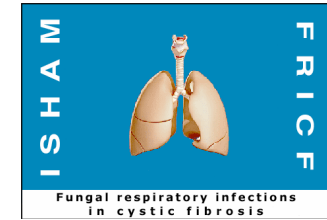


*First Meeting of the ISHAM Working Group on
"Fungal respiratory infections in Cystic Fibrosis"*



Risk Factors Associated with ABPA or Bronchial Colonisation with *Aspergillus spp.*

from the experience of the Cystic Fibrosis Reference Centres in Marseille, France



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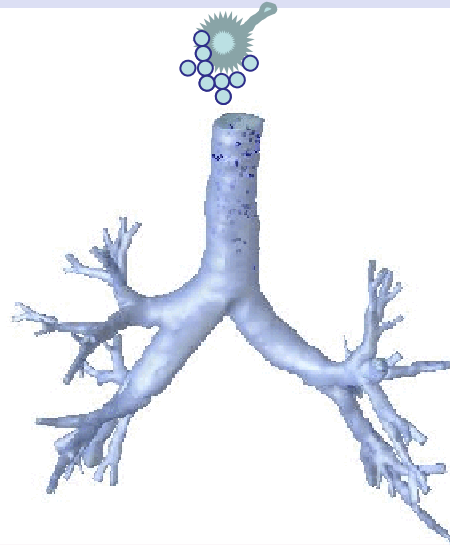
Inhaled *Aspergillus* conidia in CF patients

Host-Pathogen interactions

***Aspergillus* Sensitisation**

13 - 26 %

Prick-test *A. fumigatus* + and/or
anti-*A. fumigatus* IgE \geq class 2



***Aspergillus* Colonisation**

12 - 46 %

Aspergillus spp. isolation
in ≥ 2 in ≥ 4
respiratory samples /year

Bargon et al. Respir Med 1999

Allergic Bronchopulmonary Aspergillosis (ABPA)

0.1 - 15 %

***Aspergillus* airway colonisation + Type I, III and IV hypersensitivity**

1. Acute or subacute clinical deterioration not attributable to another aetiology
2. Total serum IgE concentration of 1000 IU/ml* (patient not under corticosteroids)
3. Immediate cutaneous reactivity to *A. fumigatus* (prick skin test wheal of 3 mm in diameter with surrounding erythema, patient is not under systemic antihistamines) or anti-*A. fumigatus* IgE.
4. Precipitins to *A. fumigatus* or in vitro demonstration of IgG antibody to *A. fumigatus*.
5. New or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.

*IgE level exceeding twice the upper limit of the age corrected normal range

Stevens DA et al. Clin Infect Dis 2003

Aspergillosis: an emerging disease in CF patients

➤ *Skov et al. Respir Med 2005*

- Yearly prevalence from **1998** to **2002** in children et adolescents with CF
 - ↑ *Aspergillus* colonisation: **7 % to 19 %**
 - ↑ ABPA: **0.3 to 4 %**

Causes ?



Scarce data

- Increasing ABPA prevalence
- Data predominantly in adults
- some ABPA risk factors studied, none identified

- *Mastella G. et al. Eur Respir J 2000*
- *Mroueh S. et al. Chest 1994*
- *Ritz N. et al. Eur J Pediatr 2005*
- *Chotirmall S. et al. Resp Care 2008*



Objective

Identify risk factors associated with ABPA or bronchial colonization with *Aspergillus* spp. in children with CF

Patients & Methods

- **Retrospective study**

- **Patients:** children followed in the Pediatric Reference Centre for Cystic Fibrosis Care (RCCFC) of the University Hospital of Marseille
- **Period:** inclusion date (beginning of the follow-up) to march 2006

- **Studied events** from inclusion to an **endpoint**
- **Endpoints:**
 - **ABPA**
 - ***Aspergillus* Colonisation**
 - **Last consultation at the RCCFC** if no *Aspergillus* event

Variables analysed

➤ **Age, gender, CFTR genotype, atopy, asthma**

➤ **Follow-up duration**

➤ **Nutritional status (BMI)***

➤ **Respiratory function (FEV1)***

➤ **Bronchial flora**

during the last 12 months

▪ ***S. aureus / P. aeruginosa***

(primo-infection, colonisation)

▪ ***S. maltophilia, A. xylosoxydans, B. cepacia***

(presence)

▪ ***Candida albicans***

(presence, frequency, duration)

➤ **Treatments:**

▪ **Inhaled corticoids** *cumulative dose in budesonide equivalent*

▪ **Azithromycine (Zithromax®)** *long-term cumulative duration*

▪ **RhDNase (Pulmozyme®)** *cumulative duration*

▪ **Inhaled antibacterial (TOBI®; COLI®)**

during the last 12 months long- / short-time regimen

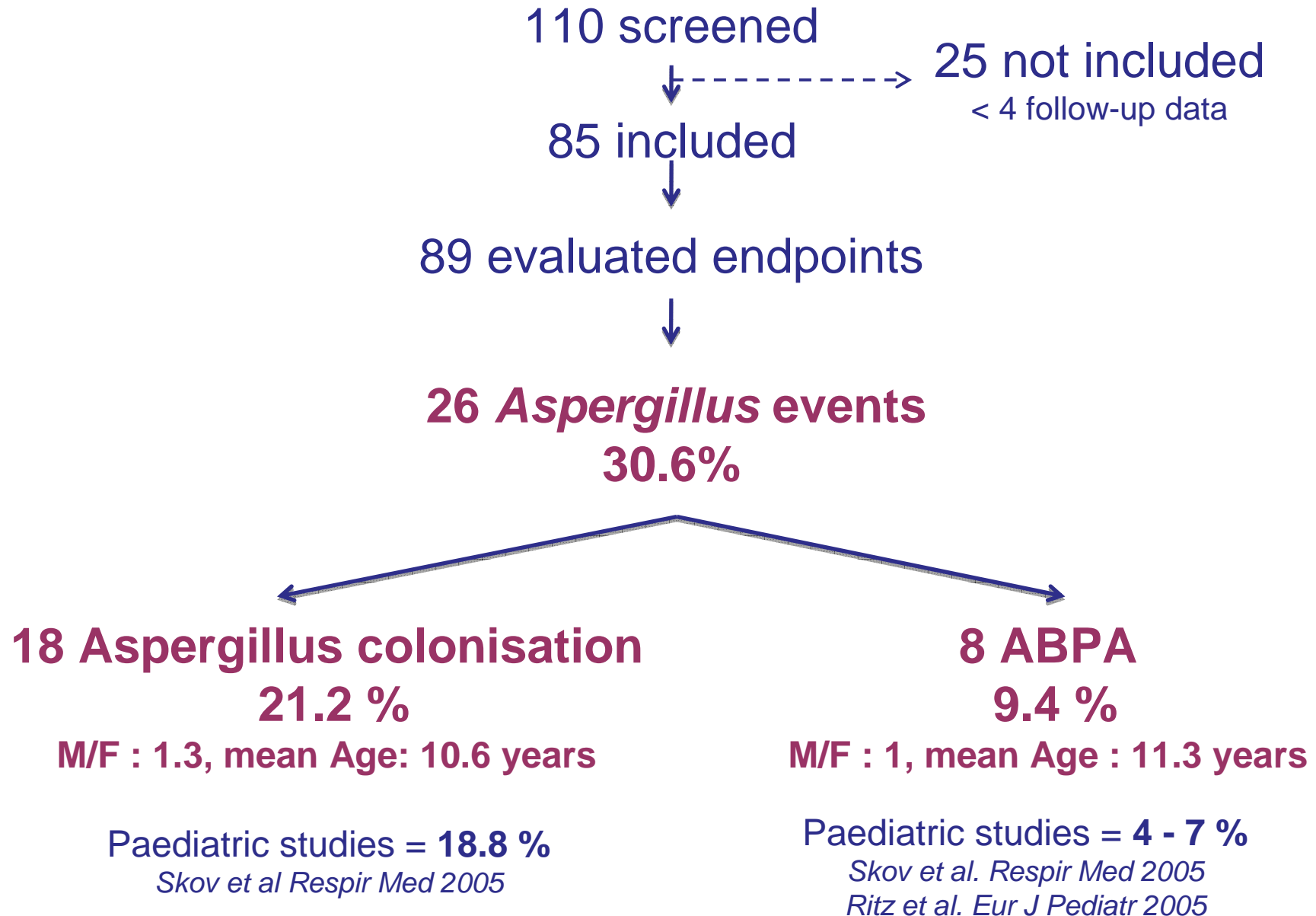
▪ **number of antibiotic regimen** (oral or intravenous) for bronchopulmonary infection *during the previous one or five years*

* Measured at the end-point [-6 to +1 months]

Statistical Analysis

- Patients presenting with an *Aspergillus* event (colonization or ABPA) were compared with those from all other patients at an endpoint
- Distinct *Aspergillus* events could be evaluated in the same patient
- **Univariate analysis** of qualitative data relied on Chi-2 or Fisher exact test
- **Multivariate analysis** relied on unconditional logistic regression.
 - All factors with $p < 0.20$ in the univariate analysis were included in a stepwise selection process to build a parsimonious model including covariates with $p < 0.05$ in the presence of other factors
- Statistical software: SAS ver. 9.1.3

Patients Flow Chart



Allergic Bronchopulmonary Aspergillosis

Factors significantly associated with ABPA

Univariate analysis

RhDNase : 100 % vs 51.9 %, $p=0.008$ (cum. duration: 47.3 vs 20.2 months, $p=0.05$)

RAST *Candida* : 60 % vs 5 %, $p=0.003$

RAST *Alternaria* : 100 % vs 12,7%, $p < 10^{-3}$

Uni- and Multivariate analysis

BMI < 3rd percentile : 50 % vs 9 %, $p=0.007$

OR=10.6, 95%CI [2.2–51.8], $p=0.004$



BMI < 3rd percentile was the only factor independently associated to ABPA

- in line with a large European study findings *Mastella et al. Eur Respir J 2000*
- Altered immunity hypothesis: poor nutrition $\rightarrow T_{reg}$ \rightarrow Th2 inhibition

Smith MJ and al. Eur J Respir Dis 1987; Montagnoli C and al. J Immunol 2006

Aspergillus Colonisation

Factors significantly associated with *Aspergillus* colonisation

Univariate and Multivariate analysis

Azithromycine: 66.7% vs 23.9 %, OR=6.4, 95 %CI [2.1-19.5], $p= 10^{-3}$

 **independent association with long-course low-dose azithromycine treatment**

Used since 2000 in patients with severe disease, chronic

P. aeruginosa colonisation. Anti-inflammatory effect ++

- ↑ quality of life, ↓ FEV1 decrease, ↓ Pulmonary exacerbations

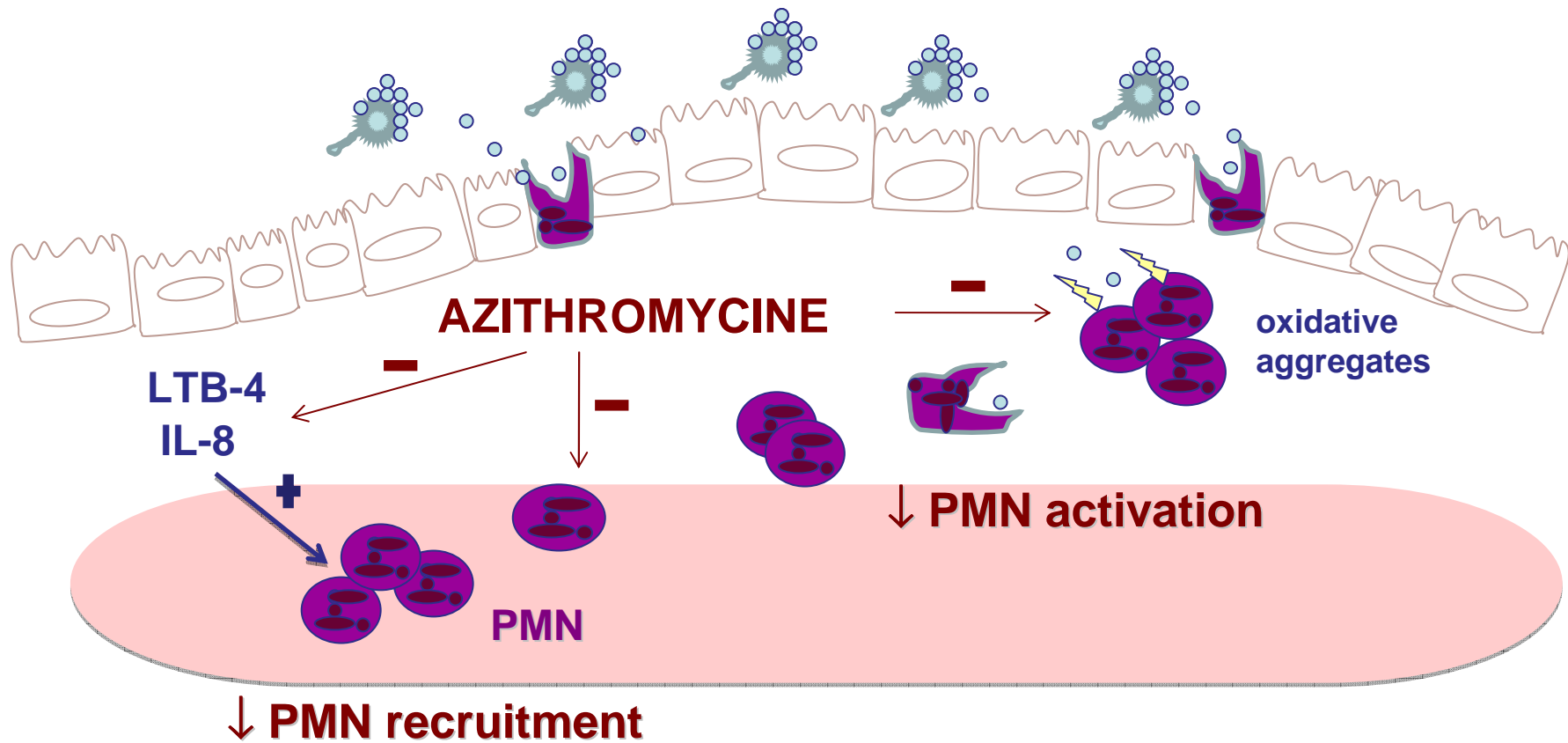
Wolter J. et al. Thorax 2002; Equi A et al. Lancet 2002; Saiman L et al. JAMA 2003;

Clément A et al. Thorax 2005

**Independent from other severe diseases criteria
in our study...**

Aspergillus colonisation and azithromycine

An immunopathological hypothesis



Bonnett CR et al. *Infect Immun* 2006. Verleden GM et al. *Am J Respir Crit Care Med* 2006

➔ **Azithromycine might facilitate *Aspergillus* colonisation via anti-*Aspergillus* first-line defences inhibition**

Conclusion

- **First extensive risk factors of ABPA or *Aspergillus* colonisation assessment in children with CF**
- **ABPA is independently associated with a poor nutritional status**
- **First evidence of *Aspergillus* colonisation independent association with long-term & low-dose azithromycine regimen**
- **Further studies are warranted to confirm these findings**

Thank you for your kind attention

