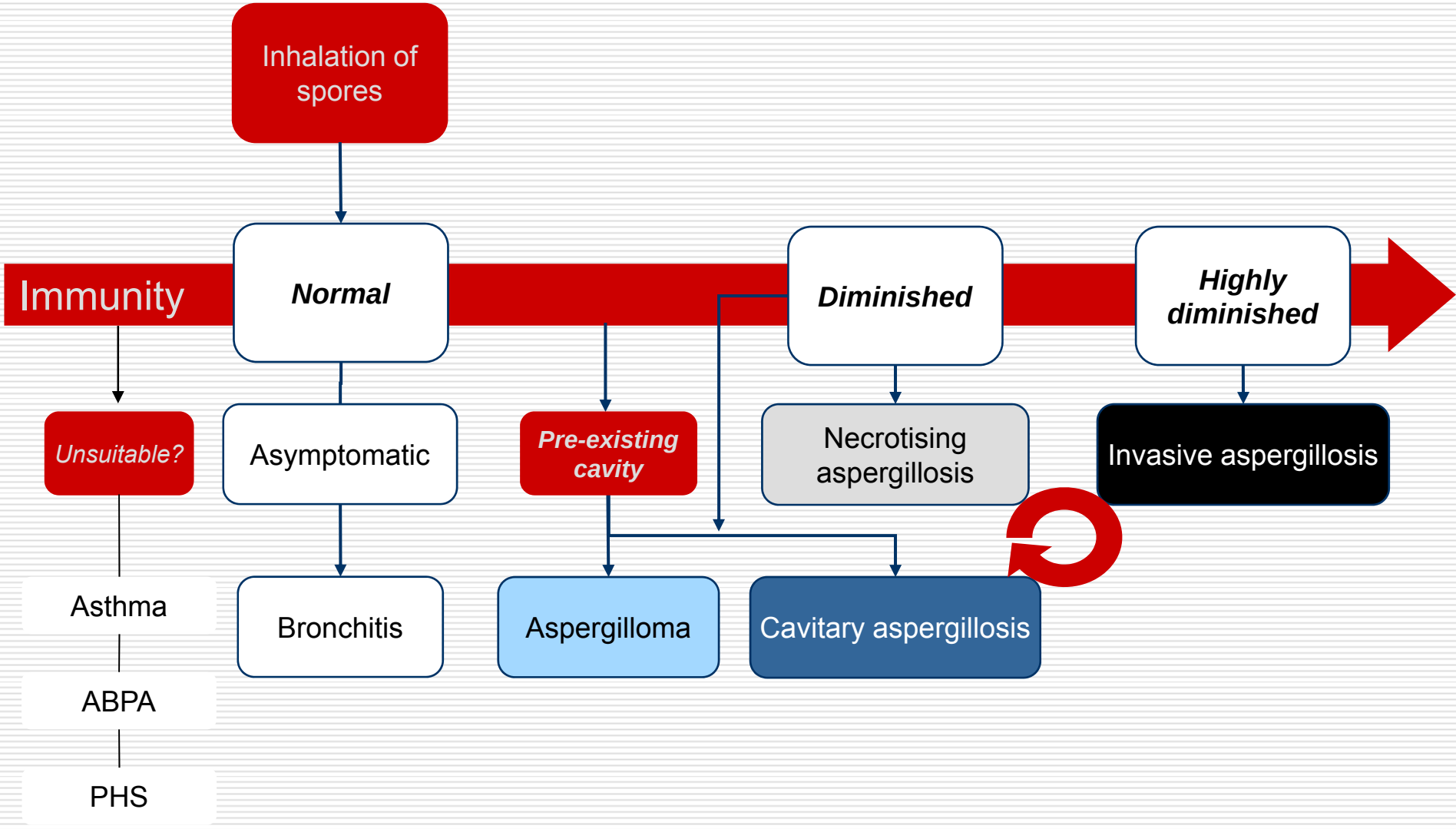

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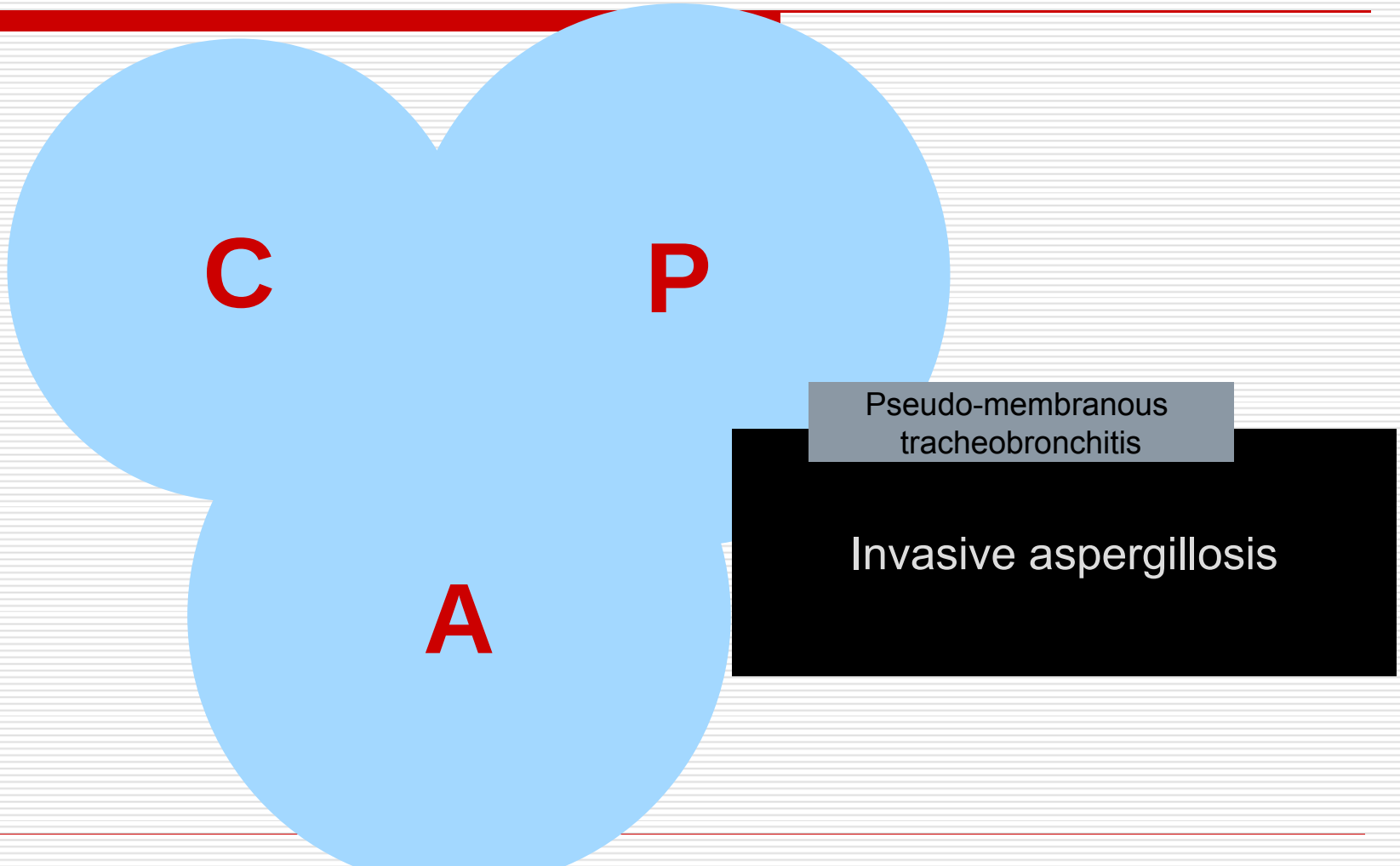
Chronic pulmonary aspergillosis



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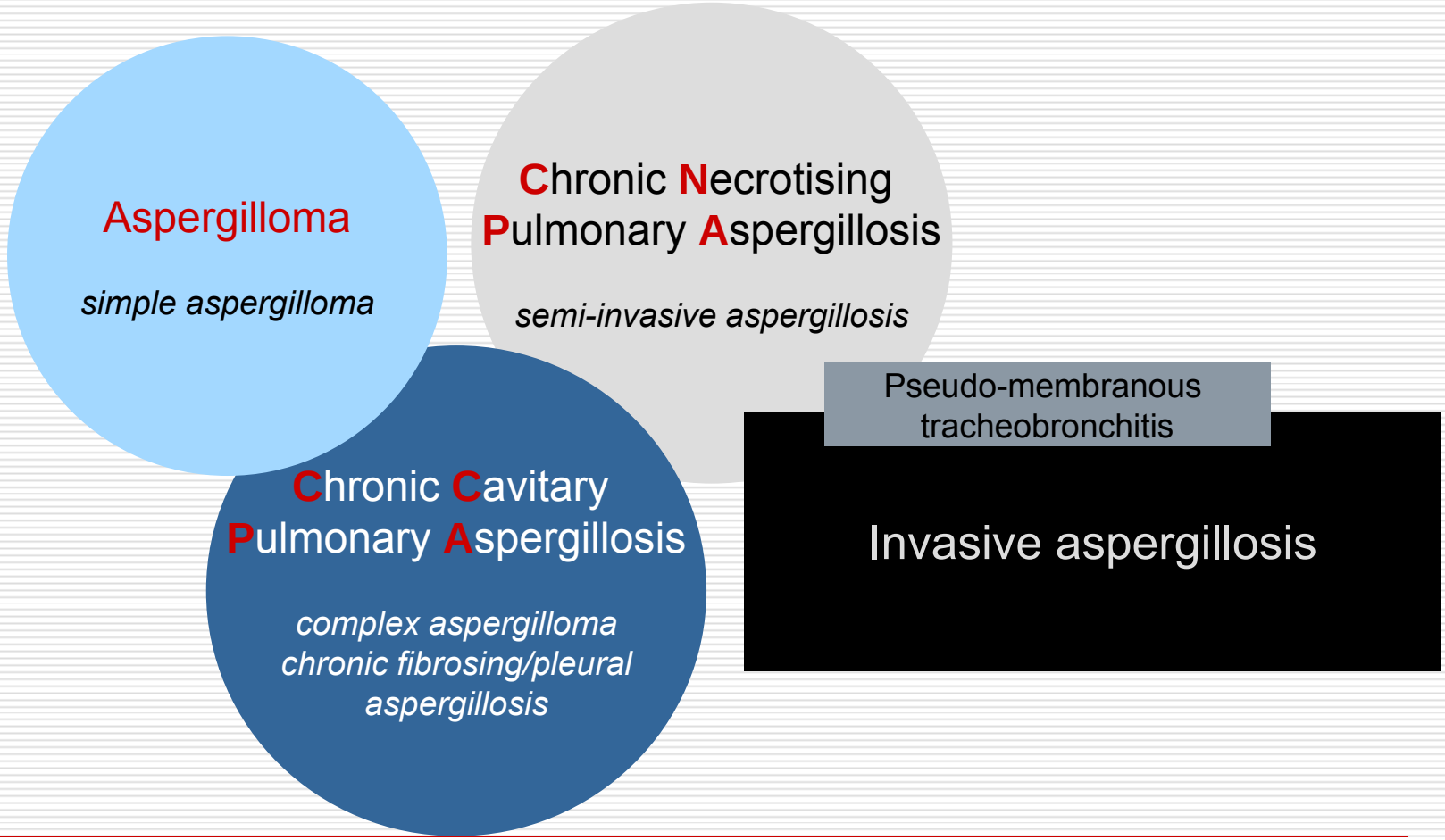
Chronic pulmonary aspergillosis

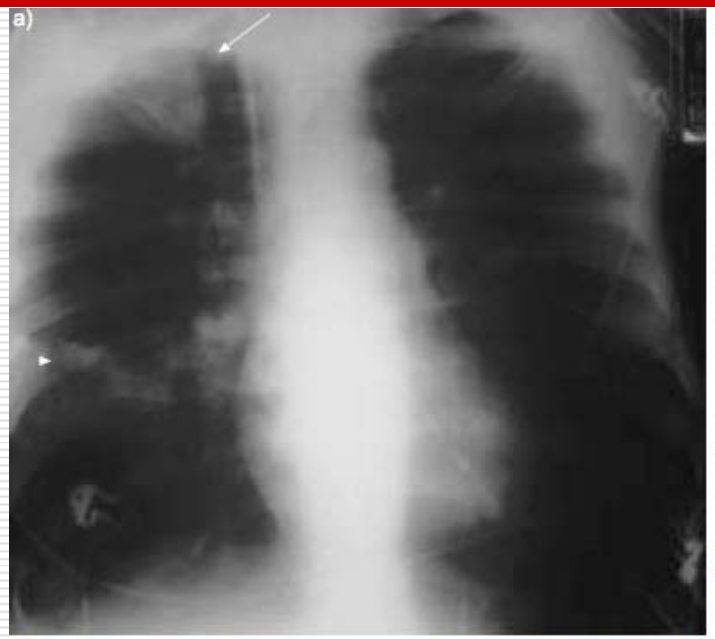


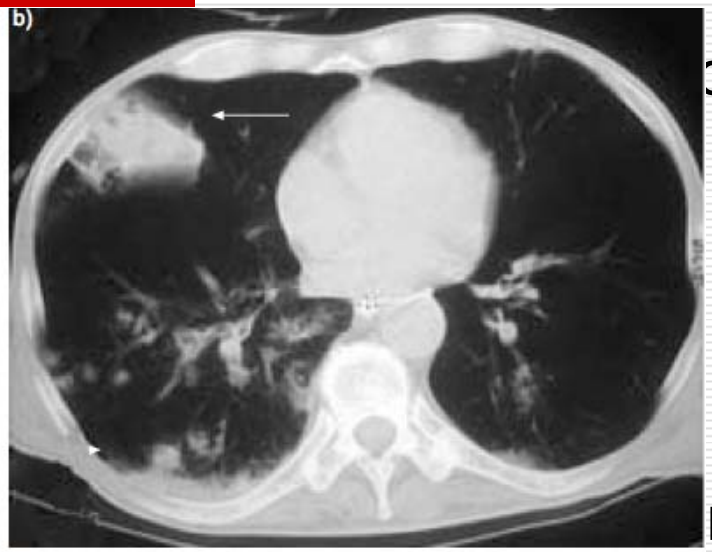
Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003

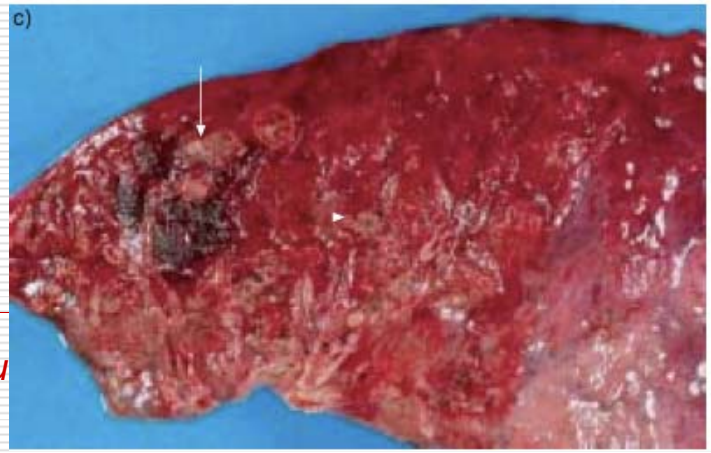
Invasive aspergillosis in COPD

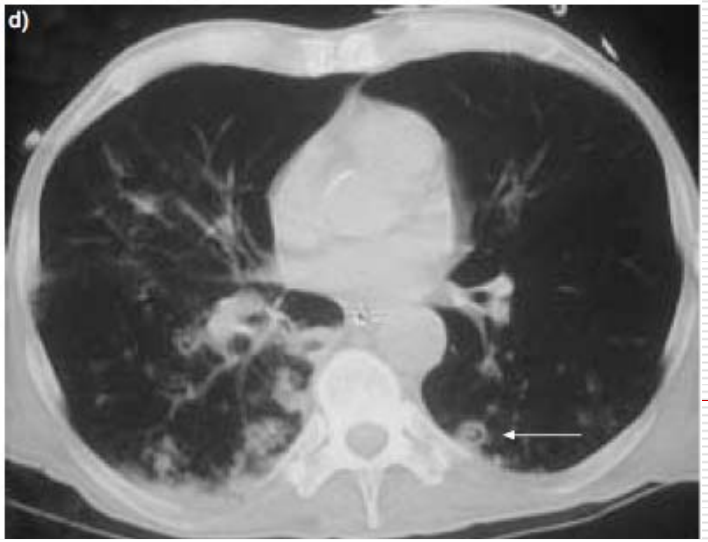
A new clinical entity?

- otics
- ng









Bulpa P, Eu

CPA, an anatomical and clinical continuum

- Underlying lung disease
  - active or sequel tuberculosis
  - bronchiectasis, COPD
  - sarcoidosis
- Comorbidities
  - smoking
  - alcohol, diabetes, malnutrition
- Prolonged exposure to steroids
  - inhaled
  - oral, small doses

Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003

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

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Adapted from Smith NL, Eur Respir J 2010

Lung disease, 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)*
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

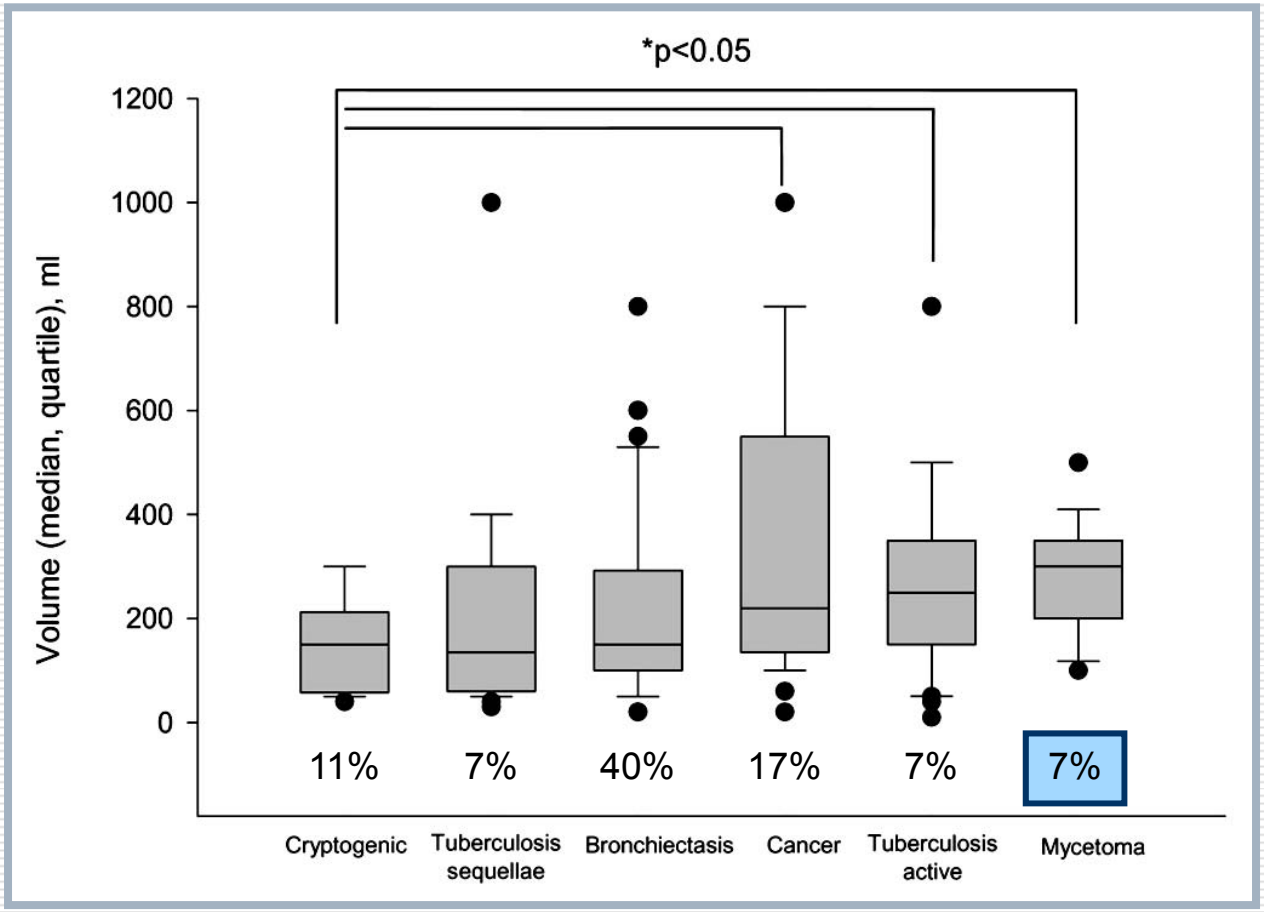
General symptoms and haemoptysis

	Chen (1997)	**Nam** (2003)	**Camuset** (2007)	**Saraceno** (1997)
Type of aspergillosis	*Aspergilloma (n=72)*	*CPA (n=43)*	*CNPA (n=15)* *CCPA (n=9)*	*CNPA (n=59)*
Cough	18 (25%)	19 (79%)	19 (79%)	33 (56%)
Expectoration	-	19 (79%)	19 (79%)	26 (44%)
Dyspnoea	4 (5.6%)	21 (87%)	21 (87%)	4 (7%)
Chest pain	3 (4%)	8 (33%)	8 (33%)	15 (25%)
Haemoptysis	**61 (91%)**	**9 (37%)**	**9 (37%)**	**4 (7%)**
Fever (T°C ≥ 38)	4 (5.6%)	7 (29%)	7 (29%)	40 (68%)

Chen J, Thorax 1997; Nam HS, Int J Infect Dis 2010; Camuset J, Chest 2007; Saraceno J, Chest 1997

Recurrent and severe haemoptysis

n=650



Farthoukh M, Respir Research 2005

Therapeutic strategy

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

Therapeutic strategy

- Treatment of underlying condition, comorbidities and haemoptysis
  - Specific treatments for underlying lung disease and comorbidities
  - Respiratory rehabilitation and re-nutrition
  - Discontinuation or reduction of corticosteroids
  - Treatment of haemoptysis by endovascular procedure
- Treatment of aspergillosis
  - Curative treatment = surgery

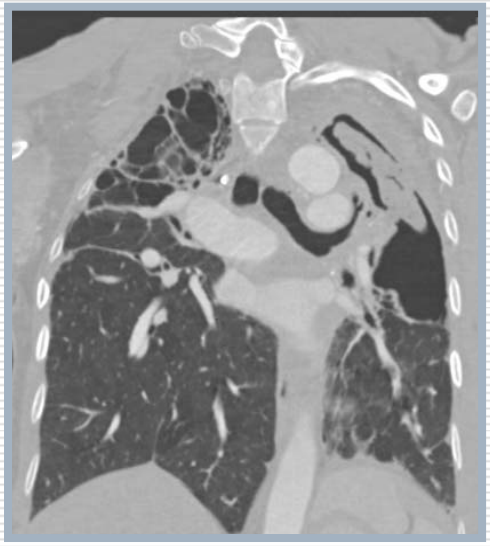
    - eradicate aspergillosis

    - avoid relapse?
  - Palliative treatment

    - antifungal treatment, systemic >>>> local

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

Endovascular treatment

- Efficiency of systemic arterial embolization

Series	n/N	1 month relapse	Late relapse
Ulfacker (1985)	8/64	0/8	4/8 (2 deaths)
Corr P (2006)	12/12	1/12	ND
Khalil A (2008)	18/470	4/14 *(1 BAE)* 2/14 *(2 BAE)*	3/5

"n" aspergilloses/"N" haemoptyses

Ulfacker R, Radiology 1985; Corr P, Cardiovasc Intervent Radiol 2006; Khalil A, AJR 2010

Surgical treatment

- Avoid haemoptysis and loco-regional extension, permanent cure, improve survival
- No randomised study
- Numerous possible procedures:
  - lobectomy, pulmonectomy, atypical resection, cavernostomy, thoracoplasty, etc.

Camuset J, Rev Pneumol Clin 2007

Surgical treatment

- Mortality 1 to >15%
- Morbidity 9 to 69% !!!
  - morbidity/mortality much lower with simple aspergilloma
  - primary morbidities and late mortality more likely linked to the underlying lung disease responsible and comorbidities
- Need for strict preoperative evaluation:
  - PFT, DLCO, V/Q scintigraphy, echocardiography, VO2 max
  - depending on comorbidities and the respiratory disease responsible

Therapeutic approach, aspergilloma

- Simple aspergilloma
  - Spontaneous lysis in 7 to 10% of cases

(BTSA, Tubercle 1970; Hammerman KJ, Chest 1973)

  - Clinical/radiological stabilisation in 25% of cases
  - No proof of efficiency of antifungal treatments by systemic route
    - Amphotericin B *(Hammerman KJ, Am Rev Respir Dis 1974)*
    - Itraconazole *(Campbell JH, Thorax 1991)*

➡ Therapeutic abstention…

Soubani O, Chest 2002; Judson MA, Curr Opin Investig Drugs 2001

Therapeutic approach, aspergilloma

- Simple aspergilloma
  - Loco-regional complications and intermediate forms progressing to other aspergillus diseases in 65 to 75% of cases
  - Unpredictable risk of severe (>30%) and fatal haemoptysis

➡ Indication for surgery…

Stevens DA, Clin Infect Dis 2000

Therapeutic approach, CCPA and CNPA

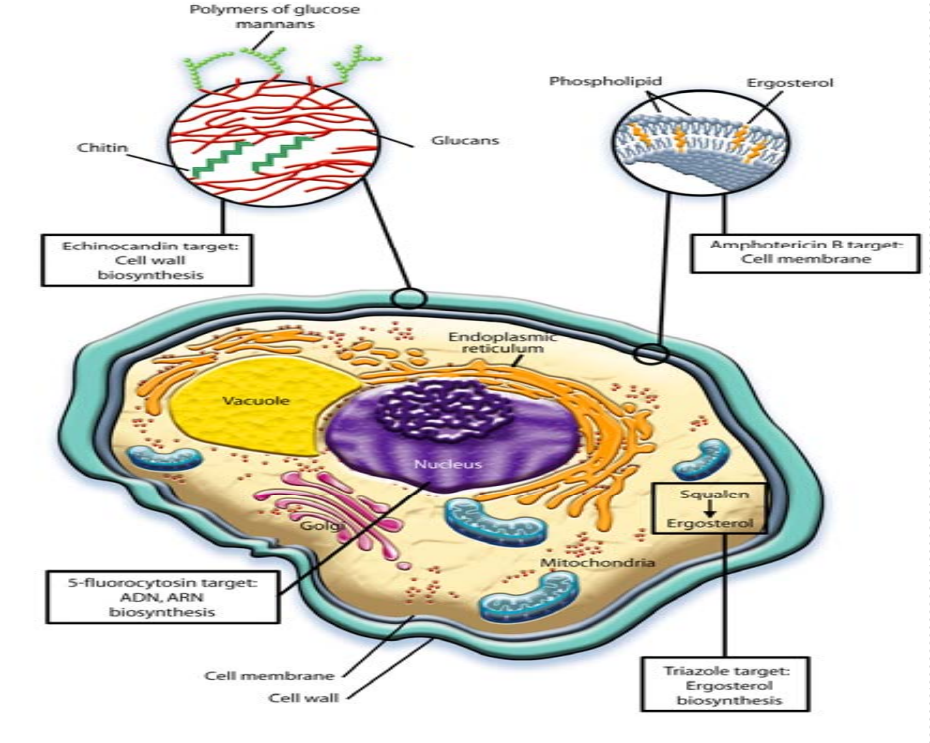
- Chronic cavitary/necrotising aspergilloses
  - Therapeutic strategy not codified
  - No methodologically satisfactory study
  - Place for surgery?
  - Indication for systemic antifungal treatment? (potentially combined with surgery if it is possible)

➡ Multidisciplinary approach…

Binder RE, Medicine 1982; Endo S, Ann Thorac Surg 2001

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



From Sanglard D. JIDIF: Optimed Ed. 2003: 29-45

Walsh T in IDSA Guidelines, Clin Infect Dis 2008

Local antifungal treatment

- Injection of Ampho. B in the aspergillus cavity or in the bronchus draining the aspergilloma in inoperable patients
  - Control of haemoptysis
  - Disappearance of the aspergilloma and/or negative result on aspergillus serology in 2/3 cases
- Limits
  - Manual preparation of Ampho. B paste
  - Case series, single centre studies

    - non-controlled?; small number of patients?
  - Complications: pulmonary abscess and anaphylactic shock

Giron JM, Radiology 1993; Yamada H, Chest 1993; Giron J, J Radiol 1998; Ikemoto I, Intern Med 2000

Systemic antifungal treatment, IV

Studies	Treatment	Type	n	Efficiency	Comments
Denning *Case series*	amphotericin B	CPA	11	82%	Definition of efficiency ?
Nam *Case series*	amphotericin B	CNPA ?	4	All dead	-
Izumikawa *Case series*	micafungin *± other antifungal*	CCPA	9	78%, "success at EOT"	Association with other antifungals in 5/9 4-week treatment (29-96 dys)
Kohno *Prospective trial*	micafungin *line?*	CPA *Aspergilloma* *CNPA*	31 *22* *9*	60%, "success at EOT" *55%* *67%*	Different response criteria for CNPA and aspergilloma Treatment duration: 13-56 dys
Khono 2 *Prospective controlled trial*	micafungin *(vs voriconazole)*	CPA	50/96	60% "success at 4 weeks"	Only 4-week treatment Very subjective criteria of evaluation

Denning D, Clin Infect Dis 2003; Nam HS, Int J Infect Dis 2010; Izumikawa K, Med Mycol 2007; Kohno S, Scand J Infect Dis 2004; Kohno S, J Infection 2010

Systemic antifungal treatment, oral

Studies	Treatment	Type	n	Efficiency	Comments
De Beule *Prospective trial*	itraconazole *>40% post ampho.*	Aspergilloma CNPA	42 44	**30%**, radiological 66%, radiological	Diagnostic criteria? Dose, duration? Evaluation of efficacy? Endpoints?
Dupont *Prospective trial*	itraconazole *line?*	Aspergilloma CNPA	14 14	**14%**, radiological 50%, radiological	Evaluation of efficiency? Endpoints? Treatment duration: aspergilloma=7 months (2-13); CNPA=5.7 months (2-11.5)
Nam *Case series*	itraconazole *line ?*	CNPA ?	39	38%, "success after ≥ 3 mo"	Probably CPA rather than CNPA Treatment duration: 6 months (IQR=6-12)

De Beule K, Mycosis, 1988; Dupont B, J Am Acad Dermatol 1990; Nam HS, Int J Infect Dis 2010

Systemic antifungal treatment, oral

Studies	Treatment	Type	n	Efficiency	Comments
Felton *Case series, National Referral Centre*	posaconazole *28% post itra- or voriconazole* *46% after toxicity*	CPA	79	61%, "success at 6 mo."	Treatment duration: 7 mo. (1-11) for naive and 7.8 mo. (<1-53) for pre-treated ≈15% of patients need dose modification after evaluation of plasma [posa.]

Felton T, Clin Infect Dis 2010

Systemic antifungal treatment, oral

Studies	Treatment	Type	n	Efficiency	Comments
Jain *Case series*	voriconazole *≈100% post itra.*	CCPA	11	64%, "clinical success at 3 mo."	No radiological evaluation
Sambatakou *Prospective trial*	voriconazole *27% post itra.*	CPA	15	67%, "success at EOT"	Pos-hoc centralised review by *D Denning* Treatment duration: 3.6 months (<1-4)
Camuset *Case series*	voriconazole *46% post itra.*	CPA *CNPA* *CCPA*	24 *15* *9*	58%, "success at EOT" *67%* *44%*	Centralised review by 2 investigators Very stringent diagnostic criteria Treatment duration: 6.5 months (4-36) P=0.04, in favor of CNPA
Khono 2 *Prospective controlled trial*	voriconazole *(vs micofungin)*	CPA	46/96	59% "success at 4 weeks"	Only 4-week treatment Very subjective criteria of evaluation

Jain LR, J Infect 2006; Sambatakou H, Am J Med 2006; Camuset J, Chest 2007; Saito Y, ICAAC, in proceedings 2009

Systemic antifungal treatment, oral

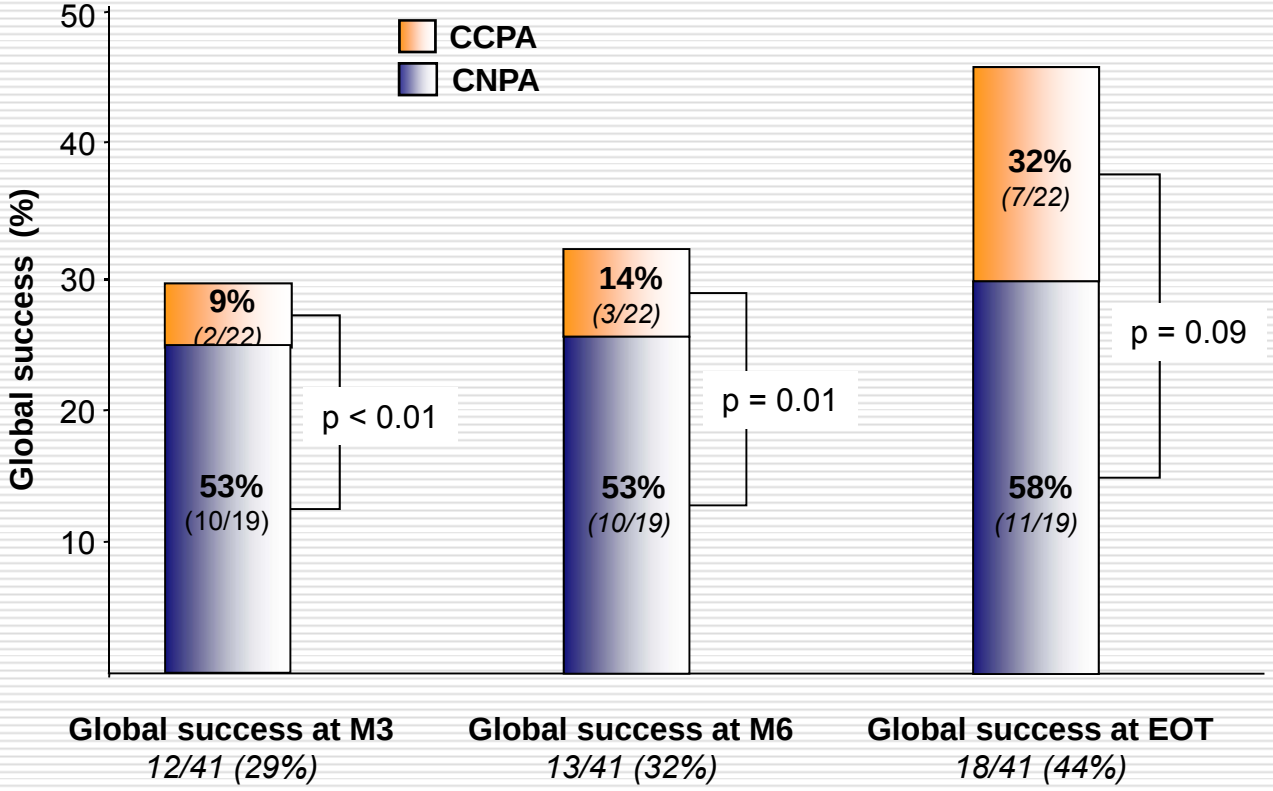
- Prospective, non-comparative, multicentre study
- Diagnostic criteria:
  - clinical+CT+mycological+serology
    - CNPA, n=19
    - CCPA, n=22
- No pre-treated patients
  - severe haemoptysis
  - eligible for surgery
  - prior systemic treatment
- Voriconazole
  - 200 mg x 2/d, 6 months
  - >6 months and <12 months
  - duration: 8.3 months (<1-13.5)
- 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, for the VERTIGO trial group

Systemic antifungal treatment, oral

- Efficiency at different endpoints



Cadranel J, for the VERTIGO trial group

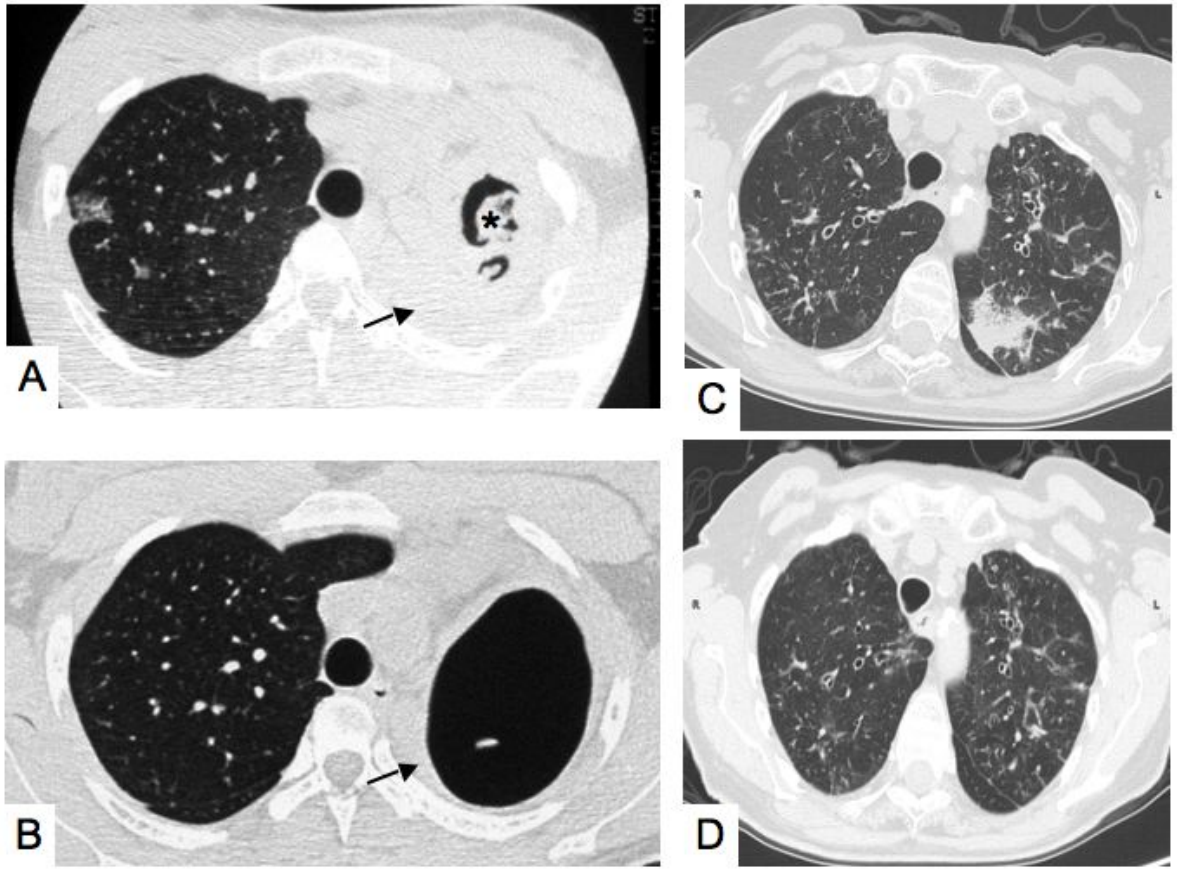
Systemic antifungal treatment, oral

- Myc
  - A
- Rac

cation of
M6 and EOT

n=31 patients)

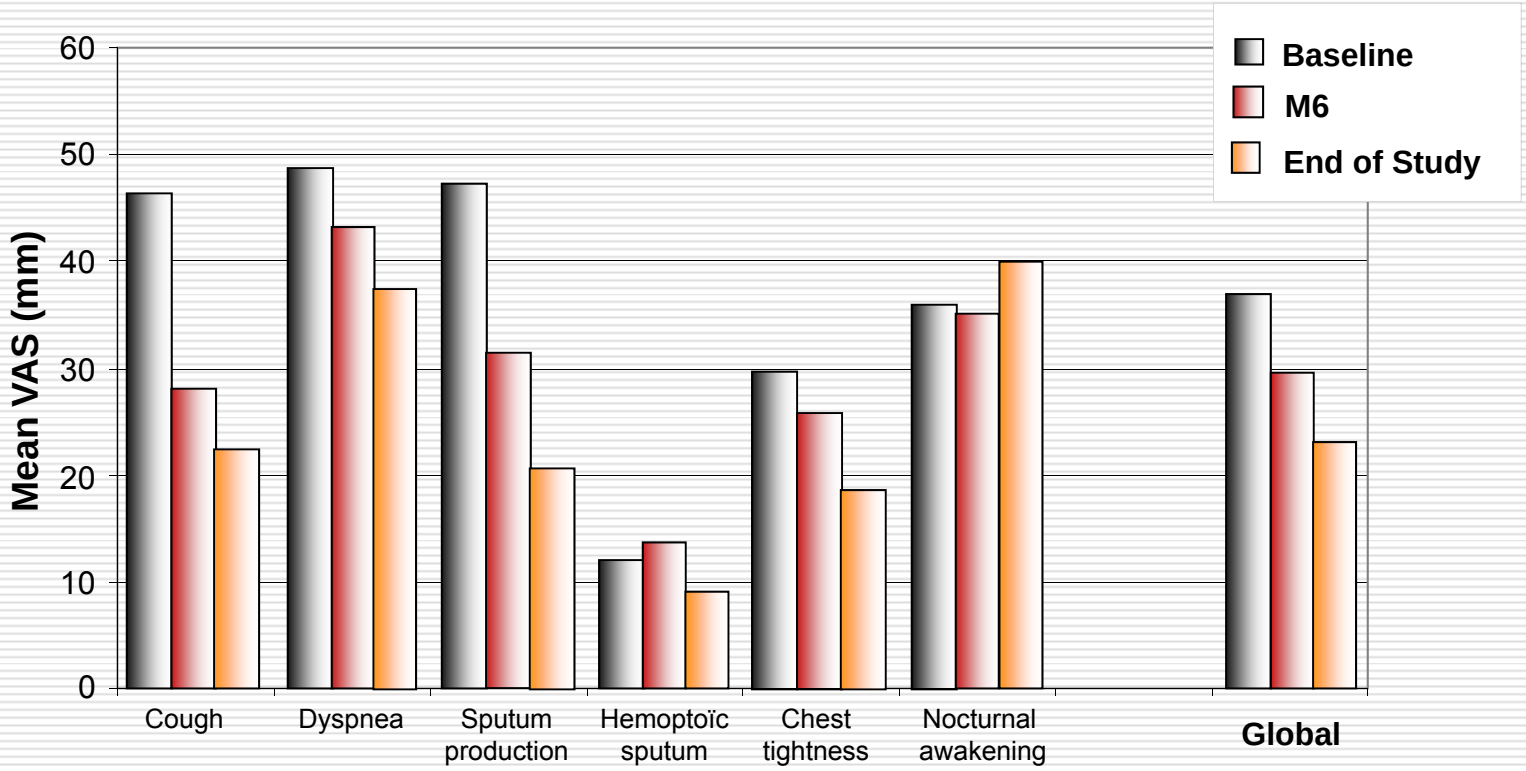
PA
PA



Cadranel J, for the VERTIGO trial group

Systemic antifungal treatment, oral

- Quality of Life



Cadranel J, for the VERTIGO trial group

Systemic antifungal treatment, oral

- Safety results
  - Treatment related adverse events with a frequency greater than 5% (i.e. in at least 3 patients):
    - visual disturbances (21%),
    - photosensitivity reactions (19%),
    - blurred vision (12%),
    - constipation, vomiting, gamma-GT increased (10% each),
    - chills, decreased appetite, headache, insomnia (8% each)
    - vertigo, nausea, cholestasis, weight loss, anorexia (6% each)
  - These side effects are consistent with the known adverse event profile of voriconazole
- Overall survival (88%)
  - 5 patients died during the study from underlying disease (bacterial pneumonia, pneumothorax, chronic respiratory insufficiency, ovarian cancer, septic shock.) None attributable to CPA.

Systemic antifungal treatment

- According to guidelines from IDSA experts

Type	Treatment		Comments
	Standard	Options	
Invasive aspergillosis	**voriconazole**	amphoB, caspo., mica., posa., itra.	
Aspergilloma	**abstention or surgery**	itraconazole or voriconazole	**medical treatment?**
Chronic necrotising aspergillosis	**voriconazole**	amphoB, caspo., mica., posa., itra.	prolonged oral treatment
Chronic cavitary aspergillosis	**itraconazole or voriconazole**	amphoB, caspo., mica., posa.	prolonged oral treatment **surgery?**

From Walsh T in IDSA Guidelines, Clin Infect Dis 2008

Managing chronic pulmonary aspergillosis infection

- Heterogeneous clinical entities
  - comorbidities ± pulmonary disease
  - pay attention to the association between COPD and steroids
- Surgery alone rarely possible
- Most often need a multidisciplinary approach:
  - surgeon, radiologist, functionalist, pneumologist…
  - impact of “booming“ in antifungal armamentarium
  - efficiency of triazole particularly in necrotizing forms
  - therapeutic sequence to define
- Important morbidity/mortality
  - mainly due to comorbidities and underlying diseases