Managing chronic pulmonary aspergillosis

Current data and recent clinical results with voriconazole

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Plan

- Rapid overview of Chronic Pulmonary Aspergillosis (CPA)
- Current therapies, with a special focus on drug treatments
- Results of the VERTIGO trial

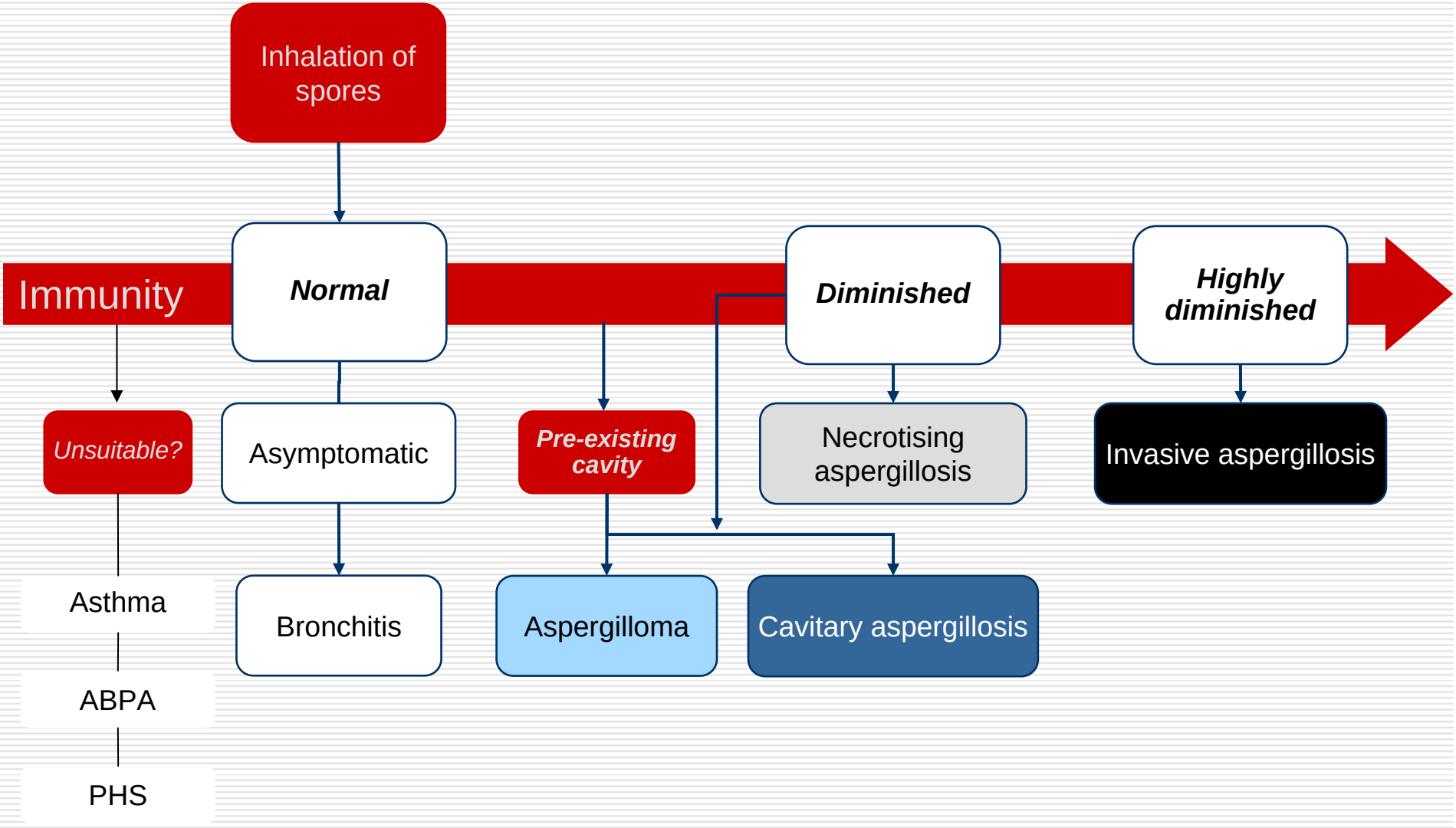
Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003

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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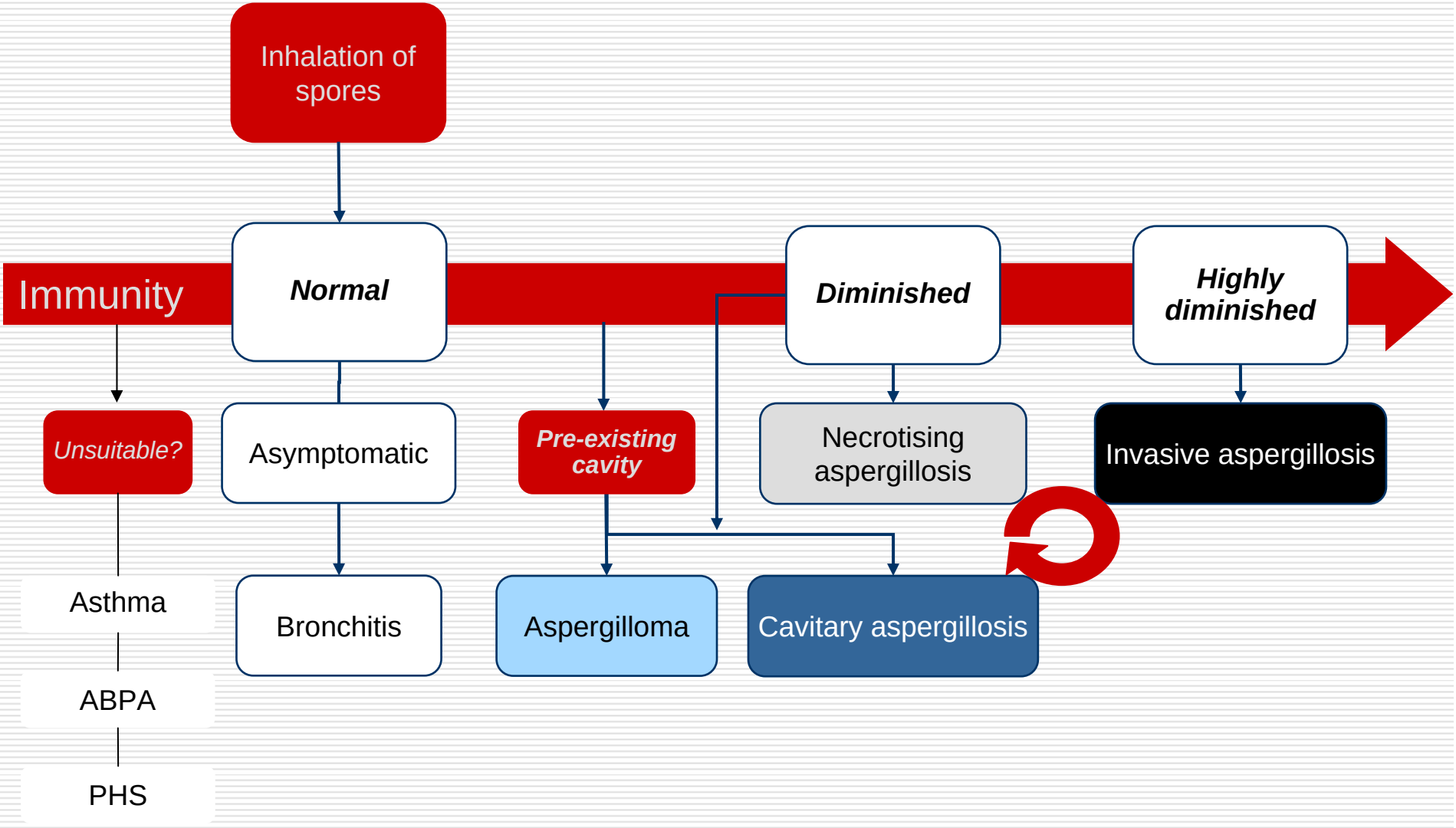

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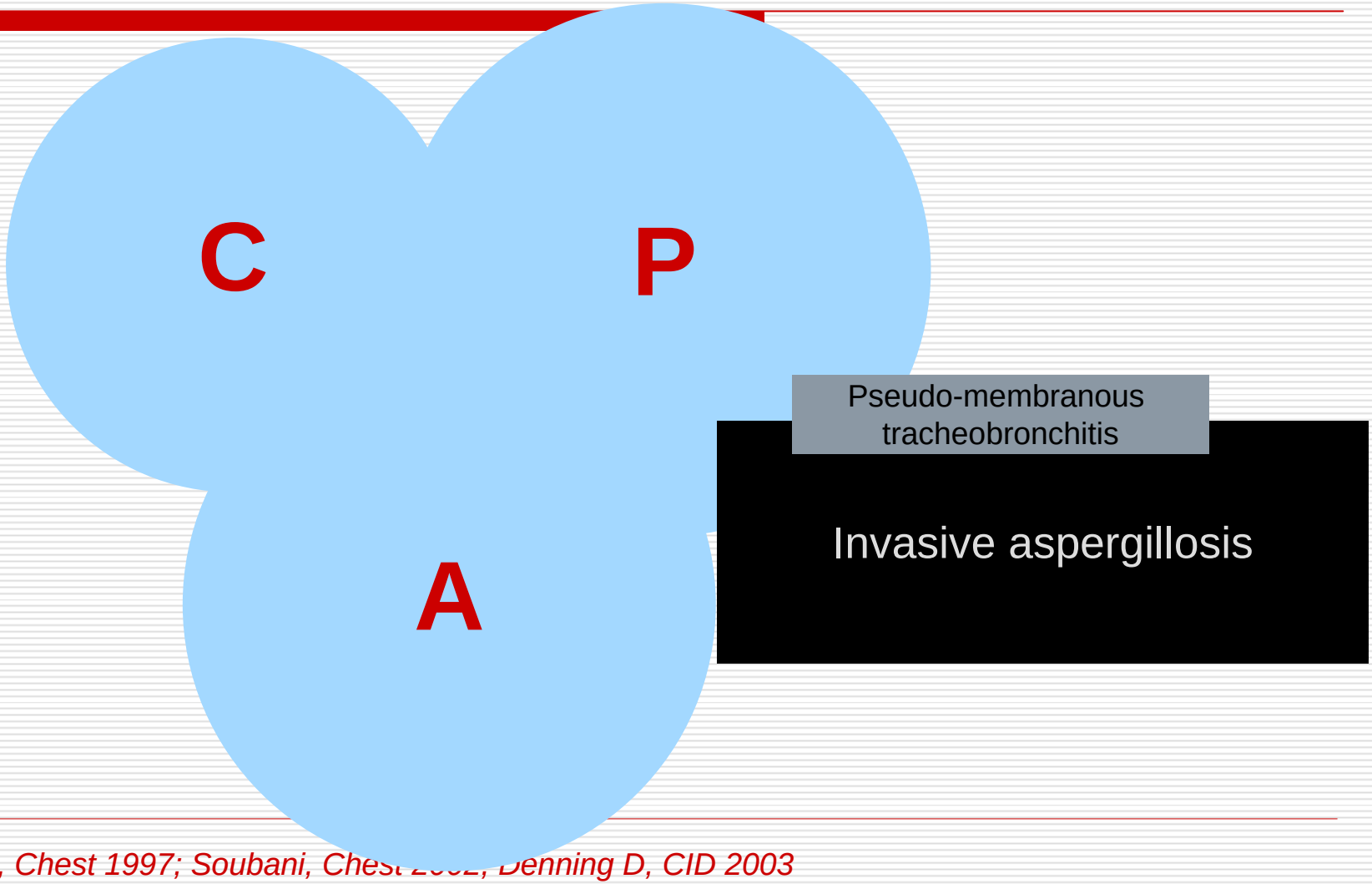
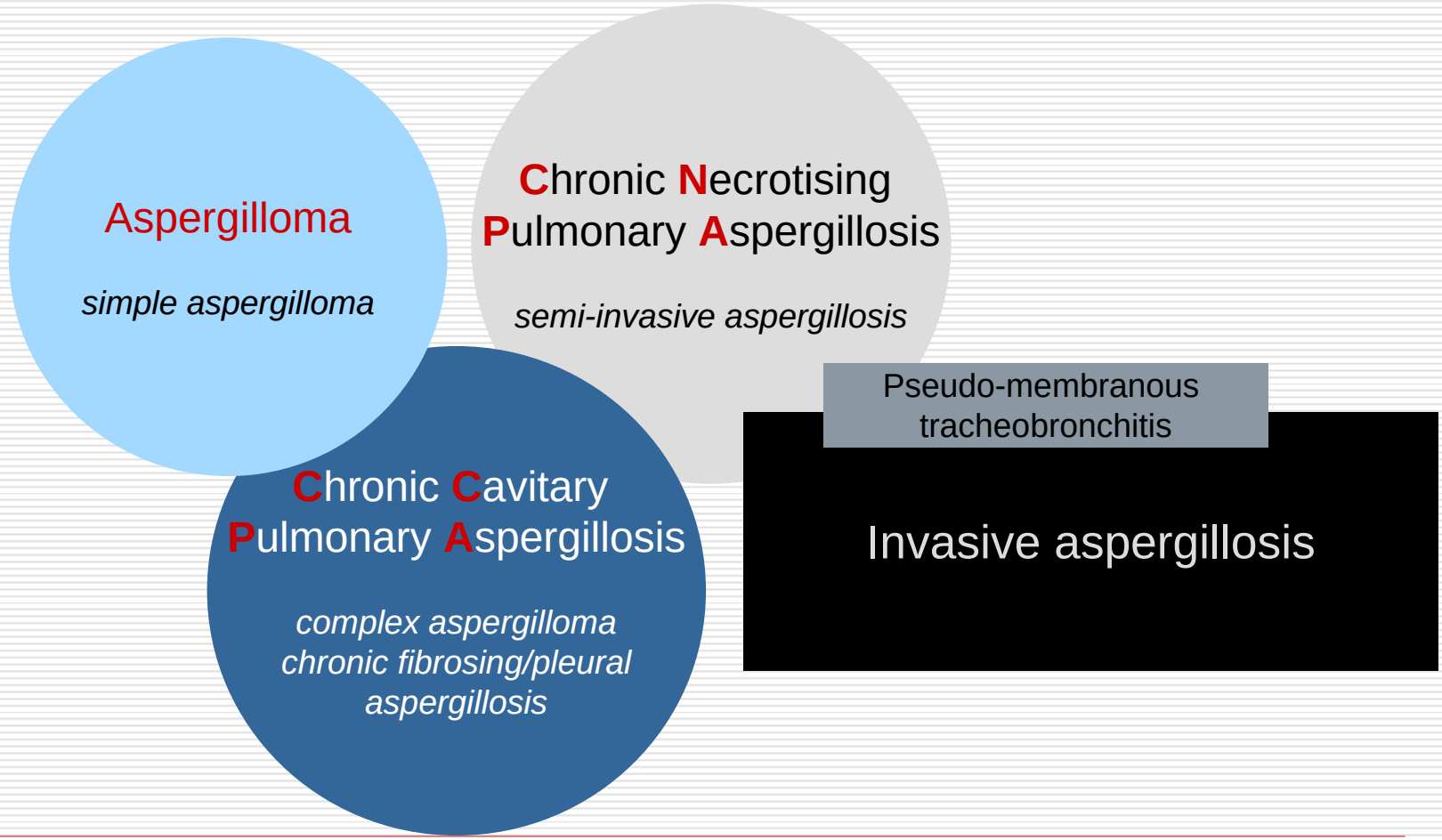
Chronic pulmonary aspergillosis



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

Chronic pulmonary aspergillosis



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

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

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
  - 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

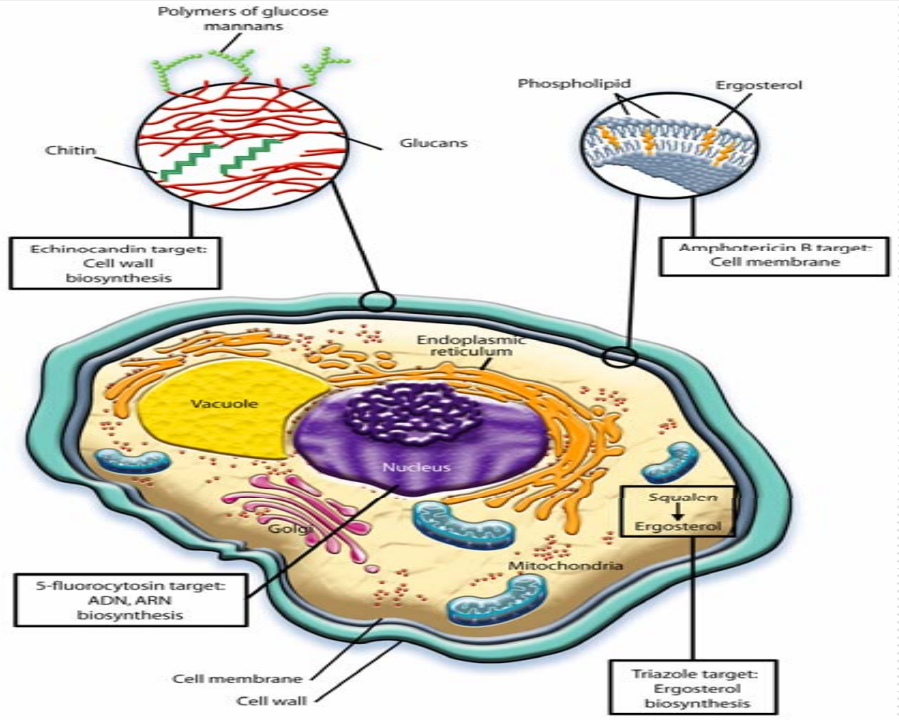
- Chronic cavitary/necrotising aspergilloses
  - Therapeutic strategy not codified
  - No methodologically satisfactory study
  - Place for surgery?
  - Indication for systemic antifungal treatment? (potentially combined with surgery if it is possible)

➡ 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
Kohno 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, Journal of Infection, in press

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, in press, by courtesy of David Denning

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
Kohno 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; Kohno S, Journal of Infection, in press

VERTIGO trial

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:

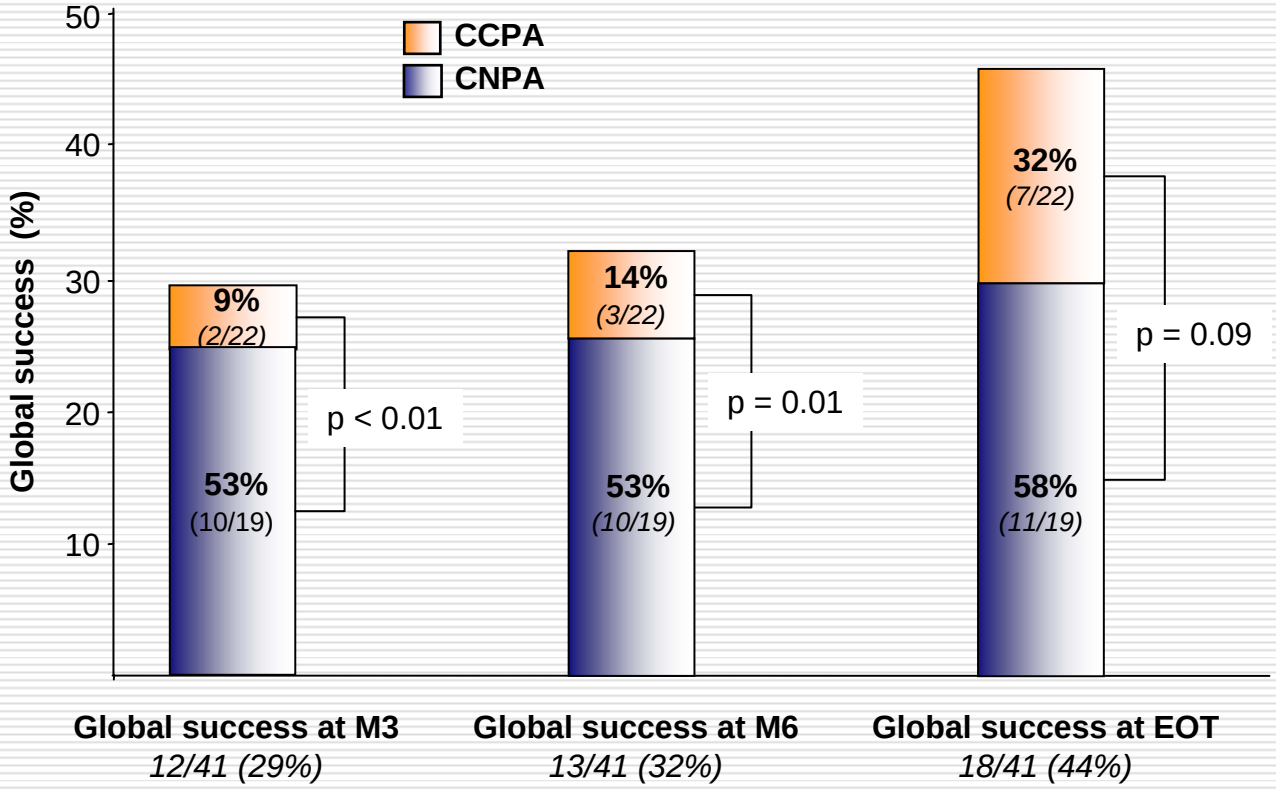
    - CT improvement (>50%) + mycological eradication at 6 months > 30%
  - secondary:
    - radiological efficiency
    - quality of life and safety
    - relapse at 6 months post EOT
    - survival

Cadranel J, for the VERTIGO trial group

VERTIGO trial

Systemic antifungal treatment, oral

- Efficiency at different endpoints



Cadranel J, for the VERTIGO trial group

Systemic antifungal treatment, oral

- Comparison with other drugs and other trials

Studies	Treatment	Type	n	Efficiency
De Beule *Prospective trial*	itraconazole *>40% post ampho.*	CNPA	44	66%, radiological
Dupont *Prospective trial*	itraconazole *line?*	CNPA	14	50%, radiological
Sambatakou *Prospective trial*	voriconazole *27% post-itraconazole*	CPA	15	67%, "success at EOT"
Kohno 2 *Prospective controlled trial*	voriconazole *(vs micofungin)* *no pre-treated*	CPA	46	59% *"success at 4 weeks"*
Vertigo trial *Prospective trial*	voriconazole *no pre-treated*	CPA *CPPA* *CNPA*	41 *19* *22*	44% *"success at 6 months"* *32%* *58%*

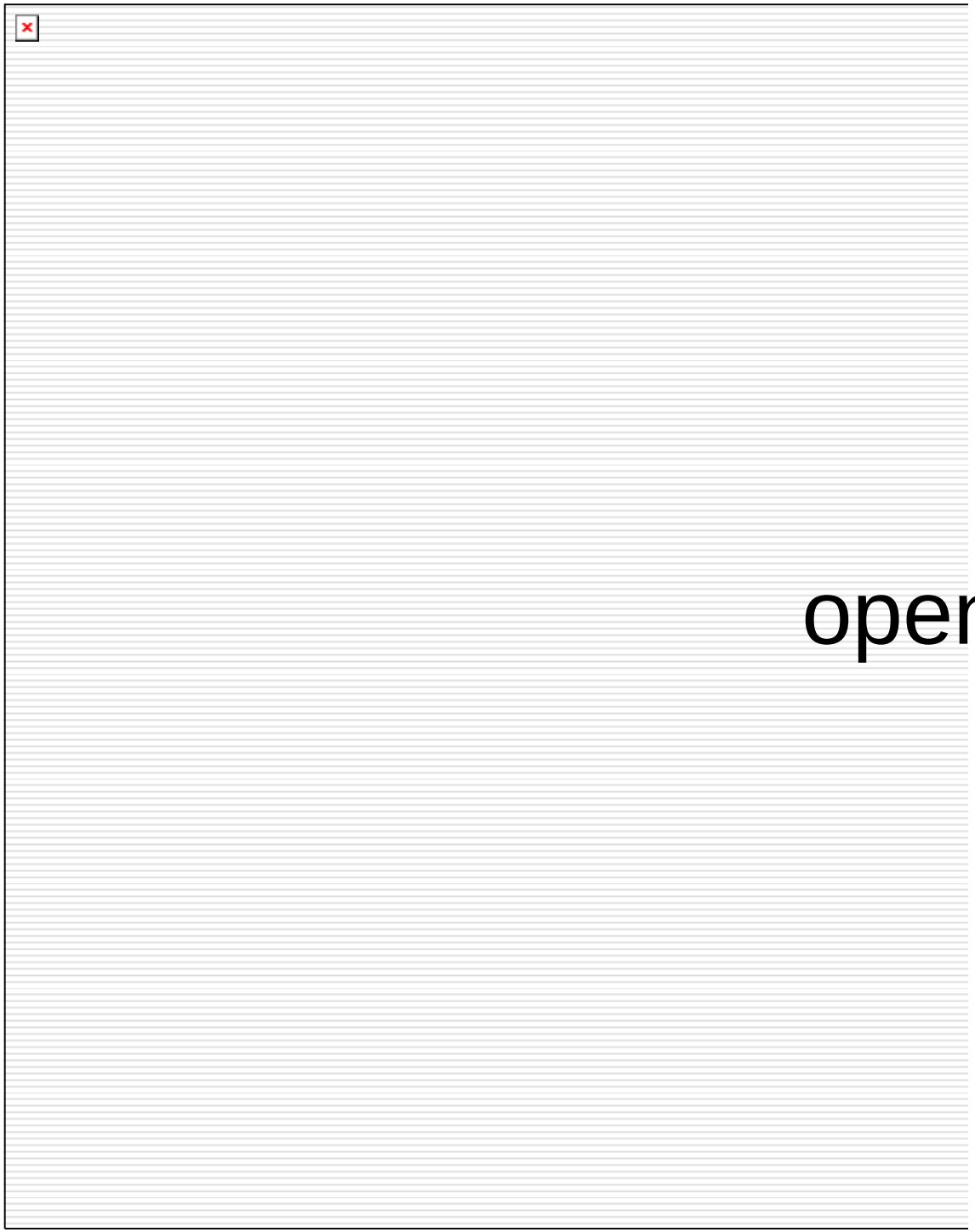
De Beule K, Mycosis, 1988; Dupont B, J Am Acad Dermatol 1990; Sambatakou H, Am J Med 2006; Kohno S, Journal of Infection, in press; Cadranel J, for the VERTIGO trial group

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



And now,
the subject is
open to discussion !

Chronic pulmonary aspergillosis

- Numerous clinical, radiological, anatomical and pathological entities
  - Simple pulmonary **aspergilloma**
  - Complex pulmonary aspergilloma
  - **C**hronic, fibrosing or pleural **C**avitary **P**ulmonary **A**spergillosis, **CCPA**
  - Semi-invasive aspergillosis
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  - Pseudomembranous tracheobronchitis caused by Asp.
  - Invasive aspergillosis

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

Systemic antifungal treatment, oral

- Comparison between itraconazole and voriconazole

Characteristics	Itraconazole	Voriconazole
Aspergillus sp. fungicide	?	+
Route of administration	oral	IV/oral
Absorption	± (meal rich in fats)	+++
Dosage	yes	no
Protein binding	+++ (98%)	++ (58%)
Hepatic metabolism	+++	+++
Urinary elimination	no	no
Toxicities	QT, anorexia, nausea, constipation, hepatitis, heart failure, alopecia	QT, anorexia, nausea, abdominal pain, hepatitis, vomiting, insomnia, vision disorder, photosensitisation

Systemic antifungal treatment

- Cavitary and fibrosing forms of CPA
  - Prolonged antifungal treatment (3 to 6 months) probably until a negative result on aspergillus serology or permanent in the context of long-term suppressive treatment
  - Itraconazole or Voriconazole
- Subacute invasive forms of CPA
  - Good response to antifungal treatment with negative result on serology without relapse
  - Voriconazole or Itraconazole
  - Voriconazole for perioperative treatment of CPA if surgery is possible, or exclusively in inoperable patients

From Walsh T in IDSA Guidelines, Clin Infect Dis 2008

Systemic antifungal treatment

- Previous retrospective studies
  - small numbers of patients
  - highly varied backgrounds
  - aspergillus diseases poorly defined
  - itraconazole alone or in combination with Ampho. B; duration of treatment poorly defined
  - endpoints poorly defined
- Prospective studies, few, non comparative and with low statistical power

Surgical treatment

Table II. – Postoperative mortality and morbidity from aspergillomas.

Authors [ref.]	Number of patients	Perioperative mortality n (%)	Perioperative morbidity n (%)
Kaestel et al. [9]	18	3 (16.7 %)	5 (28 %)
Babatasi et al. [10]	84	4 (4.8 %)	58 (69 %)
Regnard et al. [11]	89	5 (5.6 %)	30 (34 %)
Park et al. [12]	110	1 (1 %)	26 (29 %)
Personne et al. [22]	220	10 (4,5 %)	20 (9 %)

Post-operative mortality of simple aspergilloma is << 0%

Camuset J, Rev Pneumol Clin 2007

Surgical treatment

Table 1 Causes of surgical mortality in 41 patients with pulmonary aspergillomas reported in the liturature

Cause of death	*No. of patients*
Respiratory failure	16 (41.0%)
Bleeding	6 (15.4%)
Pneumonia	3 (7.7%)
Underlying disease	3 (7.7%)
Myocardial infarction	2 (5.1%)
Sepsis	2 (5.1%)
Aspergillosis	2 (5.1%)
Miscellaneous*	5 (12.8%)

* Including bronchopleural fistula, empyema, hypoxic encephalopathy, aortic graft thrombosis, disseminated intravascular coagulopathy.

Chen JC, Thorax 1997

Surgical treatment

Table 2 Surgical complications (n = 171) in 109 patients with pulmonary aspergillomas reported in the literature

Types of complication	*No. of complications*
Bleeding	38 (22.2%)
Residual pleural space	33 (19.3%)
Bronchopleural fistula	27 (15.8%)
Empyema	23 (13.5%)
Respiratory insufficiency	14 (8.2%)
Air leakage	11 (6.4%)
Wound infection	5 (2.9%)
Sepsis	3 (1.8%)
Pneumonia	2 (1.2%)
Atelectasis	2 (1.2%)
Retained secretions	2 (1.2%)
Miscellaneous*	11 (6.4%)

* Including pleural effusion, wound dehiscence, lobar infarction, paralytic ileus and unknown in seven patients.

Chen JC, Thorax 1997

Conflict of interest statement : J Cadranel

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