Actualités sur l'aspergillose broncho-pulmonaire allergique

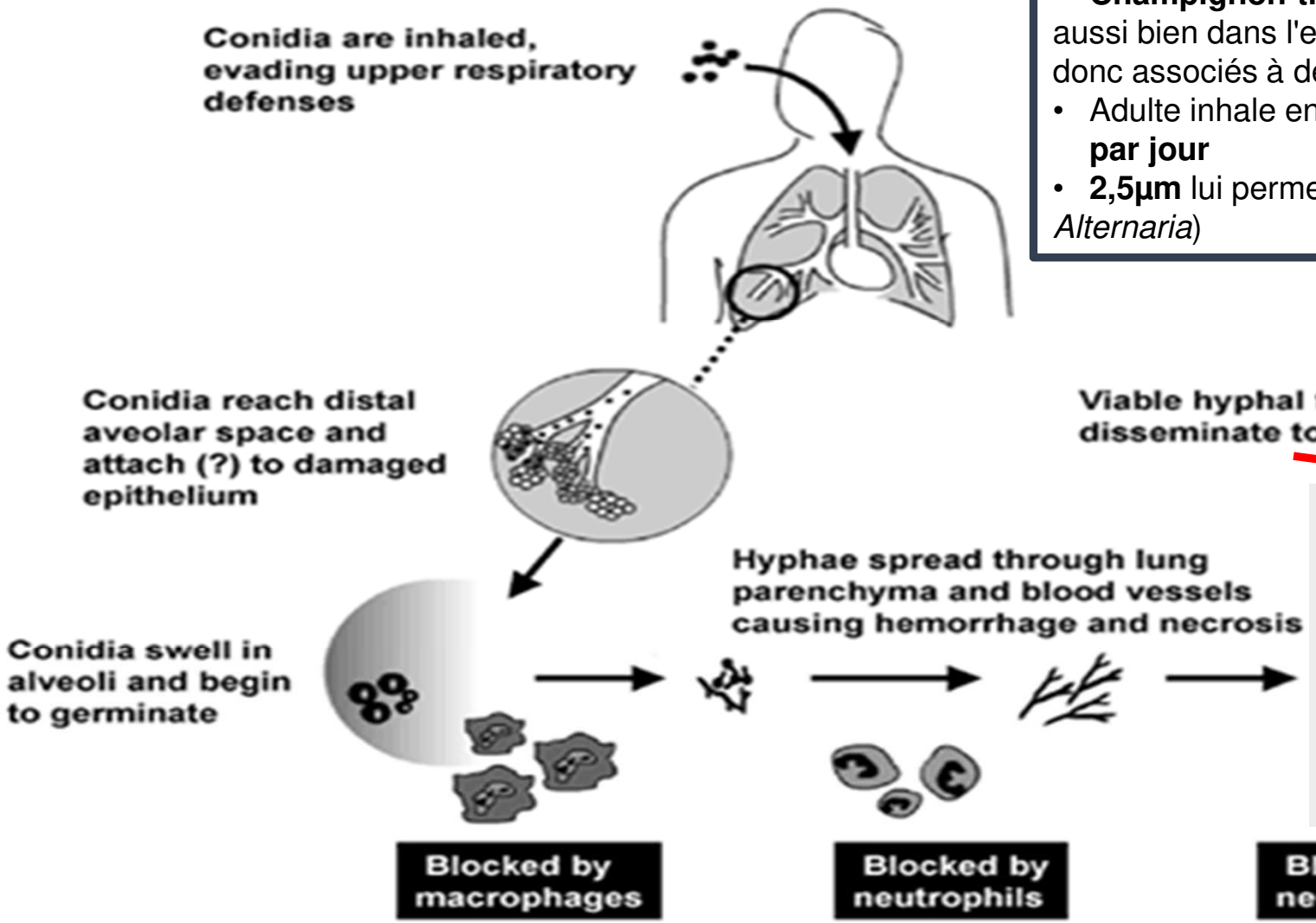
Les menaces de la colonisation aspergillaire

Cendrine Godet
Hôpital Bichat-Claude Bernard-APHP
SPIF 2022

Déclaration d'intérêts

SUBVENTION ET AVANTAGES À TITRE COLLECTIF	RÉMUNÉRATION ET AVANTAGES À TITRE PERSONNEL
Pfizer Gilead MSD Astellas SOS Oxygène-ISIS-CF Sante-Elivie-Vivisol Sandoz AstraZeneca	Pfizer Gilead MSD Basilea Pulmatrix SOS Oxygene

- **Champignon thermotolérant** se développant aussi bien dans l'environnement et dans le corps et donc associés à des manifestations allergiques
- Adulte inhale environ **100 conidies d'** ***A. fumigatus*** **par jour**
- **2,5µm** lui permet de gagner les alvéoles (vs 18 à 68µm *Alternaria*)



- **Chez les prédisposés ABPA les conidies germent en hyphes dans les voies respiratoires et s'accumulent dans le mucus sans dissémination**
- **relargage de protéases et dommage épithélium avec inflammation prédominante à éosinophilie**

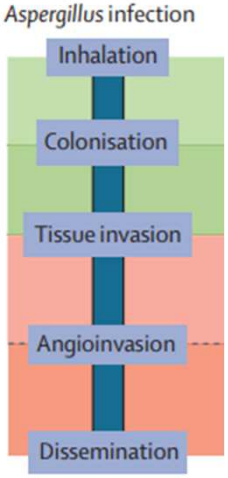
Clin Chest Med 43 (2022) 99–125

Inhalation de spores

Colonisation

Hôte
-Hypersensibilité
-Déficit immunitaire local
Déficit immunitaire général

-Pathogénicité
-Antigénicité



Hypersensibilité | **Défense normale** | **Immunodépression modérée** | **Immunodépression sévère**

Élimination

Cavité préexistante

Dénutrition
Corticoïdes, IS
Alcool
Tabac
Diabète

-Neutropénie
-ACSH
-Corticoïdes ≥ 0.3 mg/kg/j pred> 3 sem
-IS (T) ≥ 90 jours :Ciclo, anti TNF, anti CD52, anal. nucléosidiques
-Déficits immunitaires congénitaux-

Asthme, ABPA, PHS

Aspergillome simple

APCC

APCN

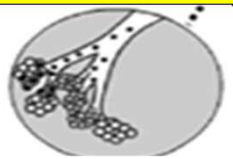
A Subaiguë

API

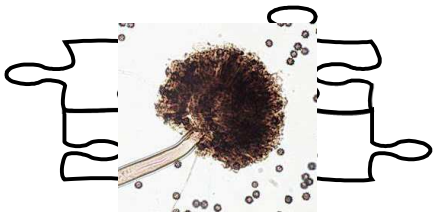
continuum

Inhalation de spores

Conidia reach distal aveolar space and attach (?) to damaged epithelium



Colonisation



Hôte

Biais de réponse immunitaire adaptative de type Th2

Prédispositions génétiques (HLA DR2- HLA DR5)

Sd hyper-IGE – déficit immunitaire en neutrophile

Déficit immunitaire local ou général

Genetic defect impliquant cytokine IL-4, IL-5, IL-13

HYPERSENSIBILITÉ

PATHOGÉNICITÉ

Persistance d'une colonisation aspergillaire

Asthme, colonisation, AS, SASF, ABPA

Clin Chest Med 43 (2022) 99–125

Maladies broncho- pulmonaires liées à l'*Aspergillus*

Manifestations infectieuses

- Colonisation aspergillaire
- Bronchite aspergillaire

- Aspergillome simple
- Aspergillose Pulmonaire Chronique Cavitaire (APCC)
- Aspergillose Pulmonaire Chronique Fibrosante (APCF)
- Aspergillose Pulmonaire Chronique Nécrosante (APCN)

- La forme invasive du non neutropénique

Manifestations d'hypersensibilité

- Aspergillose broncho-pulmonaire allergique
- Asthme avec sensibilisation aspergillaire (AS)
- Asthme sévère avec hypersensibilisation fongique (SAFS)
- mopathie d' hypersensibilité à *rgillus*

Denning D et al, Eur Respir J, 2016
Patterson TF et al, CID, 2016

Formes de chevauchement

Link between *Aspergillus* airway Colonization/Sensitization/Infection and

- COPD exacerbations
- Asthma severity and exacerbations
- Bronchiectasis and COPD
- CF patients
- Worse lung in TB

- Wu et al 2021/ Tiew et al…2021
- Rapeport et al 2020, Agbetile et al 2012…
- Everearts et al….2017
- Baxter et al 2013; Al Shakirchi et al 2021 ….
- Dhooria et al…2017

Isolation of filamentous fungi from sputum in asthma is associated with reduced post-bronchodilator FEV_1

J. Agbetile[1,2,*], A. Fairs[1,*], D. Desai[1,2], B. Hargadon[2], M. Bourne[2], K. Mutalithas[1,2], R. Edwards[1,2], J. P. Morley[1], W. R. Monteiro[2], N. S. Kulkarni[2], R. H. Green[2], I. D. Pavord[2], P. Bradding[1,2], C. E. Brightling[1,2], A. J. Wardlaw[1,2] and C. H. Pashley[1]

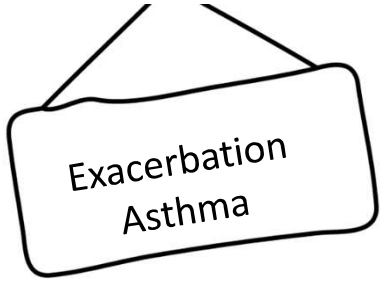
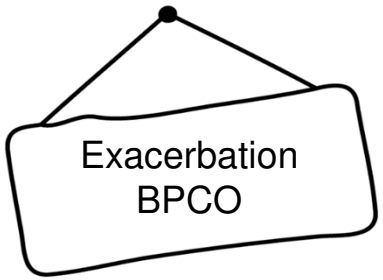


Table 1. Demographic data

	Asthma patients (n = 126)				Comparing three groups
	No fungi cultured (n = 58)	Any fungi (n = 68)	P-value	Healthy controls (n = 18)*	P-value
Age in years (range)	55 (21–84)	58 (24–83)	0.23	40 (21–67)	< 0.001
Smoking history (pack years)†	0 (0–4)	0 (0–10)	0.51	0 (0–3)	0.44
Gender (male)	41%	53%	0.20	50%	0.42
Serum total IgE kU/L†	159 (43–494)	207 (89–718)	0.08	31 (9–50)	< 0.001
Atopic§	55%	61%	0.57	17%	0.01
Age of asthma onset, years†	34 (9.5–47.25)	25 (5.25–46)	0.65	-	-
Duration of asthma, years†	22 (10.75–42.5)	23 (7–41.75)	0.89	-	-
FEV_1% of predicted, post-bronchodilator	82.8 (24.8)‖	70.8 (25.4)‖	< 0.01	111.6 (11.0)¶	< 0.001
Volume change post-bronchodilator, (mL)†	100 (50–250)	50 (0–150)	0.01	-	-
Fungal sensitization, (any)	38%	56%	0.08	6%	< 0.01
• *Aspergillus fumigatus* (positive/n)	17/58	35/68	0.02	0/18	
• *Penicillium chrysogenum*	5/36	17/48	0.04	0/12	
• *Botrytis cinerea*	3/31	8/41	0.30	0/12	
• *Alternaria* alternata	6/39	11/58	0.80	1/8	
• *Cladosporium herbarum*	7/38	13/57	0.80	0/8	
GINA treatment					
GINA 5	38%	44%	0.58	-	-
GINA 4	55%	51%			
Inhaled corticosteroid dose (μg)†¶	1600 (800–2000)	2000 (1600–2000)	0.04	-	-
Number with bronchiectasis, n (%)	17 (35)	32 (51)	0.06	-	-
Total cell count × 10^3 mg of sputum‡	3.151	3.451	0.91	-	-
Sputum neutrophil (%)‡ (95% CI)	58.09 (48.8–69.2)	51.65 (42.5–62.8)	0.47	-	-
Sputum eosinophil (%)‡(95% CI)	2.52 (1.5–4.2)	2.09 (1.4–3.2)	0.61	-	-

Respiratory *Aspergillus* Colonization Was Associated With Relapse of Acute Exacerbation in Patients With Chronic Obstructive Pulmonary Disease: Analysis of Data From A Retrospective Cohort Study

Yi-xing Wu[†], Yi-hui Zuo[†], Qi-jian Cheng[2], Yi Huang[3], Zhi-yao Bao[4], Xiao-yan Jin[5], Xi-wen Gao[6], Chun-lin Tu[7], Wei-ping Hu[1], Jing-qing Hang[8], Wei-qin Wang[5], Feng-ying Zhang[5] and Jing Zhang[1]



Patients With *Aspergillus* Colonization
Were at a High Risk of Relapse of AECOPD

TABLE 4 | Prognosis of hospitalized COPD patients with or without *Aspergillus* colonization.

	Patients with *Aspergillus* colonization ($n = 26$)	Controls ($n = 72$)	*P*-value
Length of hospital stay (days)	12 (7,22)	13 (10,15)	0.759
ICU admission	2 (7.7)	9 (12.5)	0.722
Hospitalization expense (RMB)	17,290 (12,601, 23,049)	17,110 (13,204, 21,348)	0.728
Mortality during hospitalization	1 (3.8)	1 (1.4)	0.462
Recurrent exacerbations within 90 days	5 (19.2)	3 (4.2)	0.029
Recurrent exacerbations within 180 days	6 (23.1)	3 (4.2)	0.010
Recurrent exacerbations within 1 year	9 (34.6)	39 (54.2)	0.087
Mortality within 1 year	3 (11.5)	0 (0)	0.017

Data are presented as medians (1st quartile, 3rd quartile) or absolute numbers (%) as appropriate. COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

The role of antifungals in the management of patients with severe asthma

W. Garth Rapeport[1*], Kazuhiro Ito[1,2] and David W. Denning[3]

Table 1 Criteria for diagnosis of fungal allergic airways diseases associated with severe asthma and their complications

Disease entity	Clinical criteria	Immunologic	Mycologic	Complications
Allergic bronchopulmonary aspergillosis (ABPA)	1. Asthma or cystic fibrosis[a] 2. Fleeting or fixed pulmonary opacities on chest radiograph 3. Peripheral eosinophil count > 500 cells/μL	1. Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity reaction to Af) or elevated IgE levels against *A. fumigatus*, 2. Elevated total IgE levels more than 1000 IU/mL (unless all other criteria is met, then total IgE levels can be less than 1000 IU/mL) 3. Elevated Aspergillus IgG or precipitating antibodies	None	Bronchiectasis Hyper-attenuated mucous Asthma exacerbations ABPA exacerbations Bronchiectasis exacerbations Fixed airways obstruction Chronic pulmonary aspergillosis Focal pleural based fibrosis areas
Allergic fungal airways disease (AFAD) or Airways Mycosis	Asthma with sensitization and/or inflammation and tissue damage including radiological abnormalities and fixed airways obstruction	Positive immediate skin test (SPT) and fungal specific IgE	Documented (PCR or culture) or presumed	Bronchial wall thickening Bronchiectasis Fixed airways obstruction
Severe asthma with fungal sensitisation (SAFS)	Severe asthma	Positive immediate skin test (SPT) and specific IgE to *Aspergillus fumigatus, Alternaria alternata, Cladosporium herbarum, Penicillium chrysogenum, Candida albicans, Trichophyton mentagrophytes*, or *Botrytis cinereal*	None	Asthma exacerbations Bronchial wall thickening Fixed airways obstruction Chronic pulmonary aspergillosis
Aspergillus bronchitis[#]	Non-immunocompromised Major symptoms of cough, breathlessness and sputum production Bronchiectasis common	May have a raised *Aspergillus fumigatus* IgG	Culture or PCR positive for Aspergillus on at least 2 occasions separated in time (to exclude colonisation)	

These entities are not mutually exclusive

[a] Rare cases are described in patients without either of these conditions. # may also be caused by other fungi including *Candida albicans* and *Scedosporium* spp. Reference [5, 6, 84]

Allergic Bronchopulmonary Aspergillosis

Ritesh Agarwal, MD, DM*, Valliappan Muthu, MD, DM,
Inderpaul S. Sehgal, MD, DM, Sahajal Dhooria, MD, DM,
Kuruswamy T. Prasad, MD, DM, Ashutosh N. Aggarwal, MD, DM

- **Prévalence in adult asthma**

AS 26%
ABPA 13%

- **Global burden 4,8 million/ 193 million asthma pop**

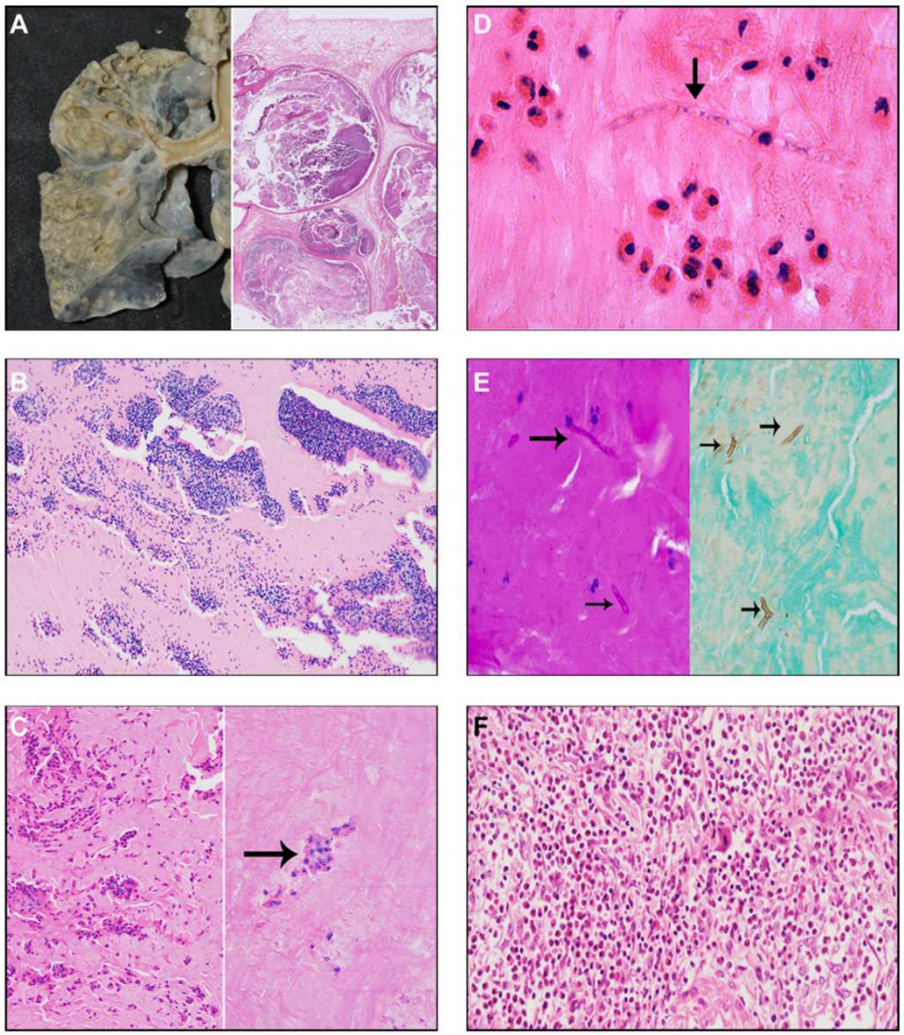
Table 1
Studies in the last decade describing the prevalence of *Aspergillus* sensitization (AS) and allergic bronchopulmonary aspergillosis (ABPA) in adults with bronchial asthma

Author (year)	Type of Study	Country	Prevalence of AS, n/N	Prevalence of ABPA, n/N (%)
Ma et al,[17] 2011	Prospective	China	11/200 (5.5%)	5/200 (2.5%)
Agin et al,[19] 2012	Prospective	Iran	42/201 (20.9%)	-
Mathur et al,[20] 2016	Prospective	India	27/300 (9%)	8/296 (2.7%)
Kozlova et al,[21] 2017	Prospective	Russia	50/140 (36%)	5/140 (3.6%)
Nath et al,[22] 2017	Prospective	India	135/350 (35.1%)	76/350 (21.7%)
Kalaiyarasan et al,[23] 2018	Prospective	India	13/70 (18.6%)	9/70 (12.9%)
Al-Saleh et al,[24] 2019	Prospective	Bahrain	19/119 (15.9%)	12/119 (10.1%)
Bhankhur et al,[25] 2019	Prospective	India	-	35/50 (70%)
Mahdi et al,[26] 2019	Prospective	Pakistan	77/150 (51.3%)	19/150 (12.6%)
Savio et al,[27] 2019	Prospective	India	122/205 (59.6%)	-
Mortezaee et al,[28] 2020	Prospective	Iran	27/200 (13.5%)	-
Rajagopal et al,[29] 2020	Prospective	India	20/57 (35.1%)	-
Sharma et al,[30] 2020	Prospective	India	30/100 (30%)	5/100 (5%)
Zia-ul-Haq et al,[31] 2020	Prospective	Pakistan	-	20/100 (20%)

*Includes fungi other than *A. fumigatus*.

Clin Chest Med 43 (2022) 99–125

PATHOLOGY : Mais qui se cache derrière l'ABPA?
Séries postmortem



Les caractéristiques histologiques de l'ABPA :

- Impactions mucoïdes
- Pneumonie à éosinophile
- Granulomatose bronchocentrique
- Bronchiectasies
- Bronchiolite (exsudative)
- Bronchiolite oblitérante
- Fibrose

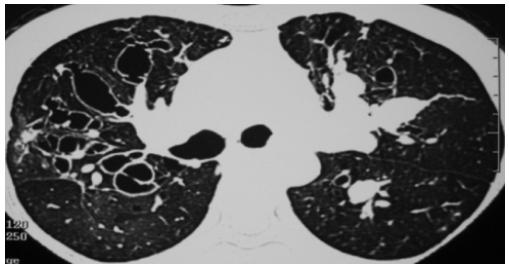
Gupta, cardiovasc pathol 2010; Bosken, Am J Surg pathol, 1988

Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis

Ritesh Agarwal, Inderpaul S Sehgal, Sahajal Dhooria & Ashutosh N Aggarwal

Date: 17 October 2016, At: 03:58

For the ABPA complicating asthma ISHAM working group



ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Table 1. Comparison of the ABPA Working Group criteria (2013) and the newly proposed criteria

ABPA working group criteria	**Newly proposed criteria**
A. Predisposing conditions	**A. Predisposing conditions**
Bronchial asthma, cystic fibrosis	Bronchial asthma, cystic fibrosis, chronic obstructive pulmonary disease, post-tuberculous fibrocavitary disease
B. Essential criteria (both must be met)	**B. Essential criteria (both must be met)**
i. Serum *Aspergillus fumigatus*-specific IgE levels >0.35 kUA/L or positive type I *Aspergillus* skin test	i. Serum *Aspergillus fumigatus*-specific IgE levels >0.35 kUA/L‡
ii. Elevated serum total IgE levels >1000 IU/mL*	ii. Elevated serum total IgE levels >1000 IU/mL*
Additional criteria (at least two of three)	**Additional criteria (at least two of three)**
i. Presence of precipitating (or IgG) antibodies against *A.fumigatus* in serum	i. Serum *Aspergillus fumigatus*-specific IgG levels >27 mg_A/L
ii. Thoracic imaging findings consistent with ABPA†	ii. Thoracic imaging findings consistent with ABPA†
iii. Peripheral blood eosinophil count >500 cells/μL (may be historical)	iii. Peripheral blood eosinophil count >500 cells/μL (may be historical)

kUA: kilounit of antibody; mgA: milligram of antibody

*An IgE value <1000 IU/mL may be acceptable, if all other criteria are met (especially if the serum *Aspergillus fumigatus*-specific IgG levels >27 mg_A/L)

†Features on HRCT chest and/or chest radiograph consistent with ABPA include transient abnormalities (i.e. nodules, consolidation, mucoid impaction, hyperattenuating mucus, fleeting opacities, toothpaste/gloved finger opacities, tram-track opacities) or permanent (i.e. parallel lines, ring shadows, bronchiectasis and pleuropulmonary fibrosis).

‡A positive type I *Aspergillus* skin test may be considered as a criterion in the place of serum *Aspergillus fumigatus*-specific IgE levels only if the latter test is not available

500 IU/mL
ISHAM 2022

Clin Chest Med 43 (2022) 99–125

New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation

Koichiro Asano, MD,[a] Akira Hebisawa, MD, PhD,[b] Takashi Ishiguro, MD, PhD,[c] Noboru Takayanagi, MD, PhD,[c] Yasuhiko Nakamura, MD, PhD,[b] Junko Suzuki, MD,[d] Naoki Okada, MD,[a] Jun Tanaka, MD,[a] Yuma Fukutomi, MD, PhD,[e] Shigeharu Ueki, MD, PhD,[f] Koichi Fukunaga, MD, PhD,[g] Satoshi Konno, MD, PhD,[h] Hiroto Matsuse, MD,[i] Katsuhiko Kamei, MD,[j] Masami Taniguchi, MD,[e] Terufumi Shimoda, MD,[k] and Tsuyoshi Oguma, MD,[a] Japan ABPM Research Program *Kanagawa, Tokyo, Saitama, Akita, Sapporo, Chiba, and Fukuoka, Japan*

TABLE I. Clinical diagnostic criteria for ABPM in patients without cystic fibrosis

1. Current or previous history of asthma or asthmatic symptoms
2. Peripheral blood eosinophilia (≥500 cells/mm^3)
3. Elevated total serum IgE levels (≥417 IU/mL)
4. Immediate cutaneous hypersensitivity or specific IgE for filamentous fungi
5. Presence of precipitins or specific IgG for filamentous fungi
6. Filamentous fungal growth in sputum cultures or bronchial lavage fluid
7. Presence of fungal hyphae in bronchial mucus plugs
8. Central bronchiectasis on CT
9. Presence of mucus plugs in central bronchi, based on CT/bronchoscopy or mucus plug expectoration history
10. High attenuation mucus in the bronchi on CT

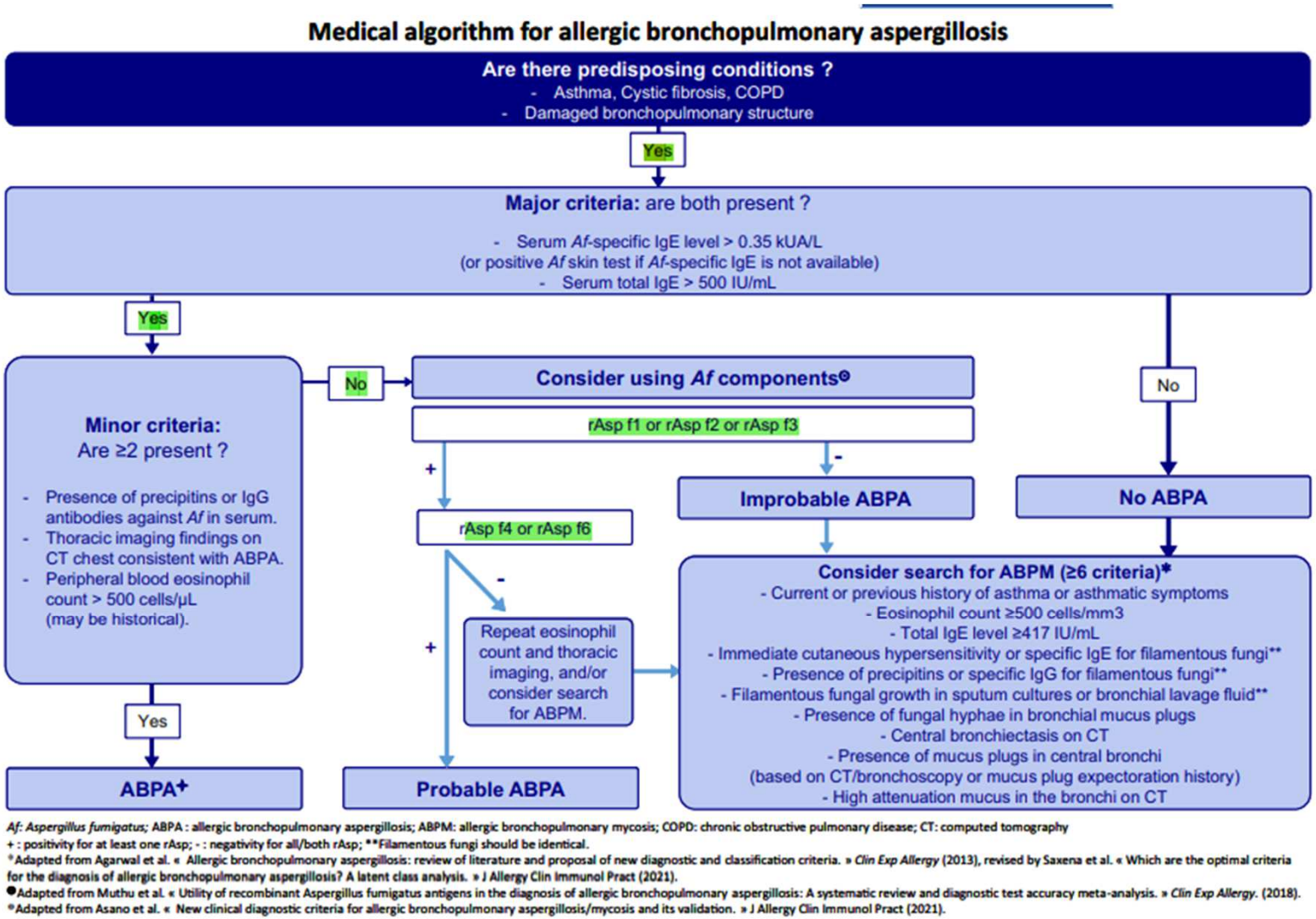
Filamentous fungi in criteria 4 to 6 should be identical.
Patients that meet 6 or more of these criteria are diagnosed with ABPM.

Key messages

- **New diagnostic criteria, consisting of 10 components, for ABPM in patients without cystic fibrosis are proposed and validated.**
- **The new criteria showed high sensitivity and specificity for ABPM, which improved on the previous criteria proposed by Rosenberg and Patterson and by ISHAM.**
- **The new criteria are useful both for *Aspergillus* and non-*Aspergillus* ABPM.**

J ALLERGY CLIN IMMUNOL
APRIL 2021

Medical algorithm: *Aspergillus fumigatus* components in the diagnosis of allergic bronchopulmonary aspergillosis



Af: Aspergillus fumigatus; ABPA : allergic bronchopulmonary aspergillosis; ABPM: allergic bronchopulmonary mycosis; COPD: chronic obstructive pulmonary disease; CT: computed tomography
+ : positivity for at least one rAsp; - : negativity for all/both rAsp; **Filamentous fungi should be identical.
*Adapted from Agarwal et al. « Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. » *Clin Exp Allergy* (2013), revised by Saxena et al. « Which are the optimal criteria for the diagnosis of allergic bronchopulmonary aspergillosis? A latent class analysis. » J Allergy Clin Immunol Pract (2021).
⊙Adapted from Muthu et al. « Utility of recombinant Aspergillus fumigatus antigens in the diagnosis of allergic bronchopulmonary aspergillosis: A systematic review and diagnostic test accuracy meta-analysis. » *Clin Exp Allergy.* (2018).
+Adapted from Asano et al. « New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation. » J Allergy Clin Immunol Pract (2021).

Lukaszewicz R, Allergy, 2022

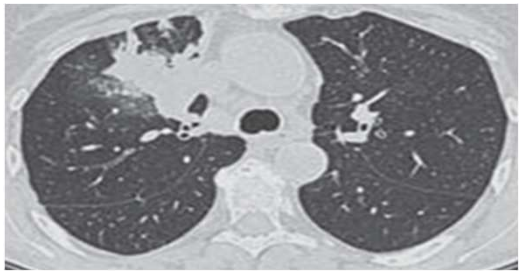
Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria

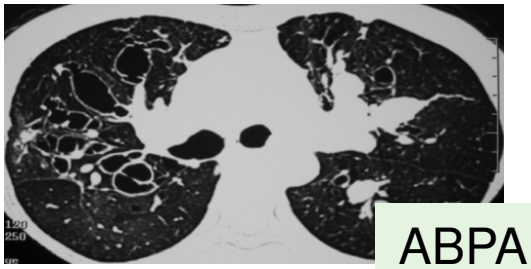
Ritesh Agarwal, Arunaloke Chakrabarti, Ashok Shah, Dheeraj Gupta, Jacques F Meis, Randeep Guleria, Richard Moss, David W Denning

For the ABPA complicating asthma ISHAM working group

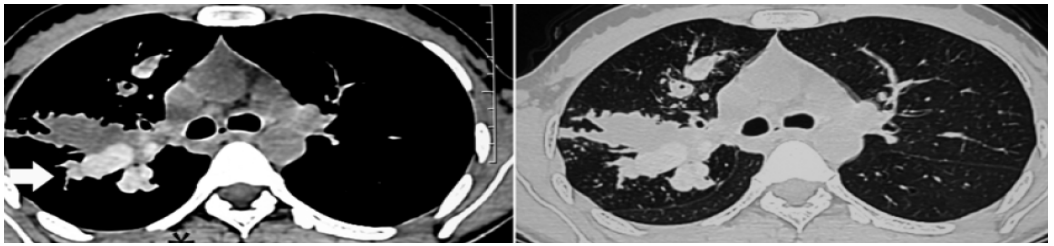
Table 6: Newly proposed radiological classification of ABPA based on computed tomographic (CT) chest findings

Classification	Features
ABPA-S (Serological ABPA)	All the diagnostic features of ABPA (Table 4) but no abnormality resulting from ABPA on HRCT chest*
ABPA-B (ABPA with bronchiectasis)	All the diagnostic features of ABPA including bronchiectasis on HRCT chest
ABPA-HAM (ABPA with high-attenuation mucus)	All the diagnostic features of ABPA including presence of high-attenuation mucus
ABPA-CPF (ABPA with chronic pleuropulmonary fibrosis)	ABPA with at least two to three other radiologic features such as pulmonary fibrosis, parenchymal scarring, fibro-cavitary lesions, aspergilloma and pleural thickening without presence of mucoid impaction or high-attenuation mucus





ABPA CB



ABPA HAM

Table 3
Clinical staging of allergic bronchopulmonary aspergillosis (ABPA) in patients with asthma

Stage	Definition	Features
0	Asymptomatic	• No previous diagnosis of ABPA • Controlled asthma (according to locally prevalent guidelines) • Fulfilling the diagnostic criteria of ABPA (Table 2)
1	Acute	• No previous diagnosis of ABPA • Clinical presentation consistent with ABPA • Conforming to the diagnostic criteria of ABPA
1a	With mucoid impaction	Mucoid impaction observed on chest imaging
1b	Without mucoid impaction	Absence of mucoid impaction on chest imaging
2	Response	• Either clinical or radiological improvement AND • Decline in IgE by ≥25% of baseline (at 8 wk)
3	Exacerbation	• Either clinical or radiological worsening AND • Increase in IgE by ≥50% from the "new baseline" established during response/remission
4	Remission	• Sustained clinicoradiological improvement AND • IgE levels persisting at or below the "new baseline" (or increase by <50%) for ≥6 mo off treatment
5a	Treatment-dependent ABPA	• ≥2 exacerbations within 6 mo of discontinuing treatment OR • Clinical or radiological worsening AND rise in serum total IgE levels, on tapering oral steroids/azoles
5b	Glucocorticoid-dependent asthma	Systemic glucocorticoids required for asthma control, while ABPA is inactive (as indicated by stable IgE levels and thoracic imaging)
6	Advanced ABPA	• Extensive bronchiectasis due to ABPA on CT chest AND • Cor pulmonale or chronic type II respiratory failure

Objectifs ET axes thérapeutiques - ABPA

- Réduction de l'inflammation locale
  - **Corticoïdes** systémiques
- Diminution de la prolifération mycélienne
  - **Traitement azolé**
- **Désobstruction** des voies aériennes
  - Drainage quotidien et endoscopie sur collapsus
- Traitement des **surinfections** bactériennes
- Eradication de l'*Aspergillus* de l'**environnement**
- Traitement d'**entretien LAmB nébulisé**
- **Anticorps monoclonaux humanisés**

2022

- Réduction de l'inflammation locale
- Traitement de l'exacerbation
- **Prévention des exacerbations**
- Limitation des effets secondaires liés aux traitements
- Arrêter ou limiter la progression des dilatations bronchiques

Clin Chest Med 43 (2022) 99–125

Axes thérapeutiques

Place des azolés

Corticoïdes : régime court

Traitement d'entretien

Nébulisation Amphotéricine B

Place des anticorps monoclonaux

Axes thérapeutiques

Corticoïdes : régime court

Place des azolés

Traitement d'entretien

Nébulisation Amphotéricine B

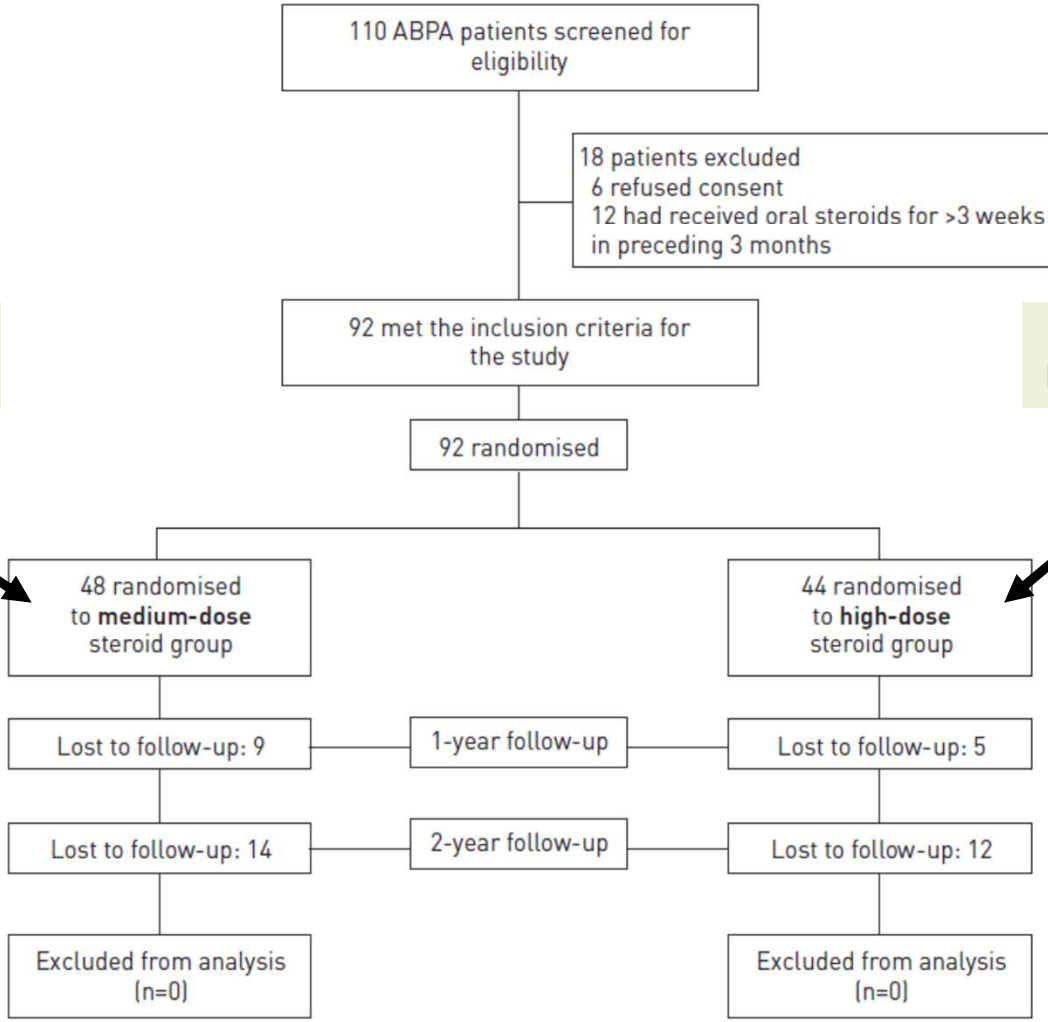
Place des anticorps monoclonaux

A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating ast

Ritesh Agarwal[1], Ashutosh N. Aggarwal[1], Sahajal Dhoori
Inderpaul Singh Sehgal[1], Mandeep Garg[2], Biman Saikia[3]
and Arunaloke Chakrabarti[4]

0,5 mg/kg/j pd 2 semaines
baisse en pallier sur 3 mois

0,75 mg/kg/j pd 6 semaines
baisse en pallier sur 12 mois



Eur Respir J 2015

A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma

Ritesh Agarwal[1], Ashutosh N. Aggarwal[1], Sahajal Dhooria[1], Inderpaul Singh Sehgal[1], Mandeep Garg[2], Biman Saikia[3], Digambar Behera[1] and Arunaloke Chakrabarti[4]

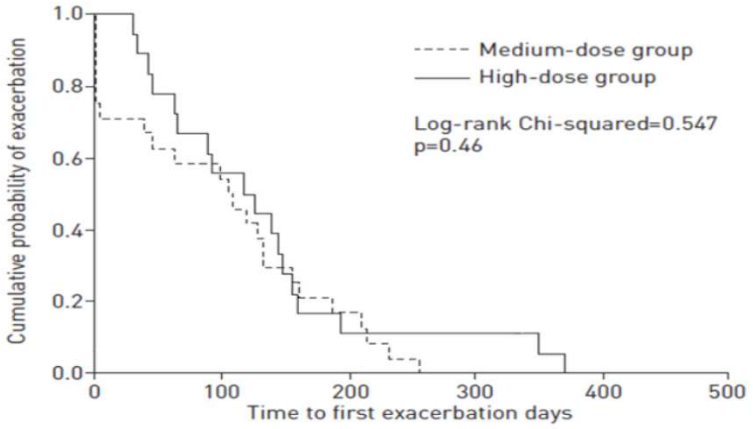


FIGURE 2 Time to first exacerbation in patients receiving high-dose *versus* medium-dose glucocorticoids. Time to first exacerbation was similar in the two groups.

TABLE 2 Study outcomes

	High-dose steroid group	Medium-dose steroid group	p-value
Subjects n	44	48	
Primary outcomes			
Subjects with exacerbations after 1 year of treatment	18 (40.9; 27.7–55.6)	24 (50; 36.4–63.6)	0.592
Subjects with glucocorticoid-dependent ABPA after 2 years of treatment	5 (11.4; 4.9–23.9)	7 (14.6; 7.3–27.2)	0.882
Secondary outcomes			
Response after 6 weeks of treatment	44 (100; 91.9–100)	42 (87.5; 75.3–94.1)	0.045
Percentage decline in IgE after 6 weeks of treatment	43.8 (36.8–50.9)	11.8 (−8.1–31.7)	0.025
Difference in FEV_1 after 6 weeks of treatment L	0.27 (0.17–0.37)	0.34 (0.23–0.45)	0.426
Difference in FVC after 6 weeks of treatment L	0.37 (0.19–0.54)	0.37 (0.26–0.49)	0.725
Time to first exacerbation after stopping therapy days	132 (84–180)	100 (65–136)	0.262
Total amount of glucocorticoid mg	4011 (3620–4401)	1694 (1578–1810)	0.0001
Glucocorticoid-related adverse reactions			
Cushingoid habitus	35 (79.6; 65.5–88.9)	14 (29.2; 18.2–43.2)	0.0001
Hypertension	1 (2.3; 0.4–11.8)	0	
Hyperglycaemia	1 (2.3; 0.4–11.8)	0	
Hypertrichosis	5 (11.4; 4.9–23.9)	0	
Acne	16 (36.4; 23.8–51.1)	10 (20.8; 11.7–34.3)	0.098
Striae	8 (18.2; 9.5–31.9)	1 (2.1; 0.4–10.9)	0.025
Weight gain (>10% of baseline)	24 (54.6; 40.1–68.3)	8 (16.7; 8.7–29.6)	0.0001
Mood changes	4 (9.1; 3.6–21.2)	2 (4.2; 1.2–13.9)	0.594

All data are presented as n (%; 95% CI) or mean (95% CI), unless otherwise stated. All outcomes are based on an intention-to-treat analysis. ABPA: allergic bronchopulmonary aspergillosis; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Eur Respir J 2015

For the ABPA complicating asthma ISHAM working group

Table 7: Treatment protocols for the management of ABPA

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Table 4. Doses of various drugs used in the management of allergic bronchopulmonary aspergillosis

Oral glucocorticoids
Prednisolone (or equivalent) 0.5 mg/kg/day for two weeks, then on alternate days for eight weeks. Then taper by 5 mg every two weeks and discontinue Patients need to be closely followed as 13% of patients may not respond and may require escalation of steroid dose
Nebulized amphotericin B
Amphotericin B deoxycholate Daily: 5-40 mg twice daily Intermittent: 20 mg (10 mg twice daily) thrice weekly *Liposomal amphotericin B* Intermittent: 25 mg twice weekly *Amphotericin B lipid complex* Intermittent: 50 mg twice weekly
Pulse methylprednisolone
15 mg/kg/day (maximum 1 gm) intravenous infusion for three consecutive days
Omalizumab
375 mg subcutaneous injection every two weeks for 4-6 months
Inhaled corticosteroids
Single agent inhaled corticosteroid therapy should not be used for controlling immunological activity of ABPA. However, they are useful agents in the management of asthma
Follow-up and monitoring
• Patients are followed up with monitoring of clinical symptoms (cough, dyspnea), chest radiograph and total IgE levels, every eight weeks • Monitor for adverse effects of treatment • Satisfactory response to therapy is suggested when there is clinical and/or radiological improvement with at least 25% decline in IgE levels • Monitor IgE frequently to establish the 'new' baseline level for an individual patient • Clinical and/or radiological worsening along with 50% increase in IgE levels suggests an exacerbation

Agarwal et al, Expert Review of Respir Med, 2016

Axes thérapeutiques

Place des azolés

Corticoïdes : régime court

Traitement d'entretien

Nébulisation Amphotéricine B

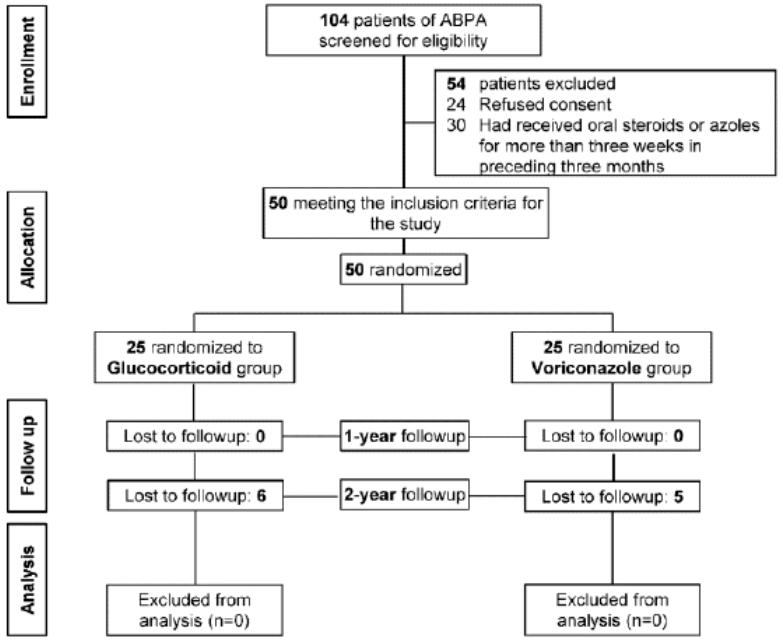
Place des anticorps monoclonaux

A randomized trial of voriconazole and prednisolone monotherapy in acute-stage ABPA complicating asthma

Ritesh Agarwal, Sahajal Dhooria, Inderpaul Singh Sehgal, Ashutosh N. Aggarwal, Mandeep Garg, Biman Saikia, Arunaloke Chakrabarti

	Prednisolone group (n=25)	Voriconazole group (n=25)	Estimate difference (95% CI)	P value
Primary outcomes				
Subjects with composite response				
After 6 weeks of treatment	25 (100%)	24 (96.0%)	0.04 (-0.10 – 0.20)	0.31
After 3 months of treatment	25 (100%)	24 (96.0%)	0.04 (-0.10 – 0.20)	0.31
Number of subjects experiencing exacerbation				
After 12 months of treatment	2 (8.0%)	3 (12.0%)	0.04 (-0.23 – 0.15)	0.64
After 24 months of treatment	3 (12.0%)	5 (20.0%)	0.08 (-0.29 – 0.13)	0.44
Other outcomes				
Percentage decline in IgE after 6 weeks of treatment	47.9 (37.3-58.4)	45.4 (36.4-54.4)	2.48 (-11.04 – 16.00)	0.66
Time to first exacerbation	339 (85-593)	248 (73-424)	91 (12 – 170)	0.30
Difference in FEV1 (mL) after 6 weeks of treatment	271 191-350)	370 (205-536)	-99 (-269 – 71)	0.69
Difference in FVC (mL) after 6 weeks of treatment	312 (234-389)	395 (262-528)	-83 (-229 – 63)	0.67
Change in score after 6 weeks of treatment	-25.1 (-17.9 to -32.3)	-22.7 (-14.2 to -31.3)	2.4 (-8.3 – 13.1)	0.99
Total number of ABPA exacerbations	0.24 (0.02-0.46)	0.52 (0.23-0.81)	-0.28 (-0.63 – 0.07)	0.12
Total number of asthma exacerbations	0.36 (0.13-0.59)	0.48 (0.27-0.69)	-99 (-0.43 – 0.19)	0.32
Adverse reactions				
Cushingoid habitus	11 (44.0%)	0	0.44 (0.22 – 0.63)	0.0001
Hypertension	0	0	-	-
Hyperglycemia	0	0	-	-
Hypertrichosis	2 (8.0%)	0	0.08 (-0.07 – 0.25)	0.49
Acne	2 (8.0%)	0	0.08 (-0.07 – 0.25)	0.49
Striae	1 (4.0%)	0	0.04 (-0.10 – 0.20)	0.99
Weight gain (%) at six weeks	6.9 (3.7 to 10.3)	0.74 (-1.4 to 2.9)	6.23 (2.14 – 10.05)	0.002
Weight gain >5%	13 (52%)	6 (24%)	0.28 (0.01 – 0.50)	0.04
Mood changes	0	0	-	-
Fatigue	0	0	-	-
Visual disturbance	0	3 (12.0%)	-0.12 (-0.30 – 0.04)	0.24
Skin rash	0	3 (12.0%)	-0.12 (-0.30 – 0.04)	0.24
Liver function test abnormalities	0	8 (32.0%)	-0.32 (-0.52 – -0.12)	0.004
Nausea	0	2 (8.0%)	-0.08 (-0.25 – 0.07)	0.49
Discontinuation of study drug	0	0	-	-
Any adverse effect	29	22	-	-

a)



c)

R Agarwal, ERJ, 2018

A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma

Ritesh Agarwal, MD, DM; Sahajal Dhooria, MD, DM; Inderpaul Singh Sehgal, MD, DM; Ashutosh N. Aggarwal, MD, DM; Mandeep Garg, MD; Biman Saikia, MD; Digambar Behera, MD; and Arunaloke Chakrabarti, MD

CHEST

TABLE 2] Outcomes of Study Subjects Treated With Prednisolone or Itraconazole (N = 131)

Outcome	Prednisolone Group (n = 63)	Itraconazole Group (n = 68)	Estimated Difference (95% CI)	*P* Value
Primary outcomes				
Subjects with response following 6 wk of treatment[a]	63 (100%)	60 (88.2%)	−11.8 (−21.5 to −3.7)	.007
Subjects with response following 3 mo of treatment	63 (100%)	60 (100%)	0 (−0.06 to 0.06)	…
Complete remission following 3 mo of stopping treatment	60 (95.2%)	59 (98.3%)	−0.03 (−0.05 to 0.12)	.39
Complete remission following 6 mo of stopping treatment	58 (92.1%)	59 (98.3%)	0.05 (−0.05 to 0.14)	.13
Percentage decline in IgE following 6 wk of treatment (n = 123)	54.5 (48.9-60.1)	51.8 (42.9-60.8)	−2.7 (−7.6 to 13.4)	.87
Percentage decline in IgE following 3 mo of treatment (n = 123)	66.9 (62.0-71.8)	65.6 (59.1-72.1)	−1.3 (−6.7 to 9.3)	.80
No. of subjects experiencing exacerbation following 1 y of treatment (n = 123)	6 (9.5%)	7 (11.7%)	−2.1 (−13.8 to 9.2)	.93
No. of subjects experiencing exacerbation following 2 y of treatment (n = 123)	14 (22.2%)	17 (28.3%)	−6.1 (−21.3 to 9.2)	.44
Secondary outcomes				
Time to first exacerbation (n = 123)	437 (307-567)	442 (369-521)	8 (−76 to 61)	.91
Difference in FEV_1 following 6 wk of treatment (n = 123)	0.33 (0.26-0.41)	0.30 (0.22-0.37)	0.03 (−0.07 to 0.13)	.20
Difference in FVC following 6 wk of treatment (n = 123)	0.37 (0.19-0.54)	0.37 (0.26-0.49)	0.08 (−0.06 to 0.22)	.42
Subjects with exacerbation following 6 mo of treatment	6 (9.5%)	6 (10.0%)	0.01 (−0.11 to 0.12)	.93
Total No. of ABPA exacerbations	0.57 (0.32-0.82)	0.83 (0.48-1.18)	−0.26 (−0.69 to 0.17)	.32
Total No. of asthma exacerbations	0.48 (0.28-0.67)	0.62 (0.36-0.87)	−0.14 (−0.46 to 0.18)	.45

Data are presented as mean (95% CI), unless otherwise stated.

[a]All other outcomes have been analyzed following exclusion of the eight subjects who failed to exhibit a response after 6 weeks of treatment.

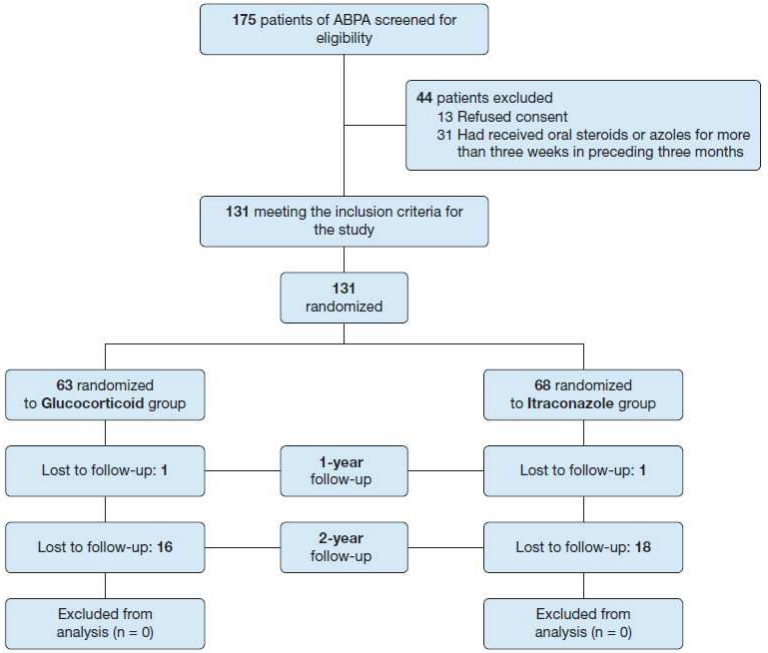


Figure 1 – *CONSORT diagram demonstrating the flow of participants in the study. ABPA = allergic bronchopulmonary aspergillosis.*

TABLE 3] Adverse Reactions Noted in Study Subjects Treated With Prednisolone or Itraconazole (n = 123)

Adverse Reaction	Prednisolone Group (n = 63)	Itraconazole Group (n = 60)[a]	Estimated Difference (95% CI)	*P* Value
Discontinuation of study drug	0	0	…	…
Cushingoid habitus	52 (82.5%)	0	82.5 (69.9 to 89.9)	.0001
Hypertension	0	0	…	…
Hyperglycemia	2 (3.2%)	0	3.2 (−3.3 to 10.9)	.50
Hypertrichosis	12 (19.1%)	0	19.1 (9.2 to 30.4)	.002
Acne	11 (17.5%)	0	17.5 (7.9 to 28.6)	.002
Striae	8 (12.7%)	0	12.7 (4.1 to 23.1)	.003
Weight gain (> 10% of baseline) at 6 wk	37 (58.7%)	2 (3.3%)	55.4 (40.7 to 66.9)	.0001
Mood changes	3 (4.8%)	0	4.8 (−2.0 to 13.1)	.24
Fatigue	3 (4.8%)	8 (13.3%)	−8.6 (−19.9 to 1.9)	.26
Liver function test abnormalities	0	9 (15%)	−15 (−26.1 to −6.0)	.001
Nausea	0	2 (3.3%)	−3.3 (−11.4 to 2.9)	.24

[a]The outcomes have been analyzed following exclusion of the eight subjects who failed to exhibit a response after 6 weeks of treatment.

Agarwal R, CHEST, 2018

For the ABPA complicating asthma ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

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Oral azoles
Oral itraconazole 200 mg twice a day, for at least 24 weeks. Oral voriconazole 200 mg twice a day, for at least 24 weeks.
Daily: 5-40 mg twice daily Intermittent: 20 mg (10 mg twice daily) thrice weekly *Liposomal amphotericin B* Intermittent: 25 mg twice weekly *Amphotericin B lipid complex* Intermittent: 50 mg twice weekly
Pulse methylprednisolone
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Agarwal et al, Expert Review of Respir Med, 2016

Axes thérapeutiques

Place des azolés

Corticoïdes : régime court

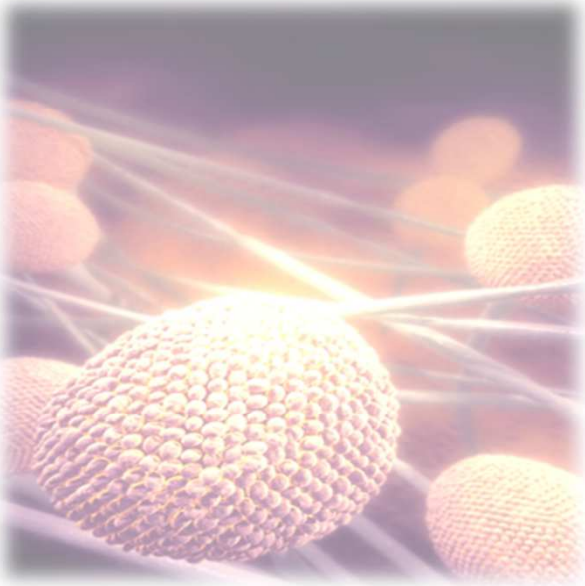
Nébulisation Amphotéricine B

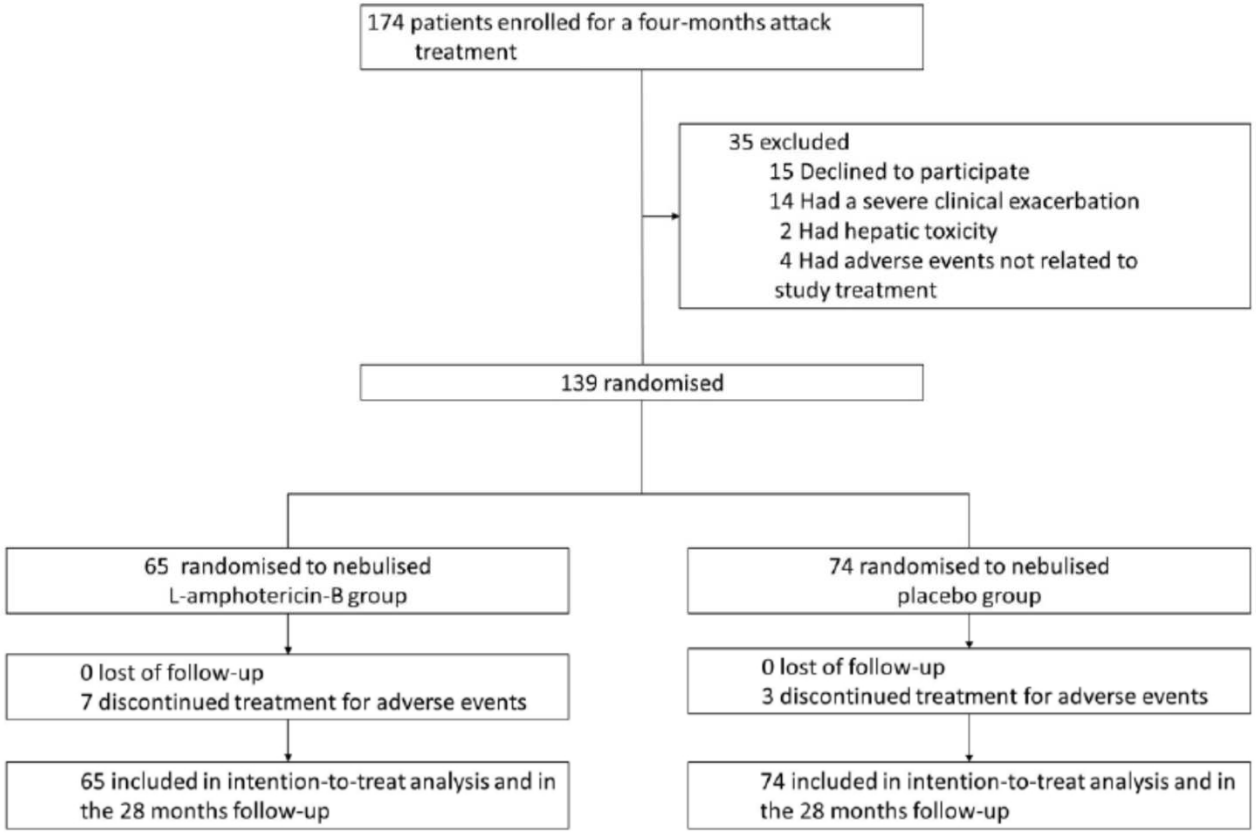
Traitement curatif

Traitement d'entretien

Place des anticorps monoclonaux

Nebulised liposomal-amphotericin-B as maintenance therapy in ABPA: a randomised, multicentre, trial





GODET C et al, Eur Resp J, nov 2021

TABLE 2 Primary and secondary outcomes according to treatment group.

	Nebulised L-amphotericin-B (N = 65)	Nebulised placebo (N = 74)	p value	Odds ratio or Rate Ratio (95% CI)
Primary outcome				
First severe clinical exacerbation at 24 months	33 (50.8)	38 (51.3)	0.95	0.98 (0.50-1.90)
Secondary outcomes				
First severe clinical exacerbation at 6 months (end of maintenance therapy)	9 (13.8)	20 (27.0)	0.06	0.43 (0.18-1.04)
First severe clinical exacerbation at 12 months	20 (30.8)	32 (43%)	0.13	0.58 (0.29-1.17)
Interval between randomisation and exacerbation at 24 months (days)	337 (168-476)	177 (64-288)	0.004	
Number of severe clinical exacerbations at 24 months	45	64	0.25	0.80 (0.55-1.17]
Number of severe clinical exacerbation per patient at 24 months	0.7	0.9	0.28	
Number of severe clinical exacerbations /number of patients with at least one severe clinical exacerbation "at 24 months			0.03	

Related or not to ABPA

GODET C et al, Eur Resp J, nov 2021

Nebulised liposomal-amphotericin-B as maintenance therapy in ABPA: a randomised, multicentre, trial

Figure 3A

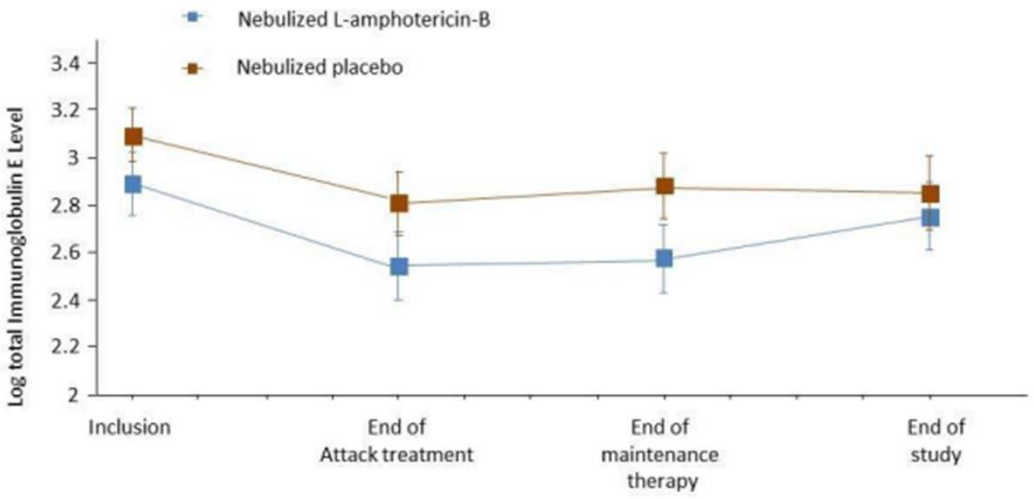
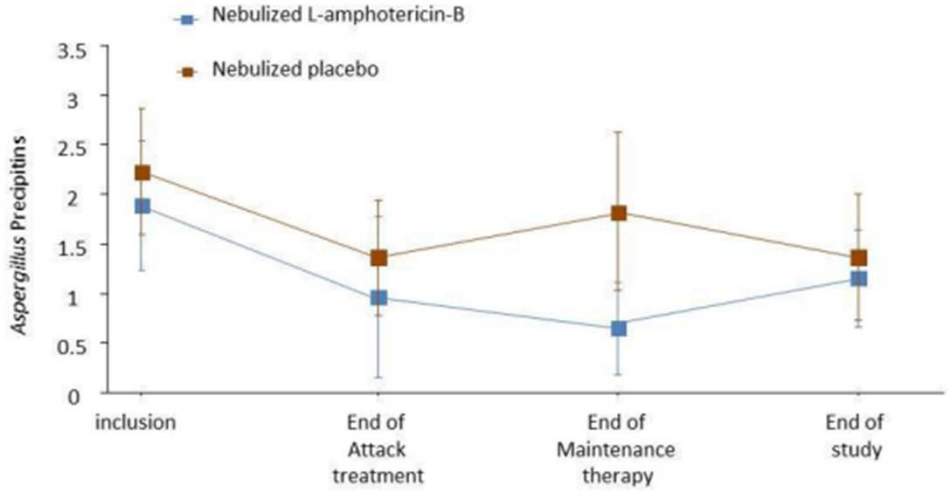


Figure 3B



GODET C et al, Eur Resp J, nov 2021

TABLE 2 Primary and secondary outcomes according to treatment group.

	Nebulised L-amphotericin-B (N = 65)	Nebulised placebo (N = 74)	p value	Odds ratio or Rate Ratio (95% CI)
Immediate tolerance of nebulised maintenance therapy				
Dyspnoea	15 (23.1)	7 (9.5)		0.02
Cough	20 (30.7)	11 (14.9)		0.02
Nausea	9 (13.8)	13 (17.6)		0.57
Vomiting	2 (3.1)	4 (5.4)		0.69
Headache	12 (18.5)	18 (24.3)		0.42
Reasons for maintenance therapy discontinuation				0.19
Decision of patient (not related to an adverse event)	4 (6.1)	1 (1.3)		
Hypersensitivity syndrome	2 (3.1)	0 (0.0)		
Persistent cough	0 (0.0)	1 (1.3)		
Severe clinical exacerbation	1 (1.5)	1 (1.3)		

GODET C et al, Eur Resp J, nov 2021

Axes thérapeutiques

Corticoïdes : régime court

Place des azolés

Nébulisation Amphotéricine B

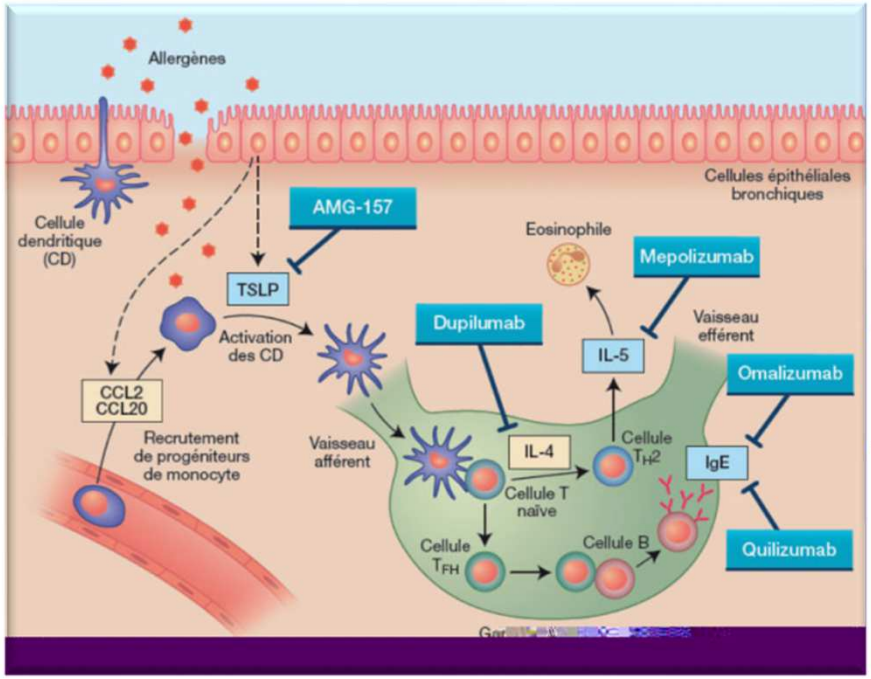
Traitement curatif

Traitement d'entretien

Place des anticorps monoclonaux

Ongoing RCTs evaluating mepolizumab, dupilumab, and Benralizumab

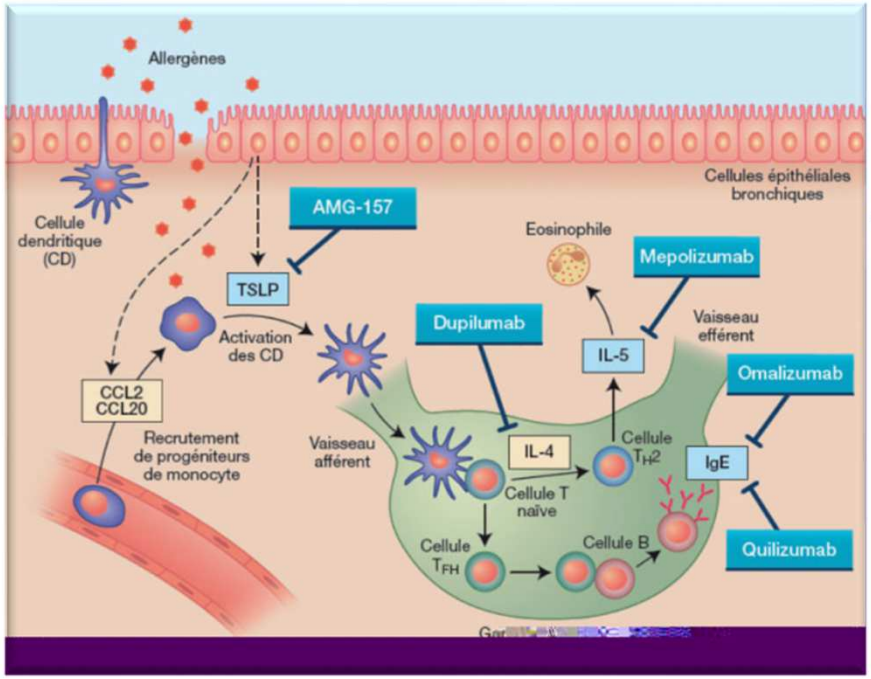
Place des AC-monoclonaux dans la prise en charge de l'ABPA?



Au cours de l'ABPA, l'inhalation de spores est suivie du développement d'hyphes aspergillaires avec induction d'une réponse lymphocytaire T (Th2 CD4⁺) et de la production d'anticorps (IgE médiée [type I] et IgG médiée [type III])

- **les Th2 libèrent des cytokines dont :**
  - IL6 stimulent la croissance des plasmocytes sécréteurs d'AC
  - IL4 qui augmentent la sécrétion d'AC de type IgE qui induisent la libération d'histamine par les mastocytes
  - IL5 qui stimule la croissance des éosinophiles
  - IL10 qui réprime la réponse des macrophages

Place des AC-monoclonaux dans la prise en charge de l'ABPA?



Les mécanismes qui sous-tendent l'**exacerbation de l'ABPA** sont complexes :

- La sécrétion accrue d'IL4 et IL5 suggère que l'inflammation type Th2 contribue à la pathogénie de l'exacerbation de l'ABPA
- Des niveaux élevés d'IgE et des anticorps spécifiques contre *A. fumigatus* suggèrent que **des bénéfices cliniques peuvent résulter du traitement avec l'omalizumab**
- Une éosinophilie marquée dans le sang et le LBA suggère que **des bénéfices cliniques peuvent résulter d'un traitement par mépolizumab ou benralizumab**

Place des AC-monoclonaux dans la prise en charge de l'ABPA?

Allergic Bronchopulmonary Aspergillosis

Ritesh Agarwal, MD, DM*, Valliappan Muthu, MD, DM, Inderpaul S. Sehgal, MD, DM, Sahajal Dhooria, MD, DM, Kuruswamy T. Prasad, MD, DM, Ashutosh N. Aggarwal, MD, DM

Clin Chest Med 43 (2022) 99–125

Omalizumab : No study has described the use of omalizumab in acute-stage ABPA.

The current use of omalizu mab is reserved for treatment-refractory ABPA or those who are intolerant to first-line treatment

Anecdotal reports and case series suggest the usefulness of therapies targeting IL-5

Due to lack of RCTs, anti-Th2 therapies should be reserved in patients with treatment-refractory ABPA, unconcontrolled asthma despite glucocorticoids, and patients encountering adverse effects with or having contraindications to glucocorticoids and antifungal triazoles.

Ongoing RCTs evaluating mepolizumab, dupilumab, and benralizumab will clarify the role of these agents in ABPA.

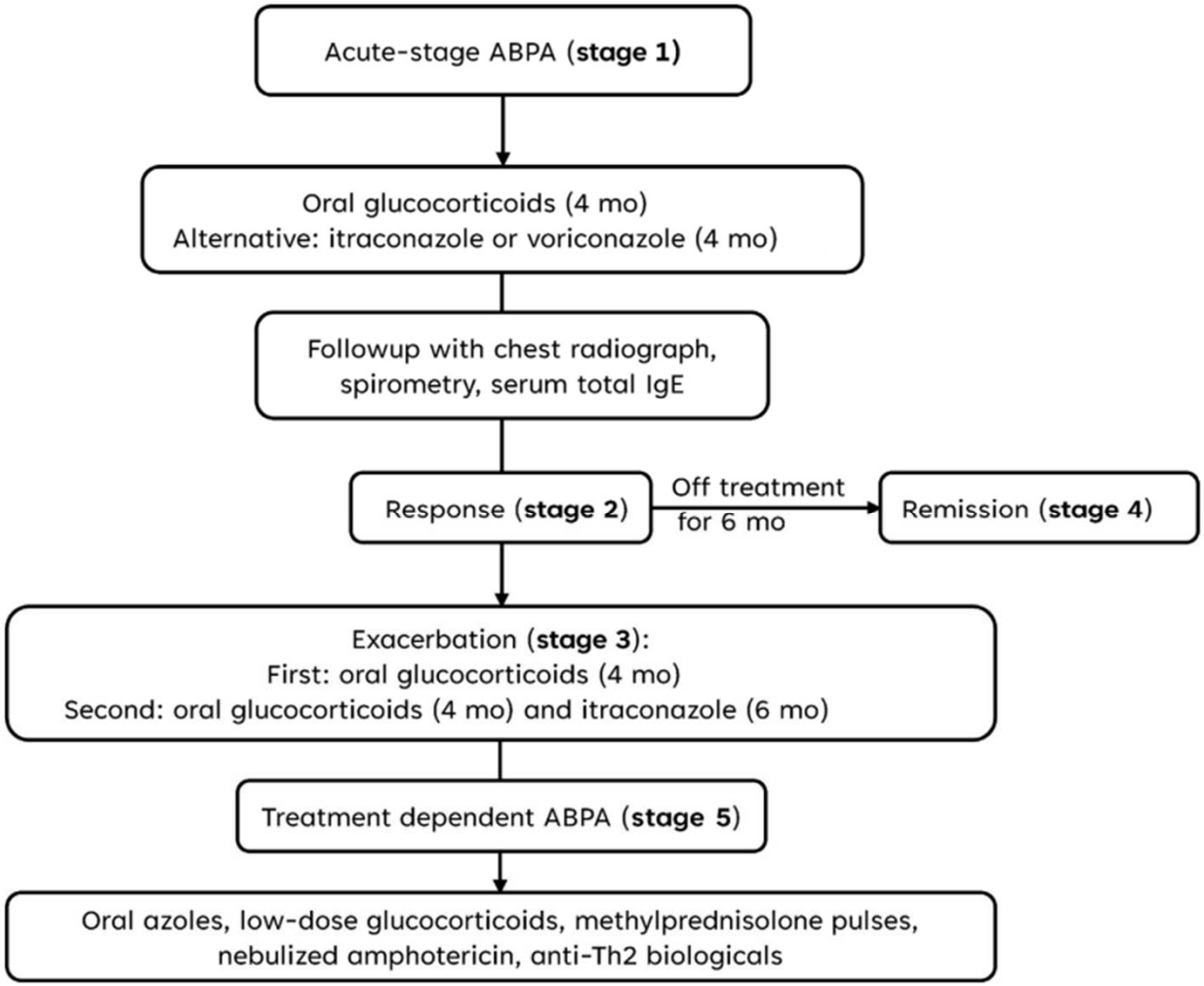
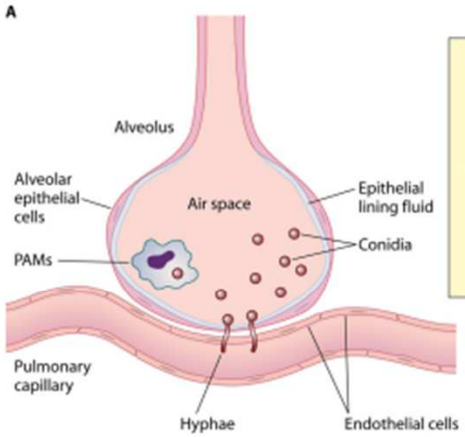
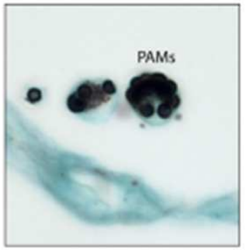


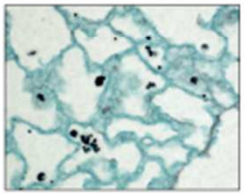
Fig. 6. Treatment algorithm for the management of allergic bronchopulmonary aspergillosis (ABPA) based on the current evidence.



Stage of disease
- Prophylaxis
- Early infection

Relevant tissues
- ELF
- Endothelial cells
- Alveolar epithelial cells
- PAMs





Tissue Penetration of Antifungal Agents

Timothy Felton,[a,b] Peter F. Troke,[c] William W. Hope[b]

Clinical Microbiology Reviews January 2014 Volume 27 Number 1

	Heart	Pericardial fluid	Liver	Pancreas	Kidney	Bone: Tissue	Bone: Synovial fluid	Prostate: Tissue	Prostate: Fluid	Brain: Tissue	Brain: CSF	Lung: Tissue	Lung: Alveolar cells	Lung: ELF	Spleen	Muscle	Reference
Fluconazole	X	X	X	X	X	X	X	X	X	X	X	X		O	X	X	(67, 70, 72, 120, 137, 200-203, 205, 219, 237, 238)
Itraconazole	X	X	O	X	X	X	O	X	X	O	X	X	X	X	X	X	(25, 56, 73, 74, 120, 121, 140, 220, 221, 239-242)
Voriconazole	X	X	O	O	X	X	X	X	X	X	X	X	X	X	X	O	(58, 80, 81, 83, 114, 142, 153, 154, 208, 224, 243, 252, 253)
Posaconazole		X	X	X						O	X		X	X			(57, 59, 85-89, 223, 244)
AmBd	X	X	X	X	X	O	X			X	X	O		X	X		(37, 52, 53, 91, 115, 123, 148, 151, 156, 210, 245-247, 249)
ABLC	X	X	X	X	X	O				O	X	X		X	X		(90, 92, 117, 125, 147, 155, 210, 246, 249)
L-AMB	X	X	X	X	X	O				X	X	X		X	X		(34, 53, 60, 90, 125, 147, 155, 210, 248, 249)
5-FC	O	X		O	O	O	O			O	X				O	O	(91, 96, 115, 116, 151, 156, 174, 250)
Anidulafungin	O	O		O	O	O				O	O	O	X	X	O		(58, 100, 102, 175, 251)
Caspofungin	X	X		O	O	O				O	X	O	X		O	O	(44, 103, 105, 113, 126, 130, 149)
Micafungin	X	X		X	O	O	X			X	X	O	X	X	O		(61, 62, 106-108, 127, 150, 252)

Pharmacological management of antifungal agents in pulmonary aspergillosis: an updated review

D. ECHEVERRIA-ESNAL ET AL. Aug 2021.

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY

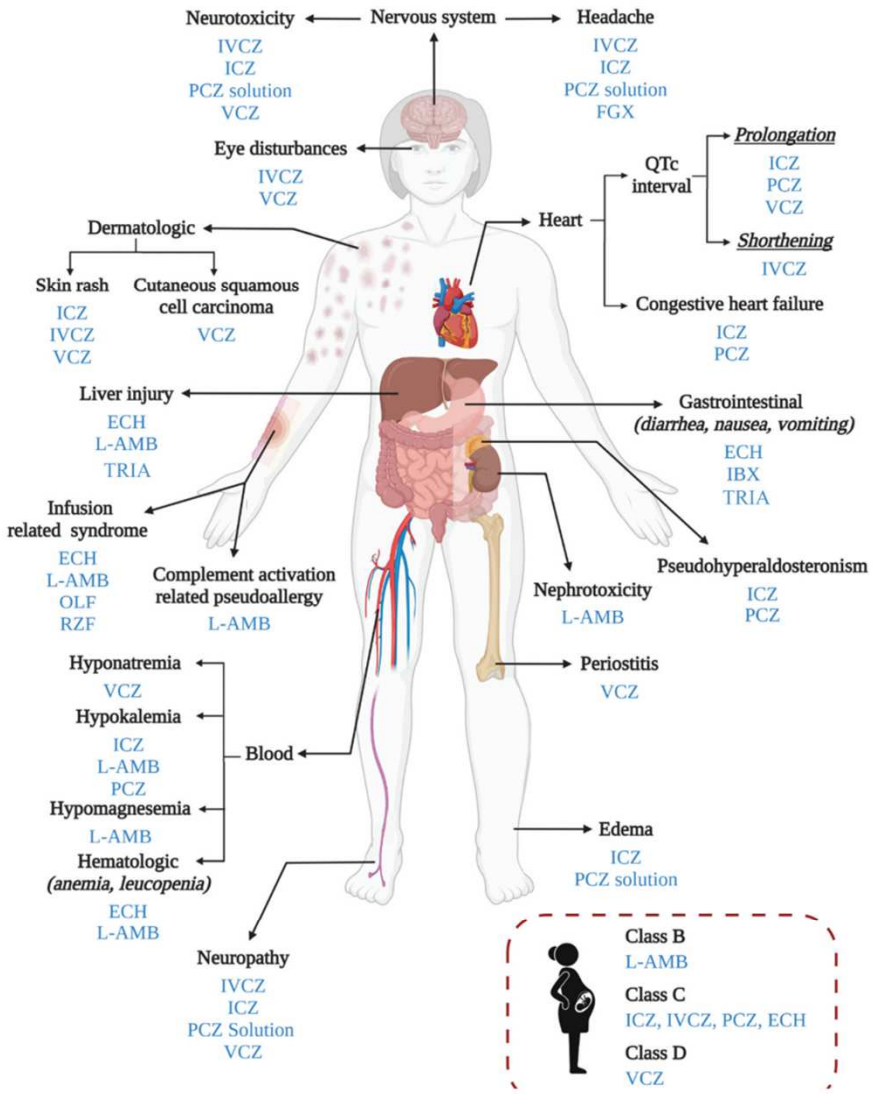


Figure 2. Summary of the main adverse effects of antifungals.

Figure legends. ECH: echinocandins; FGX: fosmanogepix; IBX: ibrexafungerp; ICZ: itraconazole; IVCZ: isavuconazole; L-AMB: liposomal amphotericin B; OLF: olorofim; PCZ: posaconazole; RZF: rezafungin; TRIA: triazoles; VCZ: voriconazole. Pregnancy risk was defined according to US FDA (131).

The role of antifungals in the management of patients with severe asthma

W. Garth Rapeport[1*], Kazuhiro Ito[1,2] and David W. Denning[3]

Rapeport *et al. Clin Transl Allergy* (2020) 10:46

35]. Persistent *Aspergillus* colonisation of the airways has been linked to adverse clinical outcomes which include higher rates of radiological abnormalities, lower post-bronchodilator FEV1, and significantly less reversibility to short acting bronchodilators in patients with a positive sputum fungal culture [8, 34–37]. A heavy burden

tion. Currently, the risk benefit relationship for antifungal therapy must be balanced by the need for prolonged therapy, systemic adverse effects, liability to drug interactions and concern over the emergence of resistance. The

tions and concern over the emergence of resistance. The recognition that the persistent presence of Aspergillus in the respiratory tract is associated with adverse outcomes enables the targeting of the sub-population most likely to benefit from antifungal treatment.

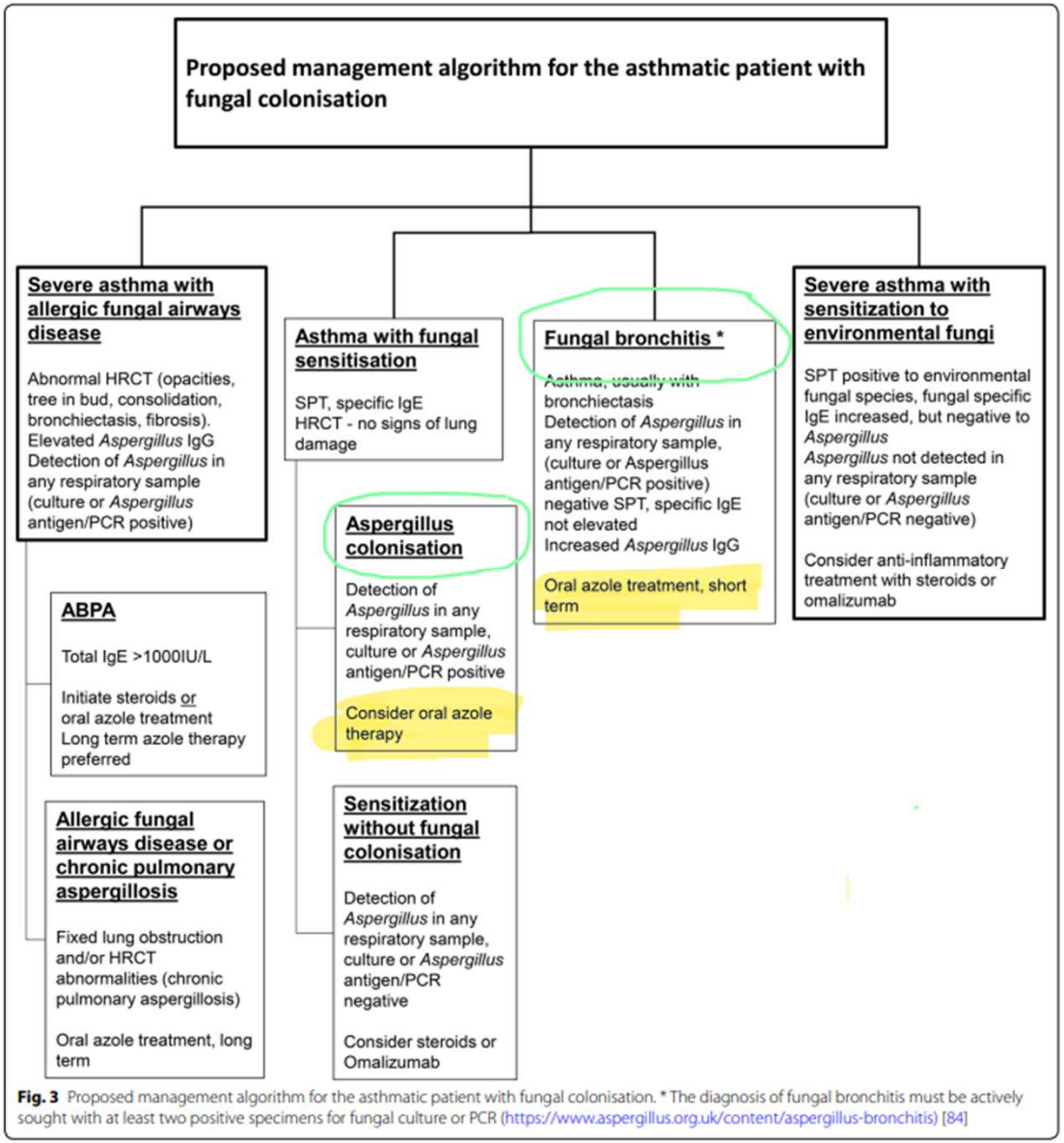
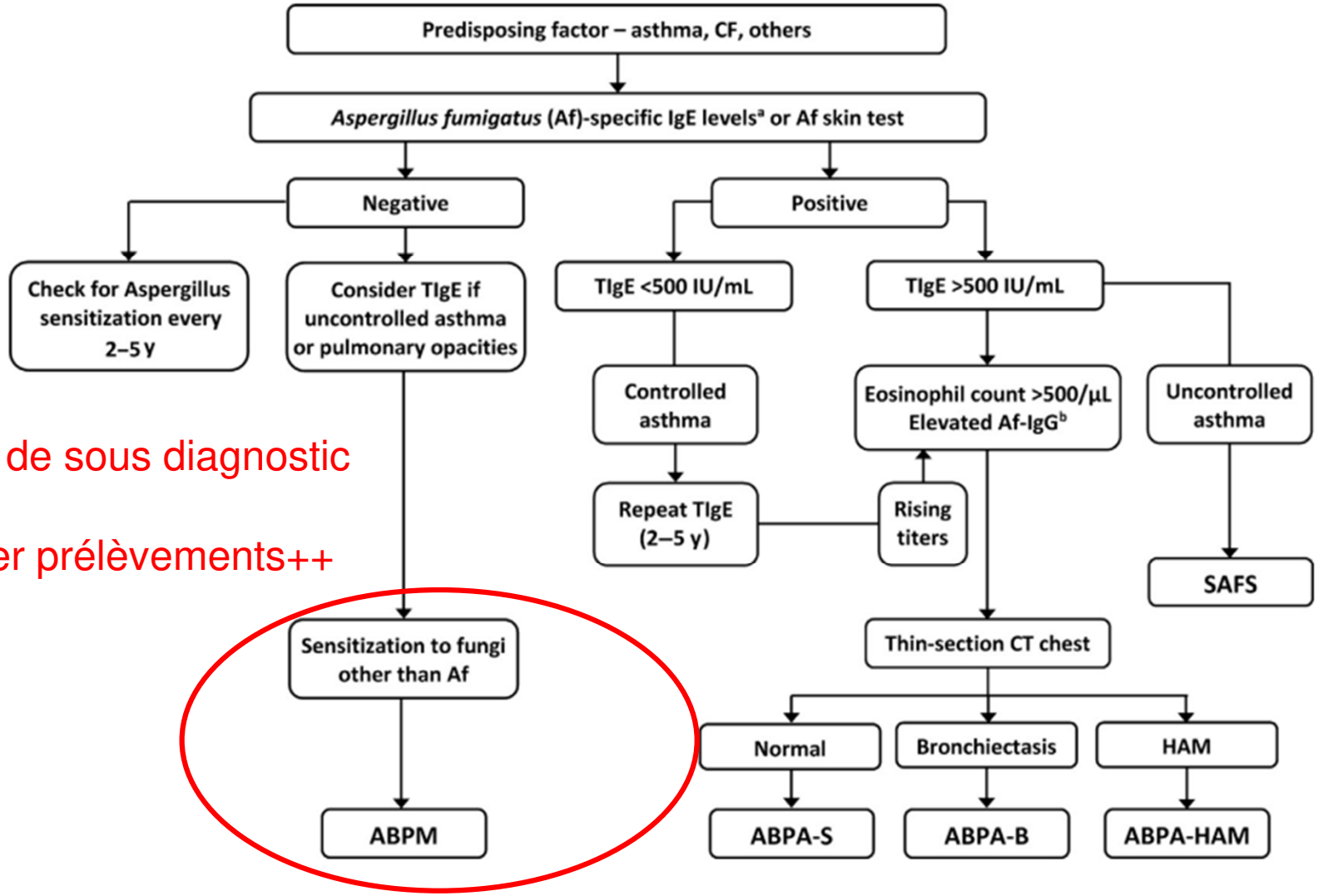


Fig. 3 Proposed management algorithm for the asthmatic patient with fungal colonisation. * The diagnosis of fungal bronchitis must be actively sought with at least two positive specimens for fungal culture or PCR (https://www.aspergillus.org.uk/content/aspergillus-bronchitis) [84]



Risque de sous diagnostic
ABPM
Associer prélèvements++

Clin Chest Med 43 (2022) 99–125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