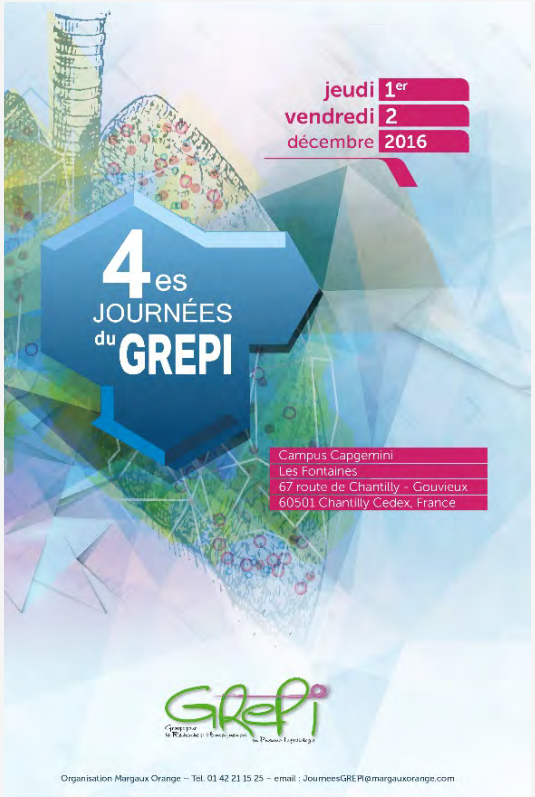


Faut-il rechercher l'*Aspergillus* dans les bronchopathies chroniques ? **Pour**

Pr Pierre-Régis Burgel

Hôpital Cochin, Paris

Liens d'intérêt

- **Aucun en relation avec cette présentation**

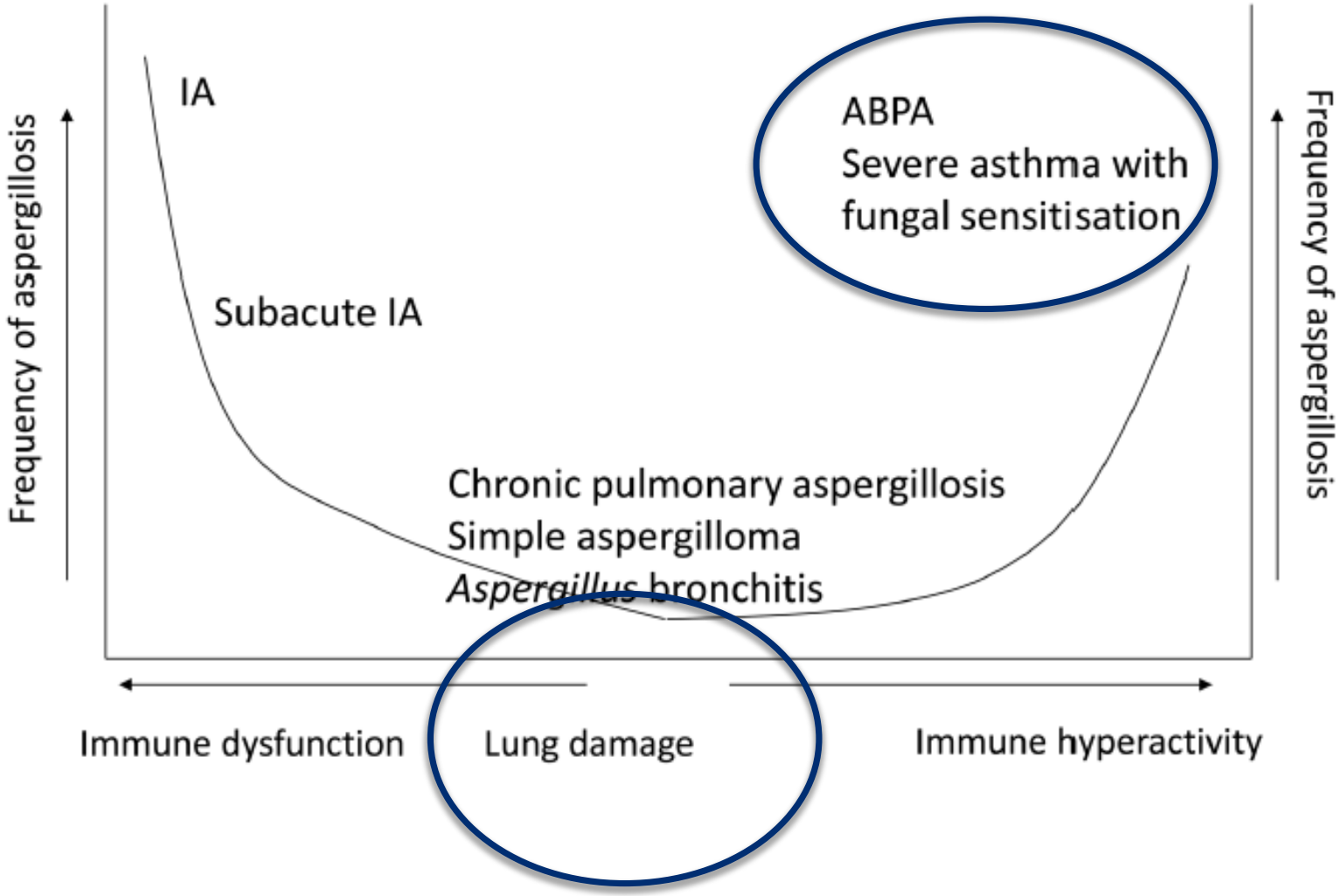
- **Autres (BPCO/mucoviscidose):**

  - **Board/conférences**: Aptalis, Astra-Zeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer, Vertex, Zambon

  - **Coordination essais cliniques**: Astra-Zeneca, Novartis

  - **Congrès**: Aptalis, Astra-Zeneca, Boehringer Ingelheim, Vertex, Zambon

Aspergillus: une expression variable en fonction du statut immunitaire



Kosmidis and Denning *Thorax* 2015; 70: 270-277

Quelle est l'ampleur du problème?

An estimation of burden of serious fungal infections in France

J.-P. Gangneux [a,*], M.-E. Bougnoux [b], C. Hennequin [c], C. Godet [d], J. Chandenier [e], D.W. Denning [f], B. Dupont [b], for the LIFE program, the Société française de mycologie médicale SFMM-study group [1]

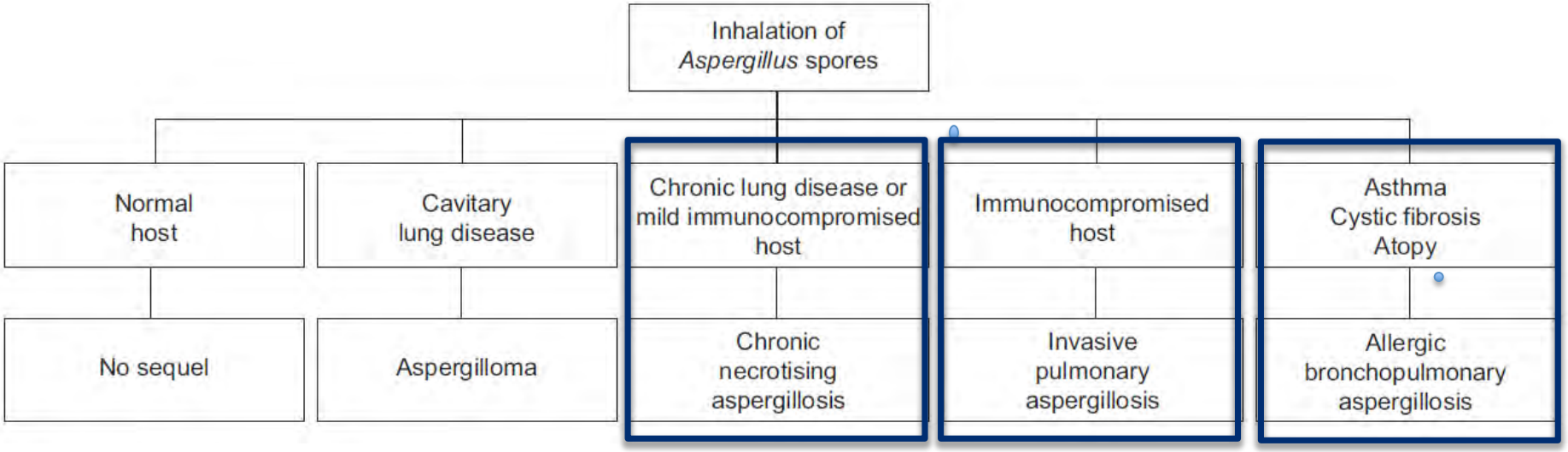
Table 1 Burden of serious fungal infections in France.
Poids épidémiologique des infections fongiques graves en France.

Infection	Number of infections per underlying disorder per year					Rate/100K	Total burden
	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.

J Mycol Med 2016 Nov 22

Quelles sont les pathologies aspergillaires dans les bronchopathies chroniques?



Invasive Pulmonary Aspergillosis in Patients with Chronic Obstructive Pulmonary Disease: An Emerging Fungal Disease

Florence Ader

***Curr Infect Dis Rep* (2010) 12:409–416**

Comment rechercher Aspergillus dans les bronchopathies chroniques?

Le prick test (SPT)	Simple, Excellente VPN	Pb de reproductibilité Ag
IDR	+ sensible que SPT	Peu fait en pratique
Taux d'éosinophiles (> 1000 /µl)	Facile, Automatisé	Peu corrélés à l'état resp
Dosage des IgE totales	Facile, combiné au SPT	Plus de faux + que SPT Pb des unités (ng ou UI/mL) Pas de valeur seuil consensus Valeur seuil f° de maladie (500 ou 1 000 UI/mL)
Dosage des sIgE	Facile, critère d'ABPA	Valeur seuil (>0,35kUA/L)
Recherche des sIgG	Facile, **tk variables**	Non spé d'ABPA
Analyse mycologique d'expectoration	Simple, peu couteux Identification	En cours de standardisation (REMIC5)

[Persat 2012; Baxter et al. 2013; Huerta et al. 2014; jin et al.2014; Denning et al.2014; Fillaux et al. 2014; Argwal et al. 2014-2015]

Merci à Laurence Delhaes, Bordeaux

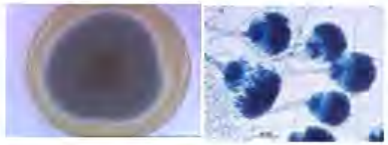
Comment rechercher Aspergillus dans les bronchopathies chroniques?

▪ Dosage des sIgE et/ou sIgG vis à vis d'Ag recombinants *[Agarwall et al. 2013]*	Facile, couteux	rAsp f4, f6 ↑ uniquement dans l'ABPA… résultats discordants entre les centres tjrs à l'étude
▪ PCR fongique (Af-PCR) de l'expectoration *[Baxter et al. 2013; Denning et al.2014]*	Plus sensible que culture	Bcp de faux +, **Pas de standardisation**
▪ Dosage du GM Surnageant de l'expectoration *[Baxter et al. 2013]*	**Plus sensible que culture**	Encore peu utilisé
▪ Analyse mycologique d'expectoration	Simple, peu couteux **Identification Maldi-tof** **Sensibilité in vitro aux azolés**	En cours de standardisation (REMIC5)

[Persat 2012; Baxter et al. 2013; Huerta et al. 2014; jin et al.2014; Denning et al.2014; Fillaux et al. 2014; Argwal et al. 2014-2015]

Merci à Laurence Delhaes, Bordeaux

Mucoviscidose

	 A. *fumigatus*
Exacerbation pulmonaire	[Baxter et al. Chest 2013]
Altération de la fonction pulmonaire	↘ FEV1 *Af* sensibilisation [Wojnarowski et al. Am J Respir Crit Care Med. 1997; Baxter et al. Chest 2013; Fillaux et al. Scand J Infect Dis. 2012] *Af colonisation persistante* [Fillaux et al. Scand J Infect Dis. 2012]
Hospitalisation (jours)	[Amin et al. Chest 2010]
Infection disséminée	IA: 4-6% dans les transplantations pulmonaires, + haut risque dans la CF [Iversen 2008]

European Cystic Fibrosis Society Standards of Care: Best Practice guidelines

3.10. How should fungal infections and severe/recurrent Allergic Bronchopulmonary Aspergillosis (ABPA) be treated?

Aspergillus fumigatus as well as other fungi are commonly found in sputum of CF patients. Whilst their relevance is not entirely clear, more recent evidence suggests that *A. fumigatus* may act as a pathogen in at least in some CF patients [42]. Sputum cultures in CF patients should therefore include assessments for fungi. Allergic bronchopulmonary aspergillosis is a well characterised complication in CF patients and should be considered in any patient with clinical deterioration not responding to antibiotic therapy [17]. Diagnostic tests include allergy skin testing, measurements of serum IgE and IgE specific to *Aspergillus*, and serum precipitins for *Aspergillus*. These tests need to be available to every CF care facility. Treatment is with oral prednisolone plus/minus antifungal therapy [17].

Clinical assessments that should be performed at least every 3 months and at times of symptomatic deterioration [43]. As airway infection is a major driver of CF lung disease airway cultures should be obtained at every clinic visit [17]. The microbiological assessment needs to include specific culture media for the range of CF pathogens to ensure that relevant organisms are not overlooked.

Journal of Cystic Fibrosis 13 (2014) S23–S42

Merci à Laurence Delhaes, Bordeaux

Dilatations Des Bronches

Distribution of the aetiologies of bronchiectasis in recent studies.

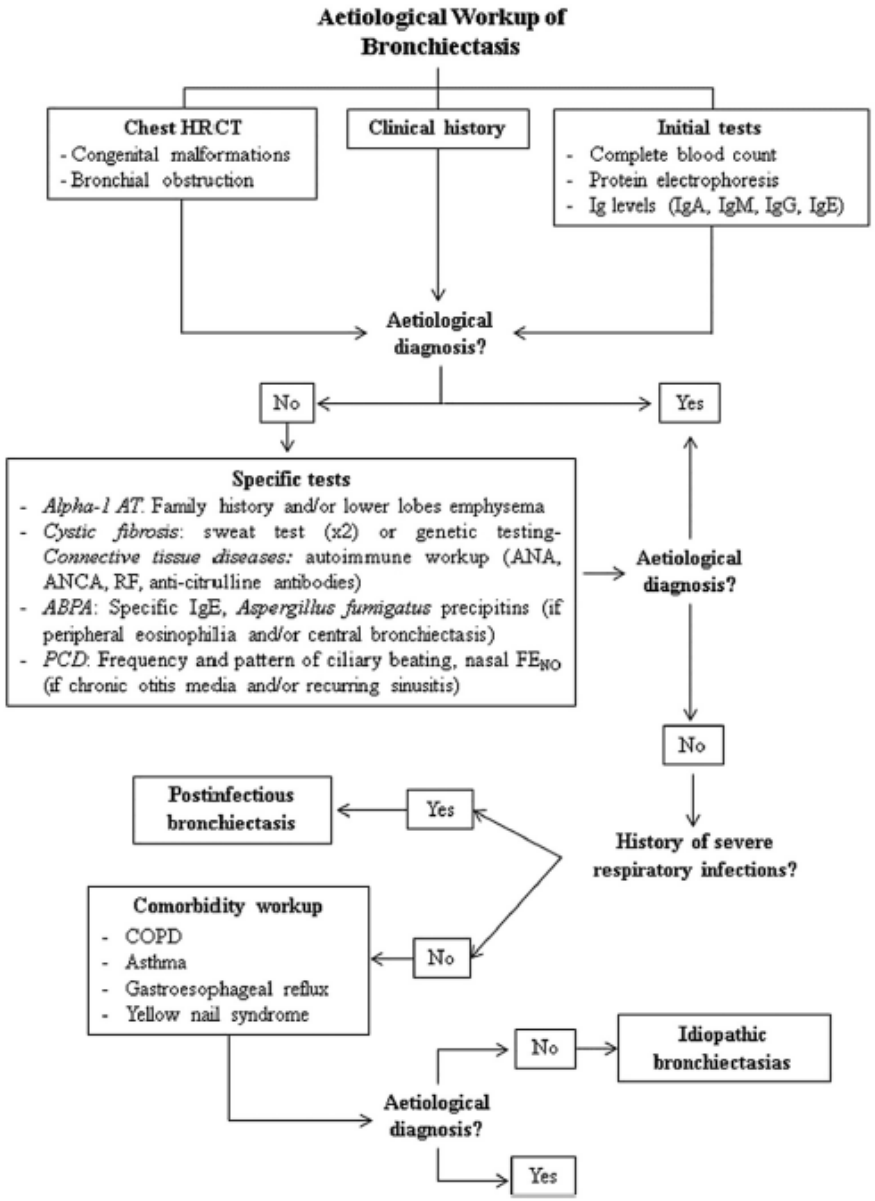
	Pasteur et al. (n = 150)	King et al. (n = 103)	Shoemark et al. (n = 165)	Anwar et al. (n = 189)	Lonni et al. (n = 1258)
Mean age (SD)	52.7 (15.2)	56 (14)	49 (16)	66.1 (11.5)	67 (58–75)[a]
Gender (% M/F)	38/62	37/63	35/65	49/51	40/60
Idiopathic (%)	53	74	26	43	40
Postinfectious (%)	29	10	32	24	20
Immunodeficiencies (%)	8	9	7	2	6
ABPA (%)	7	4	8	4	5
Connective tissue diseases (%)	2	2	2	5	10
COPD (%)	–	–	–	12	15
Asthma (%)	–	–	–	3	3
Inflammatory intestinal disease (%)	1	–	3	2	2
Cystic Fibrosis (%)	3	0	1	<1	0
Ciliary dysfunction (%)	2	1	10	1	2
AAT Deficiency (%)	0	0	0	1	<1
Aspiration/GER (%)	4	0	1	1	<1
Panbronchiolitis (%)	<1	0	2	0	0
Young's Syndrome (%)	3	1	3	<1	0
Yellow nail Syndrome (%)	–	–	2	–	<1
Congenital defect of the airway (%)	<1	0	–	–	<1
Pink's disease (%)	<1	–	–	<1	<1
Other (%)	–	–	Mycobacteria Infection: 2	–	Bronchial obstruction: <1

SD: standard deviation; ABPA: allergic bronchopulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; AAT: Alpha-1 antitrypsin; gastro-oesophageal reflux (GER).

[a] Data presented as median (interquartile range).

Suarez-Cuartin *Respir Med* 116 (2016) 70-77

Dilatations Des Bronches



Suarez-Cuartin *Respir Med* 116 (2016) 70-77

What are the features of allergic bronchopulmonary aspergillosis (ABPA) as a cause of bronchiectasis?

- All patients with bronchiectasis should be assessed for evidence of ABPA which is a clinical diagnosis based on presentation and immunological tests (*Aspergillus*-specific IgE and IgG). **[D]**

What blood tests should be performed?

The following should be measured in all patients:

- serum immunoglobulins (IgG, IgA, IgM) and serum electrophoresis; **[A]**
- serum IgE, *Aspergillus fumigatus* RAST/CAP and aspergillus precipitins. **[C]**

Pasteur BTS guidelines
Thorax 2010; 65:i1-i58.

Asthme

Box 3-10. Indications for considering referral for expert advice, where available

Difficulty confirming the diagnosis of asthma

- Patient has symptoms of chronic infection, or features suggesting a cardiac or other non-pulmonary cause (Box 1-3, p8) (immediate referral recommended)
- Diagnosis is unclear even after a trial of therapy with ICS or systemic corticosteroids
- Patients with features of both asthma and COPD, if there is doubt about priorities for treatment

Suspected occupational asthma

- Refer for confirmatory testing and identification of sensitizing or irritant agent, specific advice about eliminating exposure and pharmacological treatment. See specific guidelines (e.g. [30]) for details.

Persistent uncontrolled asthma or frequent exacerbations

- Patient's symptoms remain uncontrolled, or patient has ongoing exacerbations or low lung function despite correct inhaler technique and good adherence with Step 4 treatment (moderate or high-dose ICS/LABA, Box 3-5, p31). Before referral, depending on the clinical context, identify and treat modifiable risk factors (Box 2-2, p17; Box 3-8, p38) and comorbidities (p47)
- Patient has frequent asthma-related health care utilization (e.g. multiple ED visits or urgent primary care visits)

Any risk factors for asthma-related death (see Box 4-1, p59)

- Near-fatal asthma attack (ICU admission, or mechanical ventilation for asthma) at any time in the past
- Anaphylaxis or confirmed food allergy in a patient with asthma

Evidence of, or risk of, significant treatment side-effects

- Patients with significant side-effects from treatment
- Need for long-term oral corticosteroid use
- Frequent courses of oral corticosteroids (e.g. two or more courses a year)

Symptoms suggesting complications or sub-types of asthma

- e.g. aspirin-exacerbated respiratory disease (p53); allergic bronchopulmonary aspergillosis

Additional reasons for referral in children 6–11 years

- Doubts about diagnosis of asthma e.g. respiratory symptoms are not responding well to treatment in a child who was born prematurely
- Symptoms or exacerbations remain uncontrolled despite moderate dose ICS (Box 3-6B, p32) with correct inhaler technique and good adherence
- Suspected side-effects of treatment (e.g. growth delay)
- Asthma and confirmed food allergy

GINA guidelines 2015

Cohorte 350 asthmatiques en Belgique

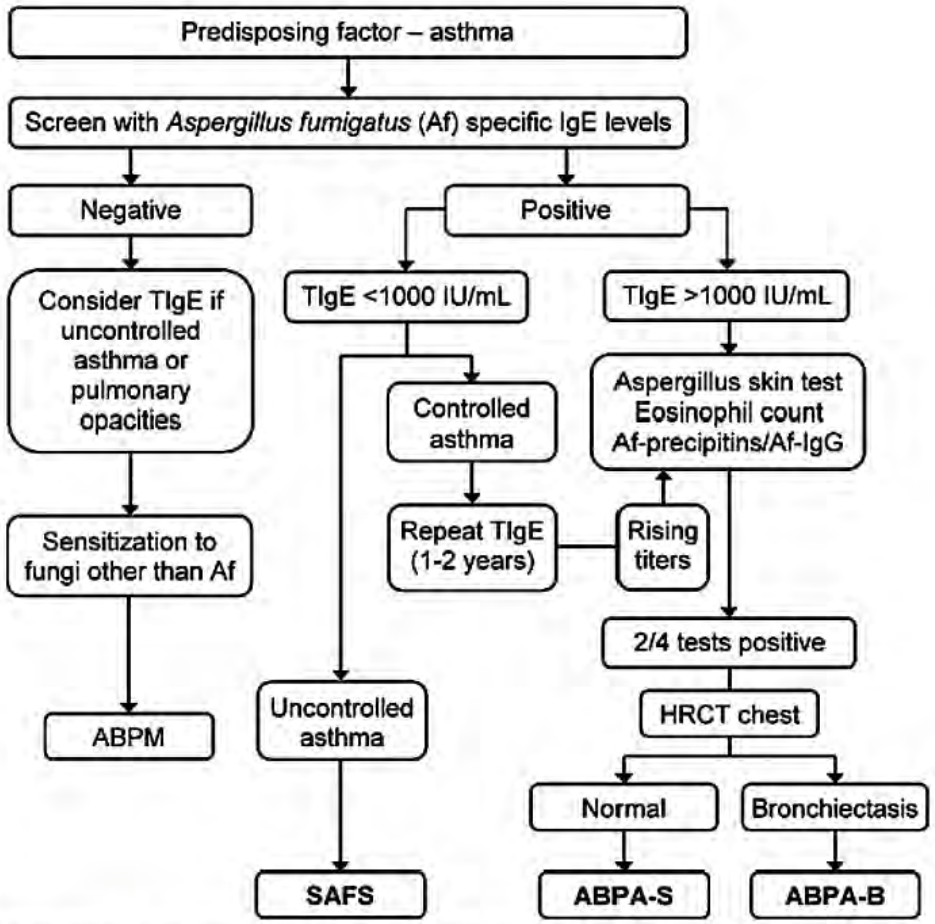
Table 1 *(continued)*

Patient characteristics	
Specific immunotherapy, %	0.6
Comorbidities (%)	
Rhinosinusitis % (Y/N/Ukn)	49% (167/151/32)
Gastrooesophageal reflux (Y/N/Ukn)	36% (124/205/21)
Nasal polyps (Y/N/Ukn)	19% (167/151/32)
Overweight (Y/N/Ukn)	47% (162/173/15)
Psychopathology (Y/N/Ukn)	19% (65/266/19)
Catamenial asthma (Y/N/Ukn)	0.9% (3/340/7)
Aspirin sensitive asthma (Y/N/Ukn)	8% (28/315/7)
Occupational asthma (Y/N/Ukn)	4% (15/328/7)
Churg Strauss syndrom (Y/N/Ukn)	3% (10/333/7)
ABPA (Y/N/Ukn)	3% (11/332/7)
Bronchiectasis (Y/N/Ukn)	16% (54/289/7)
Emphysema (Y/N/Ukn)	7% (24/319/7)
Treatment of comorbidities	
Proton pump inhibitors	39%
Anti-depressive/anxiolytics	17%/14%
Intranasal steroids	39%
Oral steroids courses during previous yr	2.03 (0–7)
Number of hospitalisations during previous yr	0.95 (0–7) (n = 113)
Number of hospitalization during the last three years	1.7 (0–8) (n = 103)

Schleich *Respir Med* (2014) 108, 1723-1732

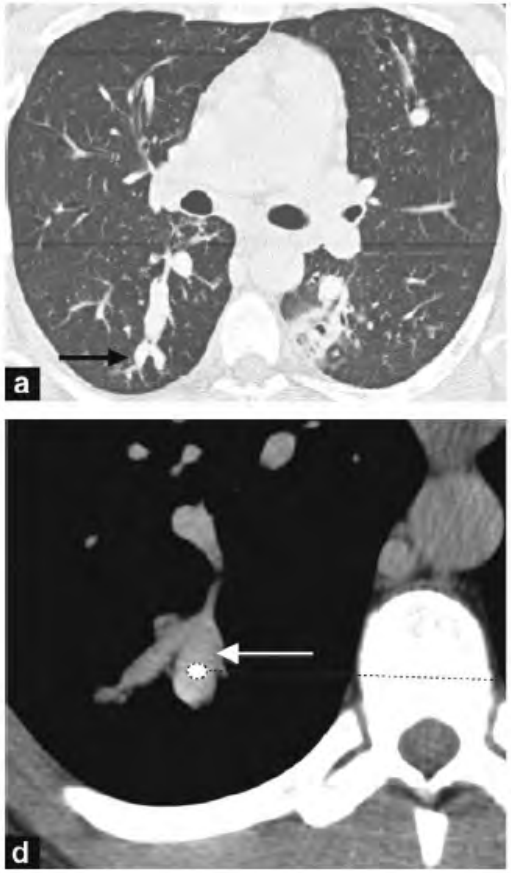
Asthme

ABPA et sensibilisation aspergillaire



gure 5 Classification of allergic fungal disease in asthma. ABPA, allergic bronchopulmonary aspergillosis; ABPA-B, ABPA-bronchiectasis; ABPA-S, 3PA-seropositive; ABPM, allergic bronchopulmonary mycosis; HRCT, high-resolution CT; SAFS, severe asthma with fungal sensitisation; TIgE, total E. Adapted from Agarwal *et al*,[64] with permission.

Agarwal R, *Clin Exp Allergy* 2013;43:850–73



Chabi *Diagnos Interv Imaging* (2015) 96, 435-442

BPCO

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

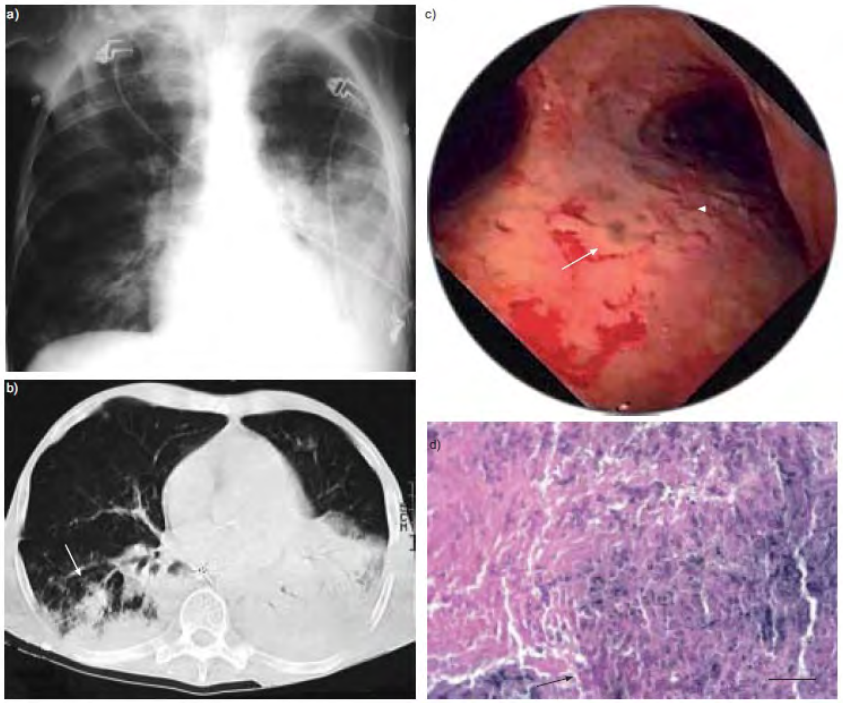
REVIEW

Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease

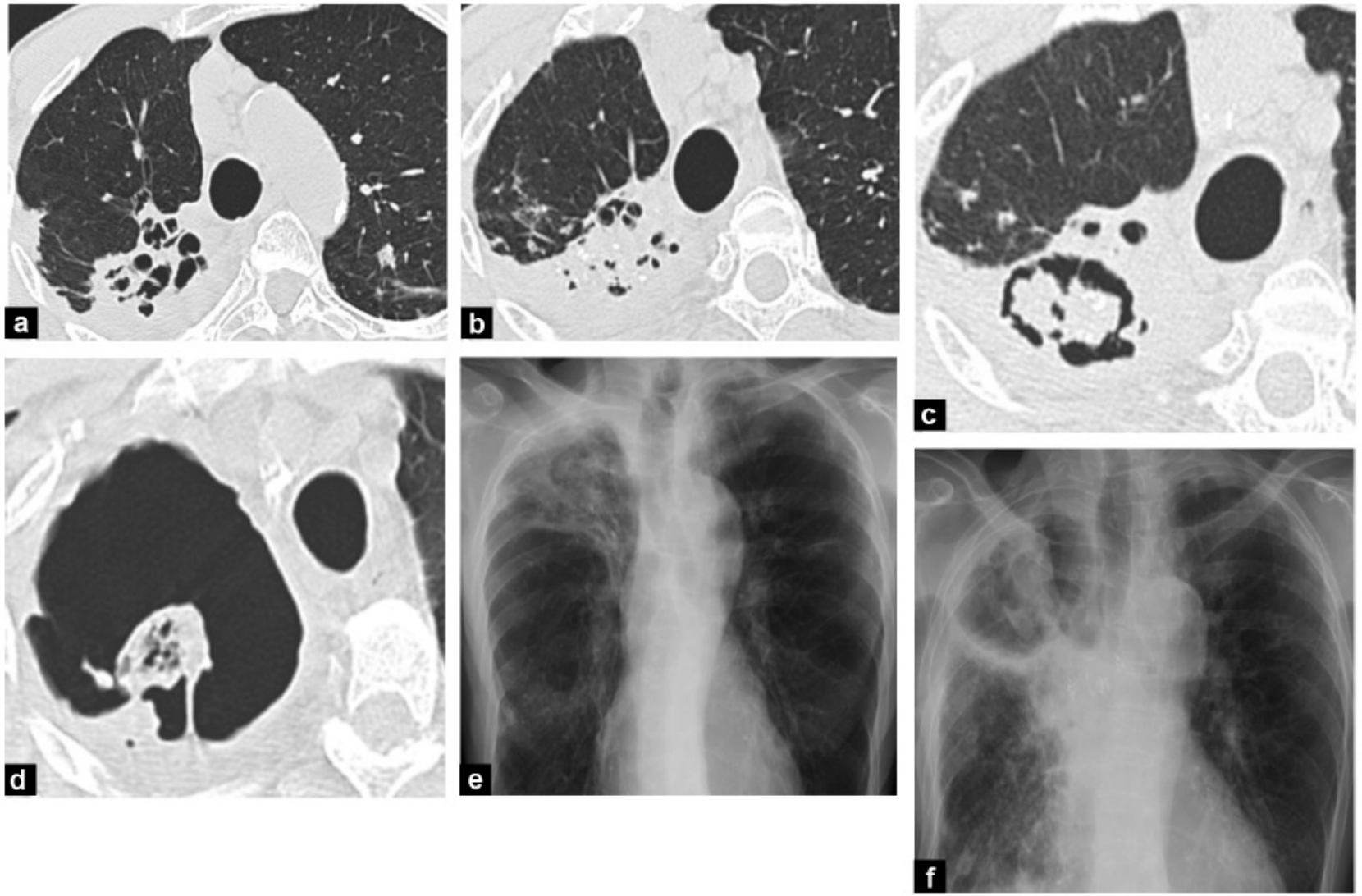
P. Bulpa*, A. Dive* and Y. Sibille#

TABLE 2 Characteristics of the patient population

Total number of patients	56
Sex	
Male	42 (75)
Female	14 (25)
Age yrs	
Mean ± SD	65.5 ± 9.3
Median (IQR)	66 (57–73)
Steroid treatment	
At admission	43
Systemic use	40
Inhaled only	3
In hospital (systemic use)	49
None	2
NA	5
Total leukocytes	
<12000	10
>12000	30
NA	16
Outcome¶	
Death	53 (95)
Survival	3 (5)



BPCO: chronic necrotizing aspergillosis



Chabi *Diagnos Interv Imaging* (2015) 96, 435-442

BPCO et sensibilisation (IgE) aspergillaire

Aspergillus fumigatus during stable state and exacerbations of COPD

128 patients BPCO

	No fungus culture	*A. fumigatus* culture	Other filamentous fungus culture	p-value
Subjects n	65	47	16	
Male	41 (63)	35 (75)	13 (81)	0.24
Age years	68 (47–87)	72 (53–86)	68 (51–82)	0.10
Current smokers	31 (48)	11 (23)	6 (37)	**0.03**
Ex-smokers	33 (51)	34 (72)	10 (63)	0.07
Pack-years smoked	56 (10–207)	49 (10–130)	57 (12–138)	0.56
Exacerbations in previous year	3 (1–12)	3 (1–8)	3 (1–10)	0.30
GOLD I	3 (5)	2 (4)	1 (6)	0.95
GOLD II	27 (42)	16 (34)	3 (18)	0.22
GOLD III	19 (28)	16 (34)	6 (38)	0.76
GOLD IV	16 (25)	13 (28)	6 (38)	0.58
Inhaled corticosteroid dose# µg	1389±86	1628±84	1754±130	**0.05**
Atopy % (95% CI)	34 (22–50)	55 (38–70)	14 (1–53)	0.07
FEV1/FVC¶ %	49±1	49±2	46±4	0.55
FEV1¶ % predicted	51±2	48±2	44±5	0.38
Peripheral leukocytes+ $\times 10^9$ cells·L^{-1}	8.7 (8.1–9.3)	7.8 (7.3–8.4)	7.9 (6.8–9.2)	0.12
Peripheral blood eosinophils+ %	2.4 (2.1–2.9)	2.5 (2.1–3.0)	2.5 (1.7–3.8)	0.56
Sputum total cell count+ $\times 10^6$ cells·g^{-1}	2.1 (1.5–3.1)	4.1 (2.9–5.9)	4.1 (2.8–5.9)	**0.03**
Sputum neutrophils %	66±3	78±3	78±6	**0.03**
Sputum eosinophils+ %	1.1 (0.6–1.2)	0.8 (0.6–1.2)	1.7 (0.7–4.2)	0.19
Total IgE§ kU·L^{-1}	39.4±156.7	57.7±165.5	46.9±151.4	0.64
CRP§ mg·L^{-1}	3±7	3±8	5±9	0.65
A. fumigatus-specific IgE >0.35f %	13	15	0	0.26
A. fumigatus IgG >40f %	18	28	15	0.26
SGRQ total units	56±2	53±2	47±4	0.14
CRQ total units	3.8±0.1	4.2±0.2	4.4±0.2	0.08
VAS total mm	167±10	162±13	157±11	0.90

Bafadhel et al. *Eur Resp J* 2014; 43: 64-71

BPCO et sensibilisation (IgE) aspergillaire

Aspergillus fumigatus during stable state and exacerbations of COPD

TABLE 3 Predictors of *Aspergillus fumigatus* sputum culture in chronic obstructive pulmonary disease subjects at stable state

	OR (95% CI)	p-value
Exacerbation frequency	0.84 (0.69–1.03)	0.09
FEV1 % predicted	0.97 (0.96–1.01)	0.32
Sputum eosinophils %	0.53 (0.24–1.20)	0.13
Total sputum neutrophil count	1.97 (1.05–3.69)	**0.03**

Bold type represents statistical significance at $p<0.05$. FEV1: forced expiratory volume in 1 s.

Bafadhel et al. *Eur Resp J* 2014; 43: 64-71

BPCO et sensibilisation (IgE) aspergillaire

Aspergillus fumigatus during stable state and exacerbations of COPD

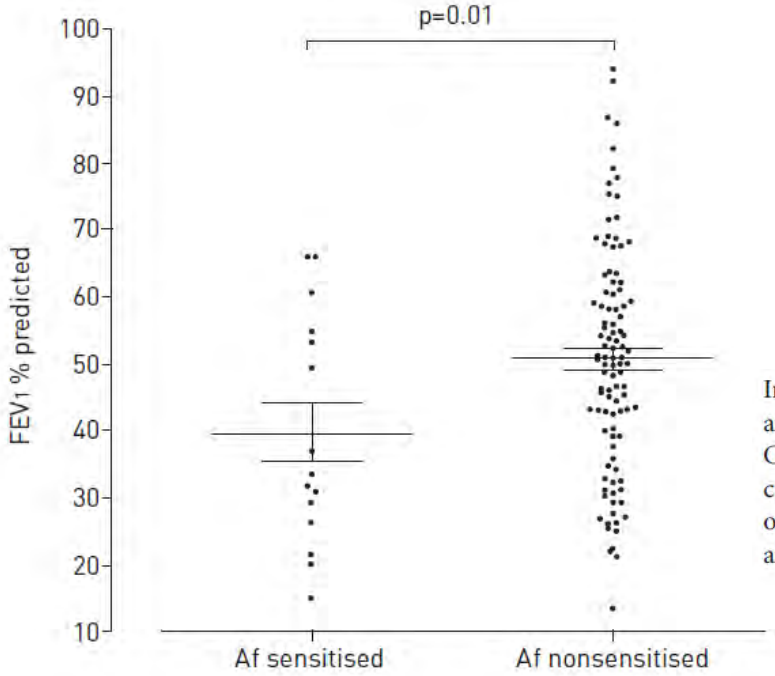


TABLE 4 Predictors of *Aspergillus fumigatus* sensitisation in chronic obstructive pulmonary disease subjects at stable state

	OR (95% CI)	p-value
Exacerbation frequency	1.17 (0.89–1.55)	0.27
FEV1 % predicted	0.95 (0.91–0.99)	**0.02**
Sputum eosinophils %	1.04 (0.34–3.23)	0.94
Total sputum neutrophil count	2.12 (0.78–5.81)	0.14
***Aspergillus fumigatus* culture**	1.23 (0.34–4.49)	0.76

Bold type represents statistical significance at $p<0.05$. FEV1: forced expiratory volume in 1 s.

In conclusion, we have shown that *A. fumigatus* in commonly found in the sputum of patients with COPD and that this is irrespective of disease severity. We have also shown that IgE sensitisation to *A. fumigatus* in COPD subjects is associated with lower lung function and that the detection of *A. fumigatus* by sputum culture is increased compared to controls but unrelated to exacerbations. However, the clinical significance of fungi in COPD and the response to antifungal therapy remains to be determined and further studies are required.

Bafadhel et al. *Eur Resp J* 2014; 43: 64-71

Conclusion

- **OUI**, il faut chercher les pathologies aspergillaires dans les bronchopathies chroniques
- Ne pas le faire revient à ignorer un nombre important de pathologies, ce qui est clairement délétère pour les patients
- Recommandations internationales:
  - Mucoviscidose
  - Dilatation des bronches
  - Asthme
  - BPCO?
- Prévalence élevée des ABPA/sensibilisations aspergillaire
- En cas d'image, de corticothérapie orale inhalée: attention aux formes invasives/chroniques