Fungal (*Aspergillus* and *Candida*) infections in Cystic fibrosis

Malena Cohen-Cymberknoh, MD

CF Center
Hadassah-Hebrew University Medical Center
Jerusalem, Israel

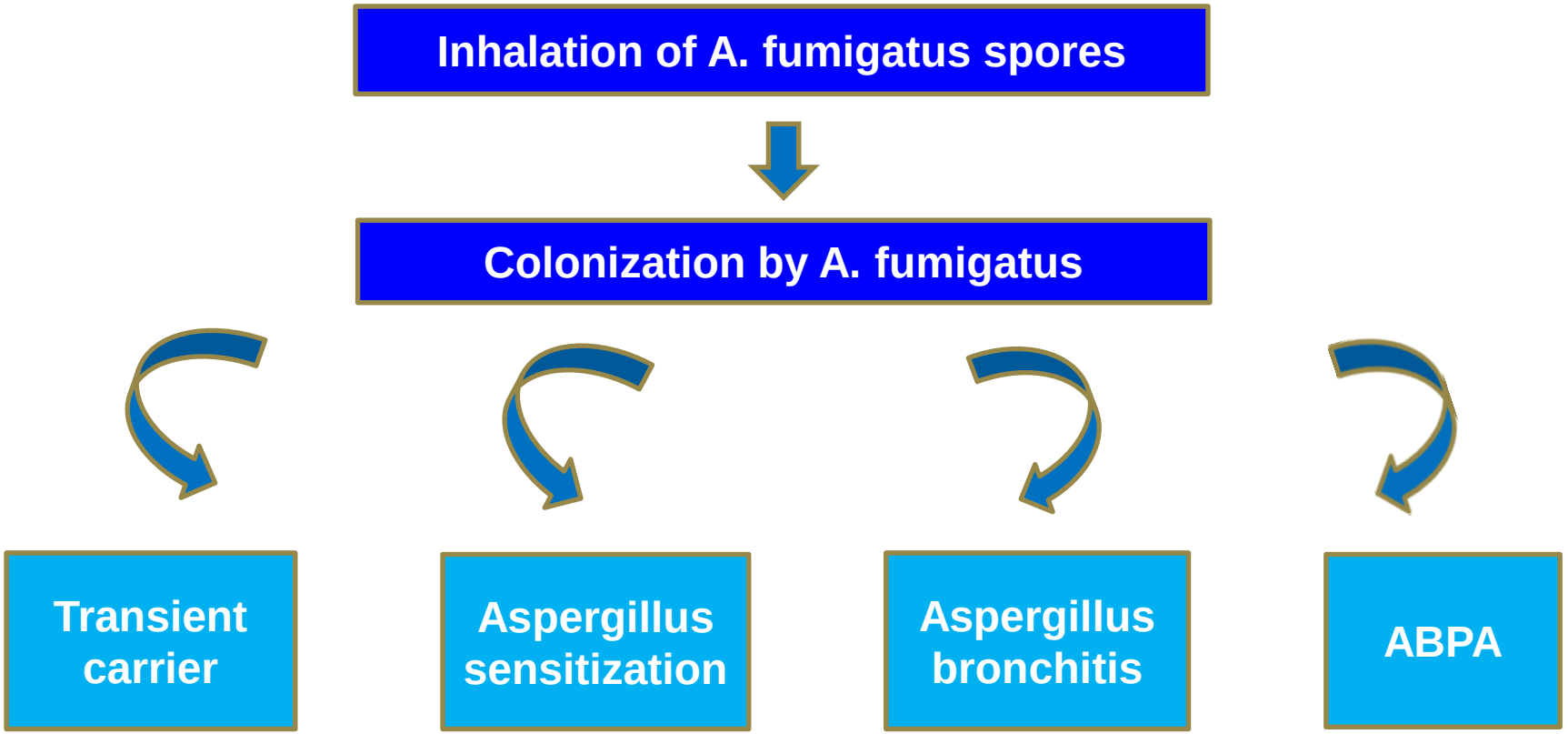
Israeli Annual CF Conference,
Herzlyia, 5-7 November 2015

Aspergillus and CF

- Over the last decade, a significant increase in the prevalence of fungi in CF respiratory cultures was reported
- *A. fumigatus* is the most common filamentous fungus involved in CF lung disease, with reported prevalence rates ranging from 6% to nearly 60%
- Abnormal mucociliary function and local immunogenic impairment promote fungal colonization whereas prolonged antibiotic and corticosteroid use facilitates fungal growth

Sudfeld, JCF 2010; Muthig Med Mycol. 2010; Maiz Chest 2002; Baxter Chest 2013

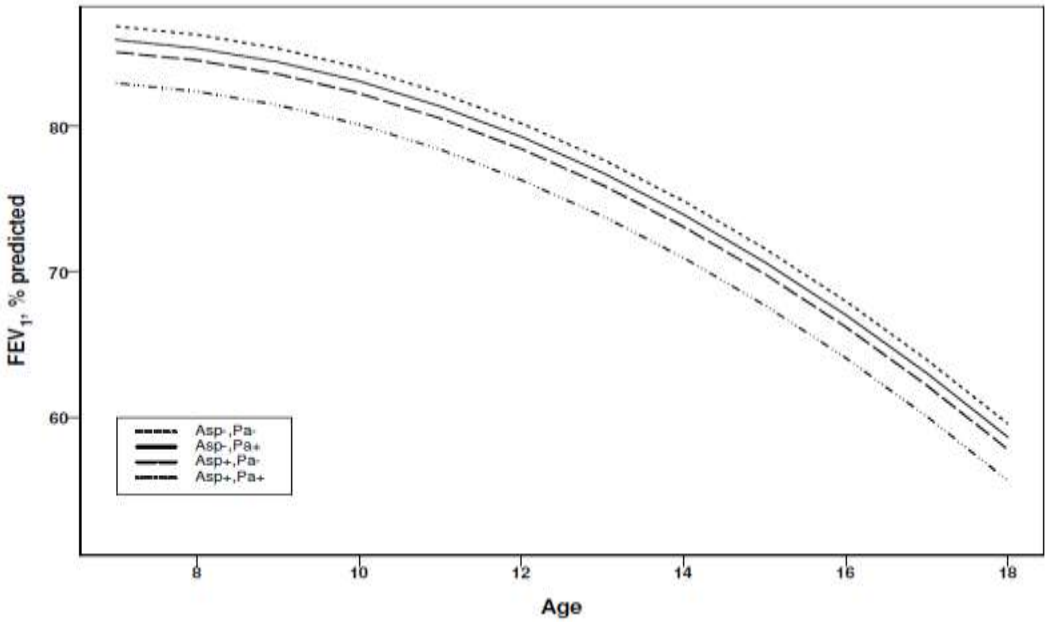
Classification of Aspergillus-related pulmonary disorders in CF



The Effect of Chronic Infection With *Aspergillus fumigatus* on Lung Function and Hospitalization in Cystic Fibrosis Patients

Reshma Amin, Annie Dupuis, Shawn D. Aaron and Felix Ratjen

- N= 230 CF patients; Hospital for Sick Children, Toronto, 1999-2006
- Persistent *A. fumigatus* infection and CFRD were associated with an increased risk of hospitalizations for pulmonary exacerbations
- Significant interaction between *A. fumigatus* and *P. aeruginosa* on FEV_1 *(p=0.0006)*



Adjusted for baseline pulmonary function, only chronic

***A. fumigatus* infection was associated with a significantly increased risk**

of pulmonary exacerbations

(RR 1.40, P= 0 .065)

Chest 2010

Aspergillus fumigatus chronic colonization and lung function decline in cystic fibrosis may have a two-way relationship

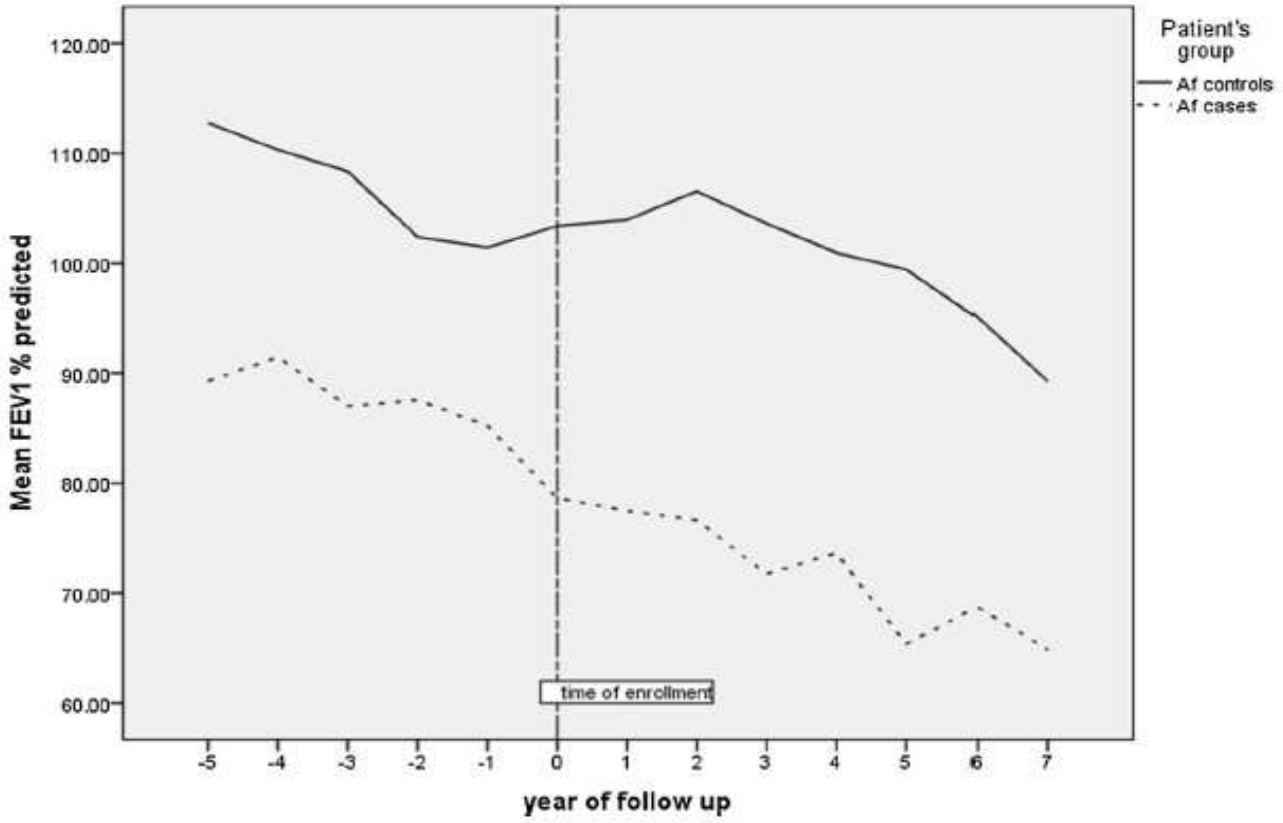
M. Noni[1] · A. Katelari[1] · G. Dimopoulos[2] · S.-E. Doudounakis[1] · C. Tzoumaka-Bakoula[3] · V. Spoulou[4]

- A case–control study of CF patients born from 1989 to 2002
- Medical records were reviewed from diagnosis until 12/2013
- Each patient chronically colonized* with *A. fumigatus* was matched with 3 control patients (never colonized by AF) for age, sex, and year of birth (±3 years)

**Chronic colonization: ≥2 positive sputum cultures in a given year*

Eur J Clin Microbiol Infect Dis 2015

Mean FEV_1 per group before and after the time of enrollment



A decreased FEV_1 baseline appears to be a risk factor for chronic colonization by *A. fumigatus*, causing a faster deterioration of lung function

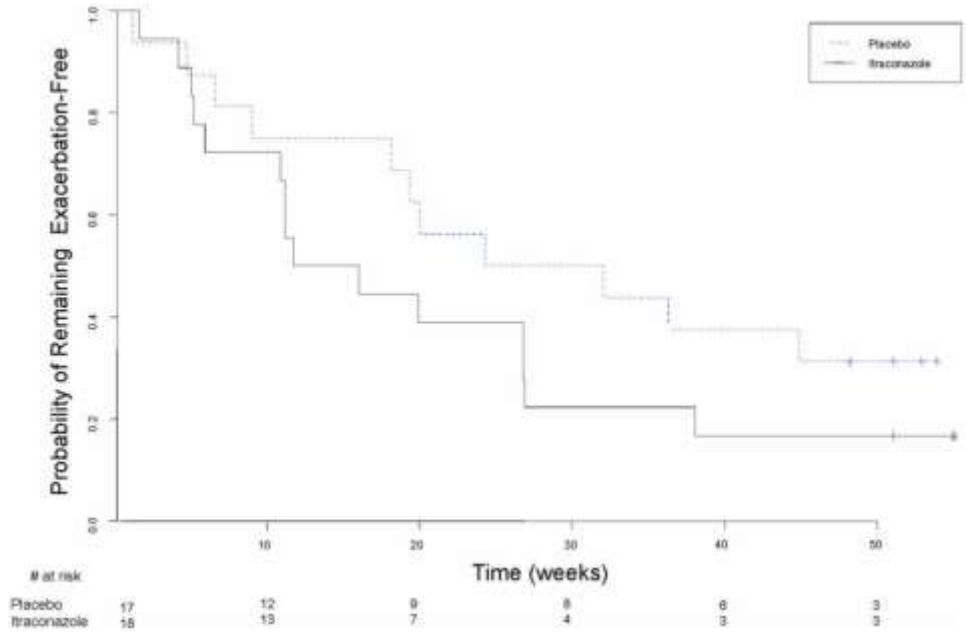
Noni et al, Eur J Clin Microbiol Infect Dis 2015

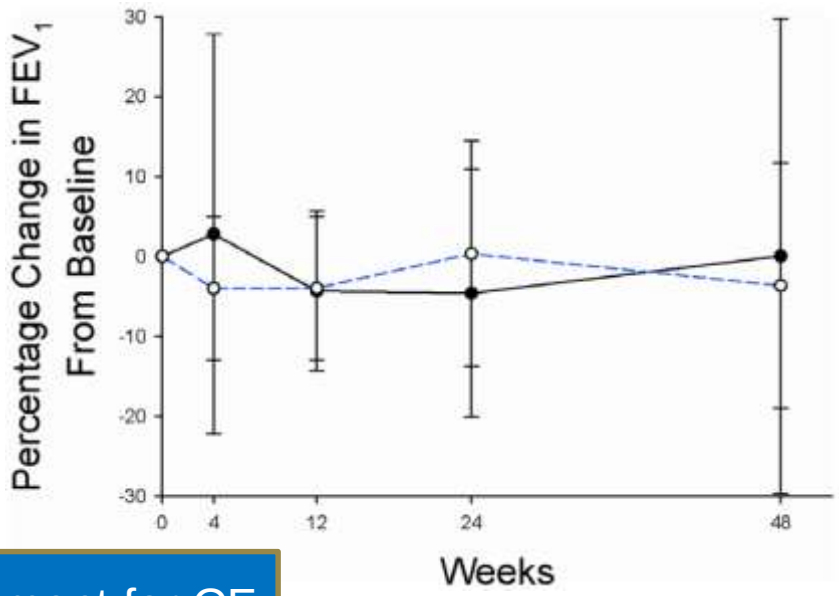
Treatment of *Aspergillus fumigatus* in Patients with Cystic Fibrosis: A Randomized, Placebo-Controlled Pilot Study

N=35 CF patients chronically positive for AF

Centrally randomized to receive for 24 weeks:

- Oral itraconazole 5 mg/kg/d (n = 18)
- Placebo (n = 17)

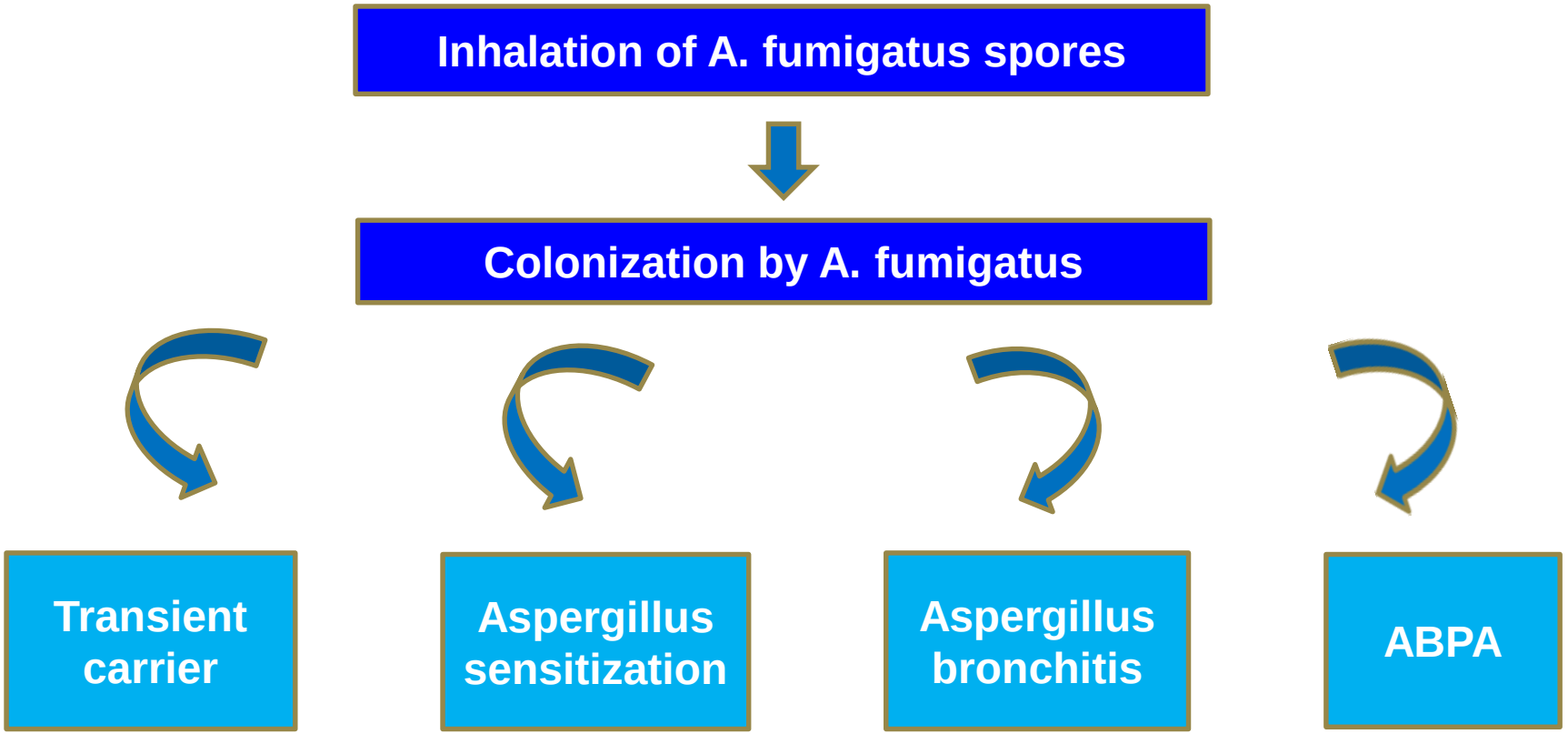




No clinical benefit from itraconazole treatment for CF patients chronically colonized with *A. fumigatus*

Aaron SD et al, PLoS One. 2012

Classification of Aspergillus-related pulmonary disorders in CF

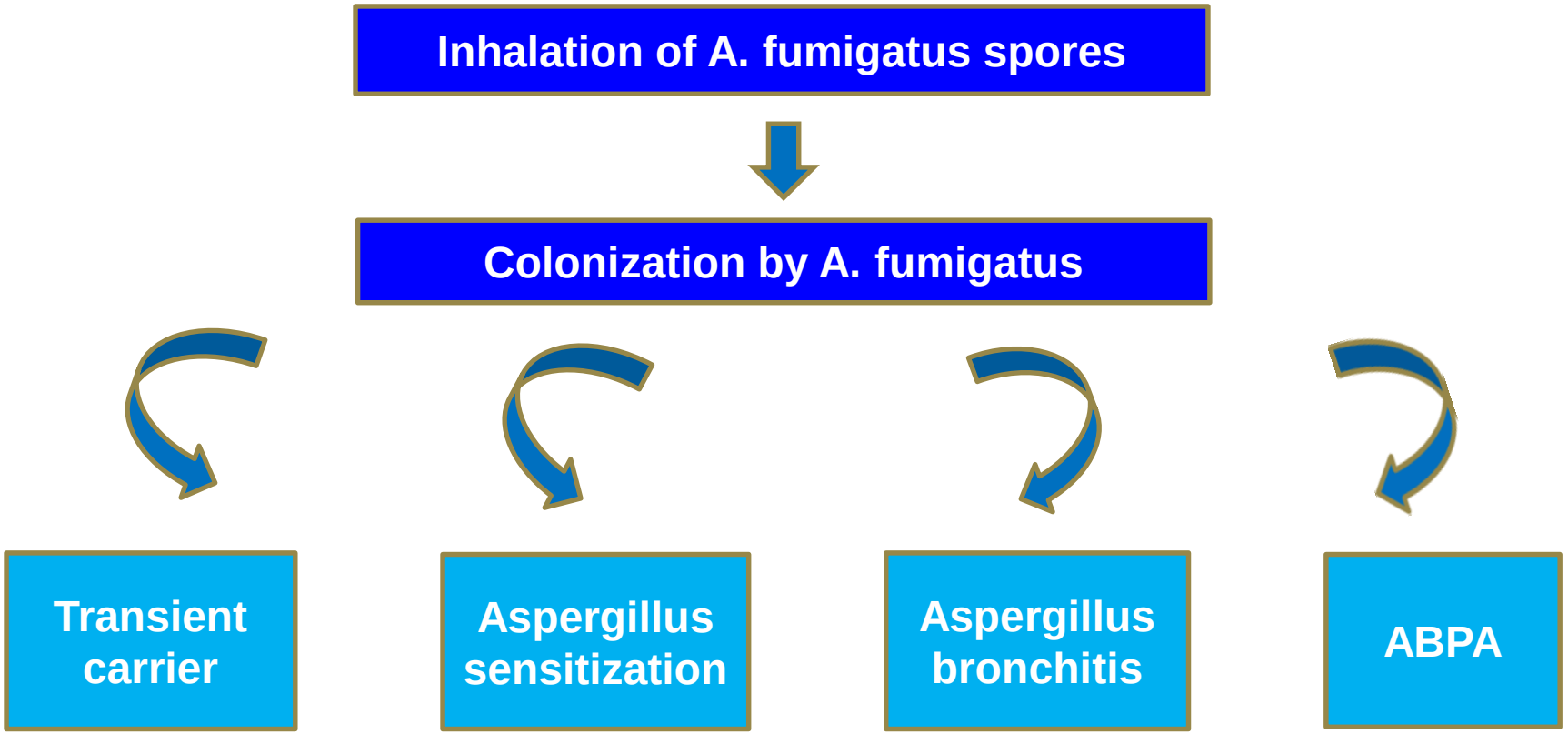


Aspergillus sensitization

- Is defined by the presence of
  - immediate skin test positivity to *Aspergillus* antigens or
  - elevated serum *A. fumigatus* specific IgE levels
- Prevalence in CF: 20% to 65%
- Associated with reduced FEV_1 in CF
  - not clear if this is a causal relationship or an epiphenomenon
- Not clear if it is a precursor to ABPA or a separate distinct aspergillosis phenotype within CF
- The use of antifungal treatment is associated with better lung function

Kanthan S et al, Pediatric Pulmonology 2007; Wojnarowski C et al, AJRCCM 1997; Fillaux J et al, Scandinavian Journal of Infectious Diseases 2012

Classification of Aspergillus-related pulmonary disorders in CF

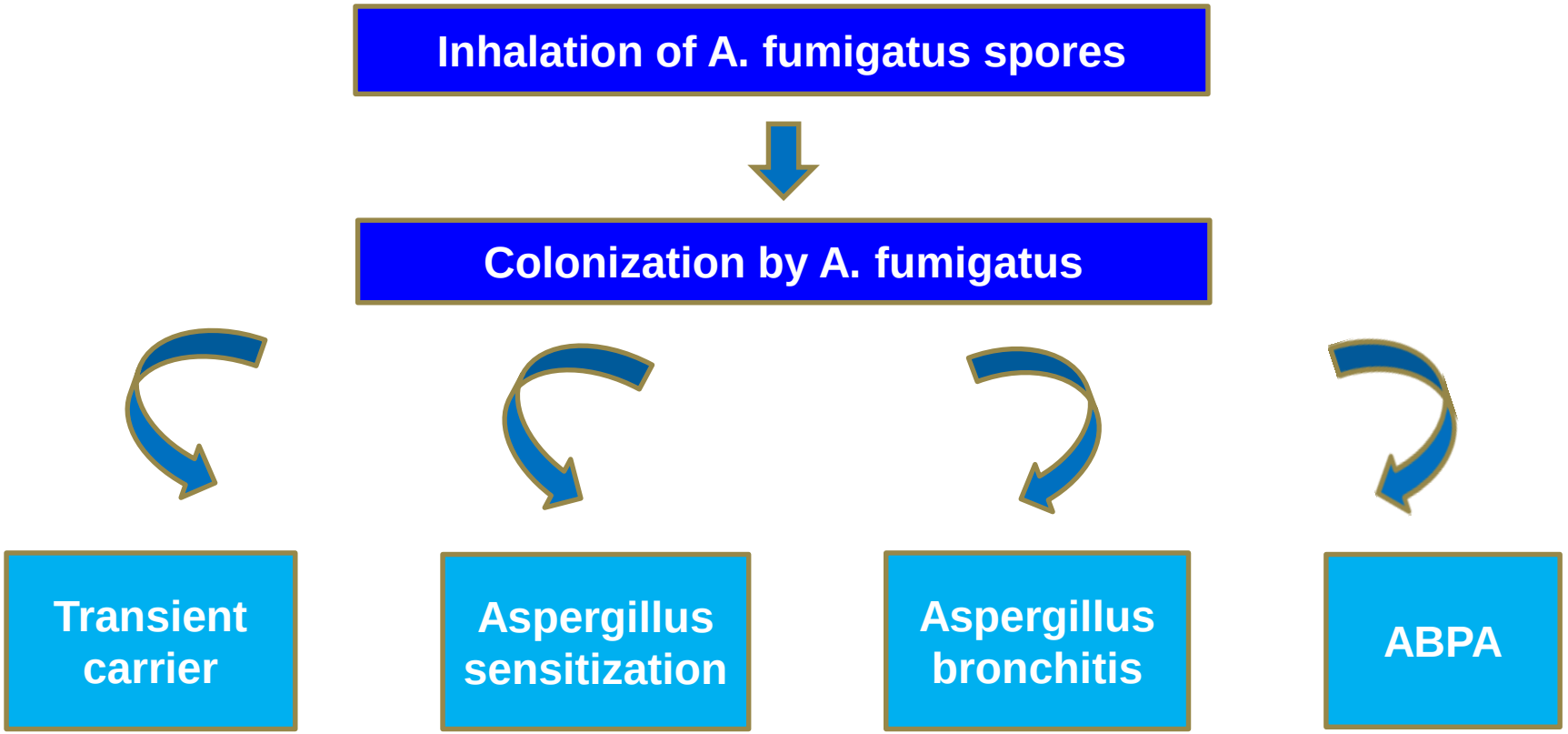


Aspergillus bronchitis in CF

- 6 CF patients with *A. fumigatus* +ve. but not meeting criteria for ABPA, with acute/subacute clinical deterioration
- No response to Abx. treatment directed to microorganisms identified in cultures, but good response to antifungal medications
- Antifungal therapy should be considered in these cases

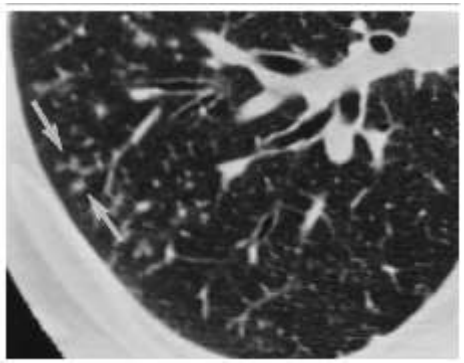
Shoseyov et al, Chest 2006

Classification of Aspergillus-related pulmonary disorders in CF

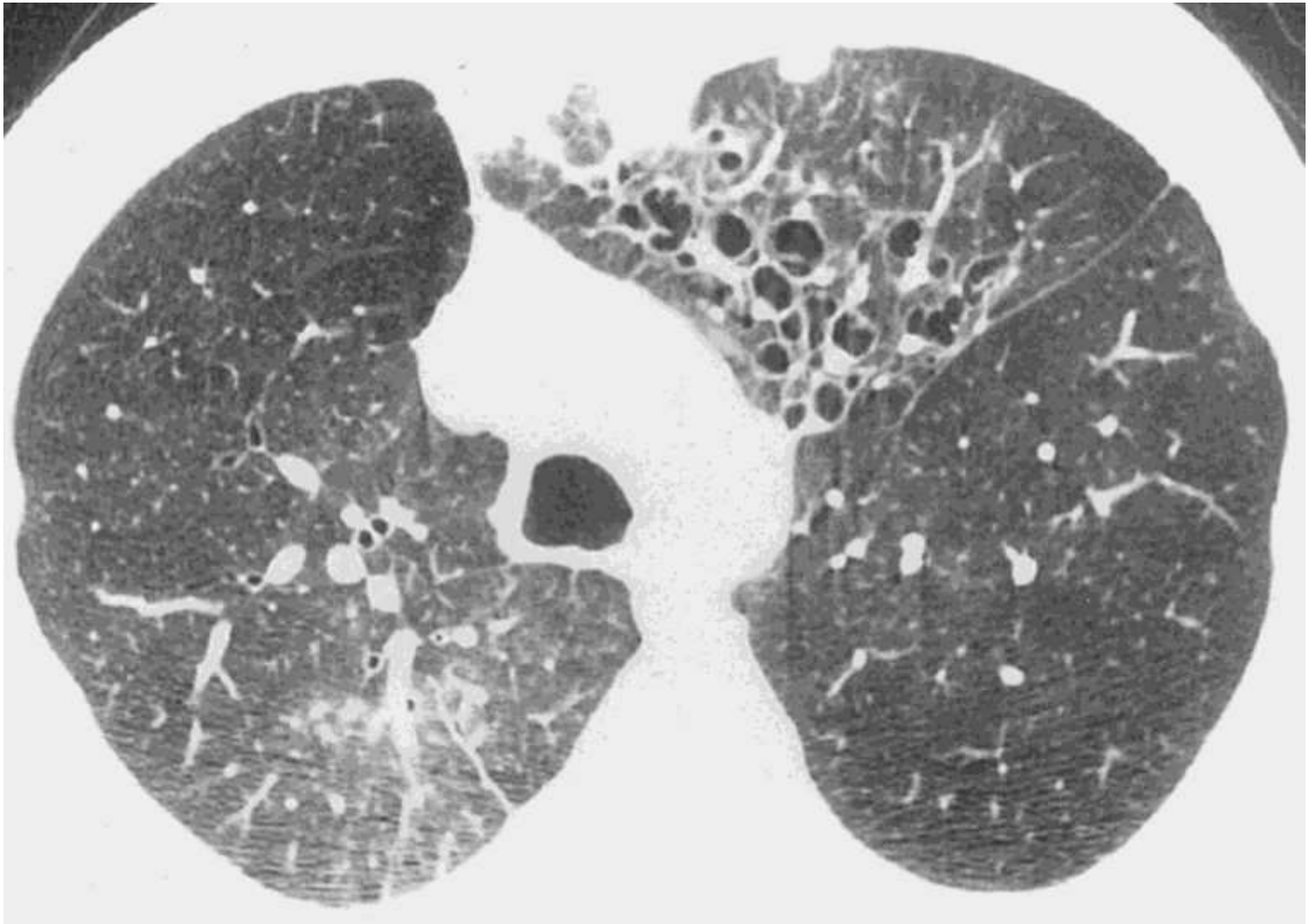


Allergic bronchopulmonary aspergillosis (ABPA)

- ABPA is a hypersensitivity reaction to *Aspergillus* antigens, mostly *A. fumigatus*
- Typically seen in patients with long-standing asthma, but also occurs in up to 15% of patients with CF
- In CF, due to overlap of symptoms, the diagnosis of ABPA is sometimes delayed or even missed, and it might result in an irreversible pulmonary damage



Chest CT: *tree in bud*, mucoid impaction



Treatment of ABPA in CF

- **Oral steroids** or
- **IV pulses of methylprednisolone*** or
- **Omalizumav****

+

- **Oral antifungal therapy** (itraconazol or voriconazol)
  for a long time period

- No randomized controlled trials evaluated the use of antifungal therapies for ABPA in CF
- Trials (not in CF) have shown clinical and serological evidence of improvement and a reduction in the use of corticosteroids

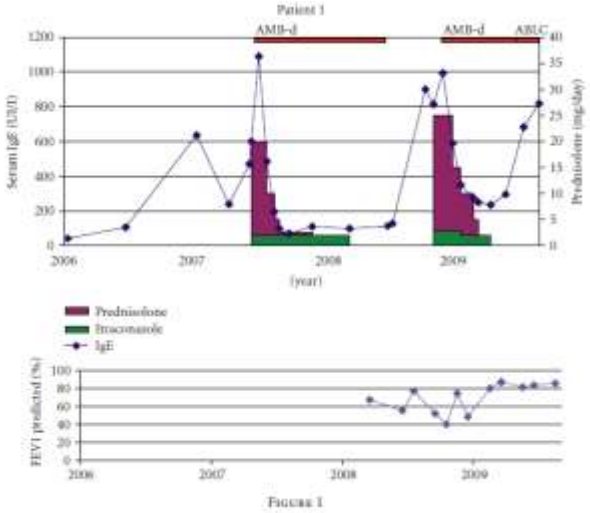
**Cohen-Cymberknoh M, Journal of Cystic Fibrosis 2009*

***Van der Ent CK, Thorax 2007, Elphick Cochrane Database Syst Rev. 2014; Lehmann S, Ther Adv Respir Dis 2014, Zicari et al, Eur Rev Med Pharmacol Sci. 2014*

Clinical Study — *International Journal of Pediatrics 2010*

Use of Nebulized Amphotericin B in the Treatment of Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis

M. Proesmans, F. Vermeulen, M. Vreys, and K. De Boeck



*AMP-B
20mg in a concentration of 1 mg/ml;
nebulization for 10–15 minutes * 3/ week

Nebulized liposomal amphotericin B for Aspergillus lung diseases: case series and literature review

Cendrine Godet, Mycoses 2015

- Five cases with pulmonary aspergillosis* (ABPA and Asp. Bronchitis) that were either difficult to control or in which patients had a contraindication to triazole therapy were successfully treated by nebulised LAmB

- Patients showed durable improvement

Candida colonization in CF

- In CF, *C. albicans* causes 95% of all Candida infections, the remainder are caused by *C. glabrata , C. parapsilosis , C. krusei* and *C. dubliniensis*
- Risk factors in CF: impaired salivation, CFRD, inhaled corticosteroid and prolonged antibiotic use
- The question is whether the growth represents harmless sputum positivity or a potential pathogen

Sputum *Candida albicans* Presages FEV_1 Decline and Hospital-Treated Exacerbations in Cystic Fibrosis

- A prospective observational study, n=89 CF patients
- Colonization with *C. albicans*: 49.4%

Table 7—*Strongest Predictors of Colonization With* Candida albicans *(Chronic or Intermittent) in CF Sputum*

Risk Factor	Adjusted OR (95% CI)[a]	*P* Value
Pancreatic insufficiency	6.647 (1.462-30.225)	.014[b]
Osteopenia	4.253 (1.147-15.769)	.030[b]
Pseudomonas colonization	8.053 (2.158-30.059)	.002[b]
Aspergillus colonization	4.961 (0.813-30.262)	.083

- *C. albicans* colonization accelerated the rates of decline of BMI and FEV_1 and increased exacerbation rate

- *C. albicans* acts as a marker for disease deterioration in CF

Chotirmall SH et al, Chest 2010

Association of Chronic *Candida albicans* Respiratory Infection With a More Severe Lung Disease in Patients With Cystic Fibrosis

Alex Gileles-Hillel, MD,[1] David Shoseyov, MD,[1,2,3] Itzhack Polacheck, PhD,[4] Maya Korem, MD,[4] Eitan Kerem, MD,[1,2,3] and Malena Cohen-Cymberknoh, MD[1,2,3*]

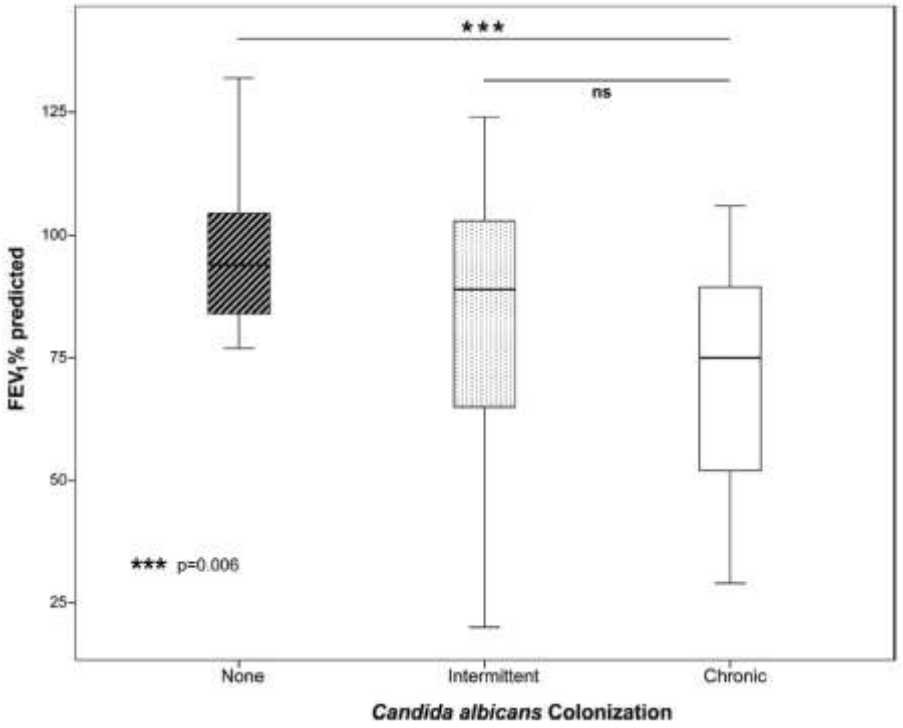
- Aim: to investigate the impact of *C. albicans* airway colonization on CF disease severity
- Longitudinal analysis of clinical data from patients followed during 2003–2009 at the Hadassah CF center
- Patients were stratified based on their *C. albicans* colonization status – chronic*, intermittent, and none
- A total of 4,244 cultures were obtained from 91 patients

  Mean age 19.7 years, range 5–68

*Chronic: ≥ 3 consecutive growth of Candida in sputum cultures or in ≥50% of cultures obtained within a 12-month period
Intermittent: +ive cultures in 25–49% of sputum samples obtained within 12 months
None: <25% +ive cultures in 12 months

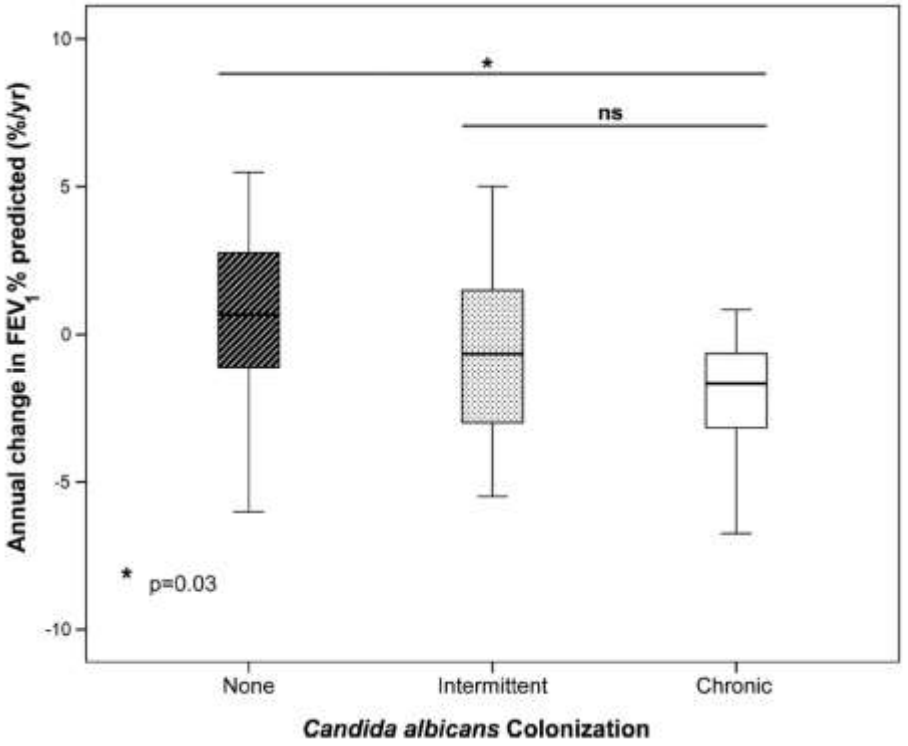
Ped. Pulmonol. 2015

Comparison of the FEV_1% between the 3 groups *at the end* of the study period



FEV_1 **Chronic** vs. **None**: 74.3±23.1% vs. 93.9%±22.2

Comparison of the *annual change* in FEV_1 % between the 3 groups



FEV_1 decline **Chronic** vs. **None** -1.9±4.2% vs. 0.7±4.5%

A. Gilleles-Hillel et al, Ped. Pulmonol. 2015

Association of Chronic *Candida albicans* Respiratory Infection With a More Severe Lung Disease in Patients With Cystic Fibrosis

Alex Gileles-Hillel, MD,[1] David Shoseyov, MD,[1,2,3] Itzhack Polacheck, PhD,[4] Maya Korem, MD,[4] Eitan Kerem, MD,[1,2,3] and Malena Cohen-Cymberknoh, MD[1,2,3*]

TABLE 2— Risk Factors for Chronic *C. albicans* Colonization (Univariate)

	OR (95%CI)	*P*-Value
Age	0.85 (0.3–2)	0.72
Gender	0.85 (0.3–2)	0.71
BMI < 20	0.61 (0.2–1.4)	0.27
FEV_1 < 60%	3.3 (1.1–9.9)	0.03
CFRD	5.4 (2–14.9)	0.001
PI	3.9 (1.3–11.6)	0.01
Corticosteroids	2.7 (1–6.9)	0.03
P. aeruginosa	1.8 (0.7–4.2)	0.18
Aspergillus spp.	5.9 (2.2–15.6)	0.0003
MRSA	6.5 (1.6–26.3)	0.008

TABLE 3— Independent Predictors of Chronic *C. albicans* Colonization (Multivariate)

	OR (95%CI)	*P*-Value
Aspergillus spp.	7.5 (1.8–30.2)	0.004
FEV_1 < 60%	5.2 (1.1–24.5)	0.03
BMI < 20	4.9 (1.1–21)	0.02

Chronic *C. albicans* airway colonization is associated with lower FEV_1, and a more rapid decline of FEV_1 in patients with CF

Ped. Pulmonol. 2015

Now, the question is…

To treat or not to treat fungal infections in CF?

Thank you!