

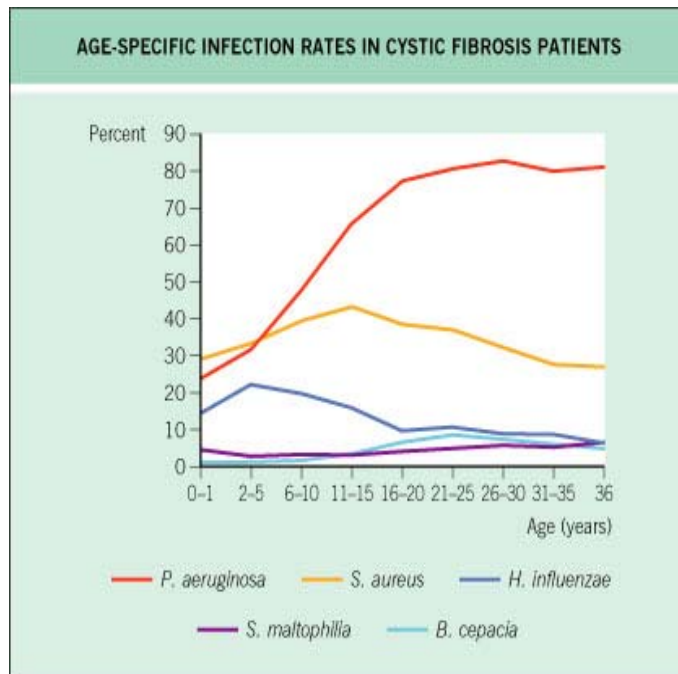
Fungal infections in cystic fibrosis

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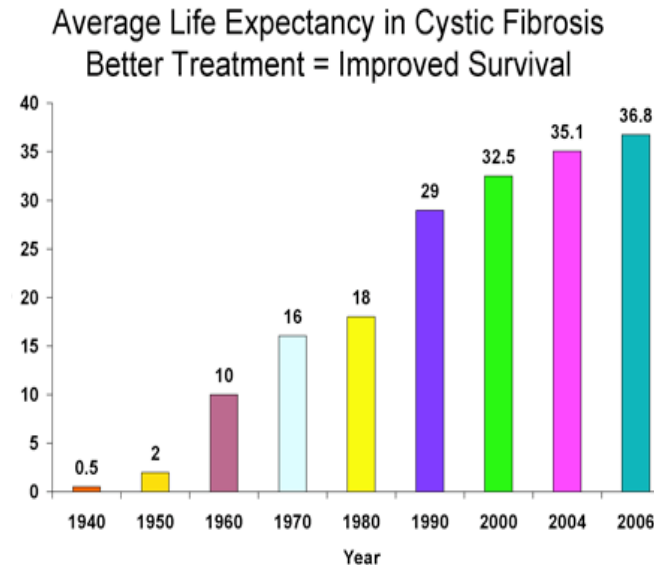


Cystic fibrosis (CF)

- An autosomal recessive disease that cause **abnormalities of ion transport** of epithelial cells and presents as a **multisystem disease**
- **Chronic infections in the lungs** are among the most prominent clinical manifestations and are related with the obstruction of respiratory ways by viscous secretions
- Mucus hypoxia and stasis may contribute to the propensity for bacterial infections, mainly due to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* and *Burkholderia cepacia*.



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Source: Cystic Fibrosis Foundation

Prevalence of *Aspergillus fumigatus* and other fungal species in the sputum of adult patients with cystic fibrosis

Mycoses, **46**, 19–23 2003

Table 1 Fungal species isolated from 369 sputum samples from 94 cystic fibrosis patients.

Fungi	In patients		In sputum samples	
	<i>n</i>	%	<i>n</i>	%
<i>Aspergillus fumigatus</i>	43	45.7	109	29.5
Other moulds				
<i>Aspergillus terreus</i>	2	2.1	2	0.5
<i>Penicillium</i> sp.	1	1.1	1	0.3
<i>Chrysonilia</i> sp.	1	1.1	1	0.3
Moulds, not further classified	3	3.2	4	1.1
Yeasts				
<i>Candida albicans</i>	71	75.5	220	59.6
<i>Candida glabrata</i>	3	3.2	19	5.1
<i>Exophiala dermatitidis</i>	1	1.1	5	1.4

Table 2 Prevalence of *Aspergillus fumigatus* in sputum of cystic fibrosis patients from different centres.

Reference, location	Patients, <i>n</i>	Age (where available), mean (range)	<i>Aspergillus</i> -positive, <i>n</i> (%)
Nelson <i>et al.</i> , ² Rochester, USA	37	14.2 (5–46)	21 (57)
Laufer <i>et al.</i> , ⁴ Wisconsin, USA	55	14.2 (2–34)	5 (9)
Schoenheyder <i>et al.</i> , ⁵ Copenhagen, Denmark	150	13 (2–35)	75 (50)
Penketh <i>et al.</i> , ³ London, UK	288	(12–51)	27 (9.4)
Bauernfeind <i>et al.</i> , ¹ Munich, Germany	102	16 (4–31)	6 (5.9)
Mroueh and Spock, ¹¹ Durham, USA	236	14.5 (1–41)	60 (25)
Becker <i>et al.</i> , ⁶ Seattle, USA	49	25.8 (18–50)	8 (16)
Milla <i>et al.</i> , ¹⁵ Delaware, USA	370	17.2	45 (12.2)
Burns <i>et al.</i> , ⁷ USA, different centres	465	21.2 (6–63)	108 (3.2)

The major clinical syndromes due to fungal infections in CF are

- Allergic Broncho Pulmonary Aspergillosis (ABPA)
- Indwelling central venous catheter related candidemias
- Invasive mycoses, especially after lung transplant



Allergic Broncho Pulmonary Aspergillosis (ABPA)

- ABPA is a long-term allergic response to *Aspergillus*, mainly observed in patients with severe, persistent asthma and in CF
- In patients with asthma clinical manifestations are episodic wheezing, expectoration of brown mucus plugs, low-grade fever, eosinophilia, and transient pulmonary infiltrates due to atelectasis. Central bronchiectasis occurs in some patients after several years of disease
- In CF bacterial pneumonia and ABPA may present with similar clinical features, and their differential diagnosis could be very difficult, not forgetting that both conditions could be present simultaneously.
- Therefore, specific criteria are used to establish the diagnosis of ABPA

Allergic bronchopulmonary aspergillosis in paediatric cystic fibrosis patients

PAEDIATRIC RESPIRATORY REVIEWS (2006) 7, 67-72

Table 3 Adaptation of the diagnostic criteria of allergic bronchopulmonary aspergillosis to patients with cystic fibrosis.²³

Two of the following criteria

Positive skin test for *Aspergillus*

Positive precipitins against *A. fumigatus*

Serum IgE higher than 1000 IU/ml

At least two of the following criteria

Bronchoconstriction

Eosinophilia higher than 1000/mm³

History of pulmonary infiltrates

A. fumigatus-positive sputum culture

Brownish sputum

Response to steroid therapy

1999

Table 4 Consensus of the Cystic Fibrosis Foundation for the diagnosis of allergic bronchopulmonary aspergillosis.¹³

M Classical criteria

Clinical deterioration

Immediate positive skin test or positive RAST

IgE > 1000 kU/l (>2398 ng/ml)

A. fumigatus-positive precipitins or presence of anti-***A. fumigatus*** IgG

Altered chest X-ray

Suggestion for annual screening

M Persistence of a clinical suspicion:

Serum IgE >500 kU/l, perform immediate skin test or RAST

Serum IgE <500 kU/l, repeat if the clinical suspicion was important

Clin Infect Dis, 2003/2004.

In these patients eosinophilia is not a useful diagnostic tool because the patients may have elevated peripheral blood eosinophils from other causes such as *Pseudomonas aeruginosa* infection.

Diagnosis and Treatment of Allergic Bronchopulmonary Aspergillosis

NICHOLAS E.

Using these criteria in CF patients the incidence of ABPA is approximately 7% (ranging 2%-15%), increasing after the 6th year of age

This is not surprising since colonization with *Aspergillus* has been shown to be age-related aslo in children with asthma

Left, fingerlike infiltrate indicative of mucous plugging.

Middle, fluid-filled and dilated bronchi indicative of central bronchiectasis.

Right, High-resolution computed tomogram characteristic bilateral parenchymal infiltrates and marked central bronchiectasis

To cut a long story short...

- ✓ After colonization, *Aspergillus* germinates to form hyphae.
- ✓ The **response to these antigens** is of the **Th2 type**, with release of cytokines IL-4, IL-5, and IL-13 (**maybe driven also by peculiar HLA**)
- ✓ The **inflammation** in the bronchial submucosa leads to excessive mucin production, extravasation of eosinophils into the bronchial mucin, intermittent **bronchial obstruction with atelectasis**, and, over time, to **bronchiectasis**
- ✓ The picture may become even worse if we consider that the bronchial secretion in CF are particularly thick and may represent a culture media for other pathogens (e.g. *Pseudomonadaceae*)

Risk factors for allergic bronchopulmonary aspergillosis and sensitisation to *Aspergillus fumigatus* in patients with cystic fibrosis

Eur J Pediatr (2005) 164: 577–582

Table 4 Cases with AFS versus controls

Univariate exact logistic regression	OR (exact 95% CI)	P
Inhaled steroids (cumulative dose in g)	8.0 (1.7–63)	0.004
Years of <i>P. aeruginosa</i> colonisation	2.0 (1.3–3.9)	< 0.001
Ever colonised with <i>S. maltophilia</i>	1.2 (0.1–17)	Not significant
BMI z-score	0.58 (0.2–1.3)	Not significant
Multivariate exact logistic regression	OR (exact 95% CI)	P
Inhaled steroids (cumulative dose in g)	26.6 (2.1–3588)	0.007
Years of <i>P. aeruginosa</i> colonisation	1.50 (1.12– infinity)	0.001
All the other variables		Not significant

Table 3 Cases with ABPA versus controls

Univariate exact logistic regression	OR (exact 95% CI)	P
Inhaled steroids (cumulative dose in g)	4.8 (0.97–38)	Not significant
Years of <i>P. aeruginosa</i> colonisation	1.0 (0.88–1.13)	Not significant
Ever colonised with <i>S. maltophilia</i>	20 (2.8– infinity)	< 0.001
BMI z-score	0.13 (0.02–0.7)	0.007
Multivariate exact logistic regression	OR (exact 95% CI)	P
Ever colonised with <i>S. maltophilia</i>	20.1 (2.8– infinity)	< 0.001
All the other variables		Not significant

Therapeutic strategies

- **Goals**

- ✓ T
 - ✓ T
 - ✓ T
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 - ✓ I
 - ✓ A possible role has been suggested for **inhaled steroids** (budesonide, fluticasone)
- But we must remember that...**
- ✓ the pharmacology of many drugs is altered in CF, and
 - ✓ we do not know anything about pharmacology of antifungals in CF and
 - ✓ there could be a major risk of drug interactions (CF patients receive a lot of drugs!) ...

- **Iatrogenic Cushing's syndrome** secondary to **adrenal suppression** after treatment with **budesonide + itraconazole: short or long, high or low doses** (Acta Paediatr. 2002;91:1008; J Cyst Fibros. 2003;2:72)
- **Adrenal insufficiency** was documented in 44% of patients treated with **itraconazole + budesonide up to 11 months after itraconazole discontinuation** (Eur Respir J 2002; 20: 127)

New drugs

Considering the risk of interactions, especially for the drugs with oral administration, or the need for daily i.v. infusion for the others

✓ nebulized liposomal amphotericin B

✓ aerosolized nanostructured itraconazole (produced by spray freezing into liquid)

could represent interesting alternatives, but at present they are not yet clinically evaluated, at least in these patients

● **Posaconazole, caspofungin micafungin, anidulafungin**

- **no data** (only 2 case reports for caspofungin in aspergillosis after lung transplant)

Aspergillus Bronchitis in Cystic Fibrosis* (CHEST 2006; 130:222-226)

- 6 cases of respiratory deterioration not responding to antibacterials in patients colonized with *A.fumigatus*, in absence of criteria for diagnosis of ABPA

- prompt therapy without

Finally, also invasive aspergillosis with “classic” aspergilloma has been described

(Clin Infect Dis 2002; 35: 106)

- a new

therapy

ABPA ?

- in any case systemic **antifungals** may be indicated **in colonized patients with respiratory deterioration** not responding to antibacterials, but there is **no indication for “empirical therapy”** in absence of colonization

Implanted CVC-related fungal infections

In patients with CF

- ✓ disease severity
- ✓ frequent antibiotic usage
- ✓ corticosteroid therapy
- ✓ diabetes mellitus

all have been associated with an increased risk of candidemia

(*) 7 episodes in 1 patient!

(**) PIVADS in 1 study only, not stratified TIVADS/PIVADS

Lung transplant becomes the only therapeutic option for end-stage lung disease in CF, but...

Type of transplant (n of procedures) (Dummer, 2005)	infections per patient	invasive mycoses (%)	proportions of infections (%)	most common site
kidney (64)	0.98	0	41	urinary tract
heart (119)	1.36	8	27	lung
heart-lung (31)	3.19	23	57	lung
liver (101)	1.86	16	23	abdomen & biliary tract

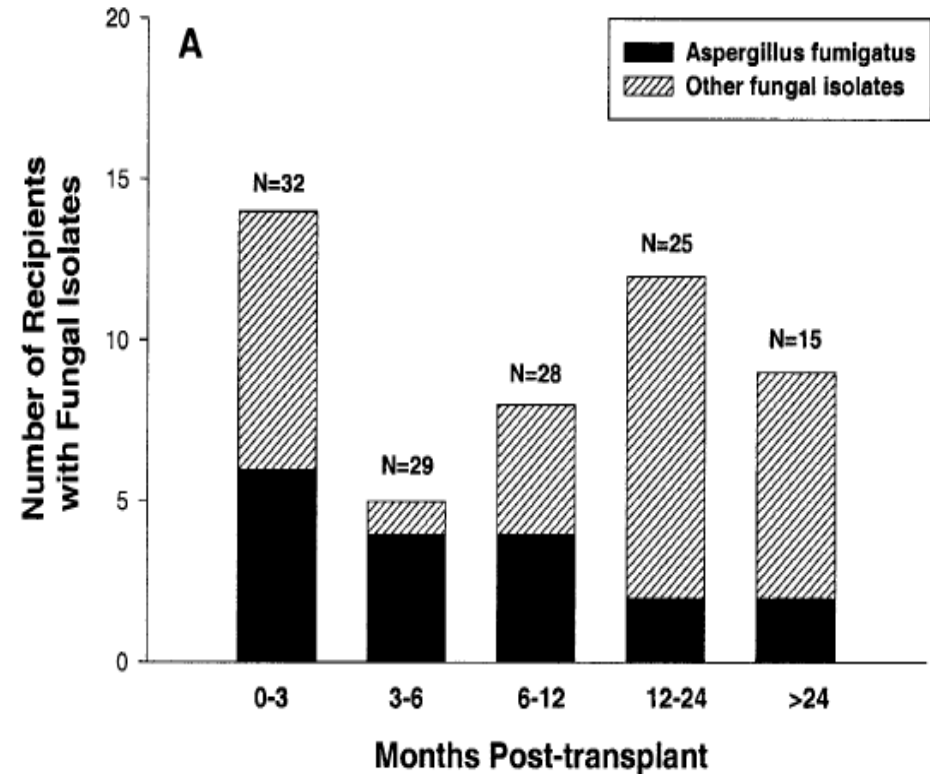
Post transplant aspergillosis in CF

(Helmi et al, Chest 2003; 123: 800)

Table 2—Characteristics of Recipients With CF*

Parameter	Preoperative Colonization (n = 17)	No Preoperative Colonization (n = 15)
Age, mean yr (range)	33 (21–55)	29 (19–40)
Gender		
Female	4	8
Male	13	7
Postoperative colonization	10 (59)	6 (40)
Deaths	3 (18)	5 (33)
Perioperative antifungal prophylaxis with nebulized amphotericin B	11 (65)	8 (53)
Cardiopulmonary bypass	7 (41)	7 (47)

*Values given as No. (%), unless otherwise noted.



Fungal infection developed in 44% (14/32) of patients

- tracheo-bronchial aspergillosis was observed in 9 (in 1 associated with pneumonia)
- isolated pneumonia was observed in 5
- survival was 21% (3/14)

Scedosporium... a new challenge?

Multifocal *Scedosporium apiospermum* spondylitis in a cystic fibrosis patient

Journal of Cystic Fibrosis
Article in Press, Corrected Proof-

Endobronchiti

Disseminated
Fibrosis Patient

Bilateral endog

Voriconazole should be the drug of choice,
but the caveats regarding interactions and
absence of kinetics data still remains...

transplantation.

Feb;139(2):370-3.

Emergence of *Scedosporium apiospermum* in patients with cystic fibrosis

Arch. Dis. Child. 2007;92:607.

Clinical Significance of *Scedosporium apiospermum* in Patients with Cystic Fibrosis

Eur J Clin Microbiol Infect Dis. 2000 Jan;19(1):53-6.

Conclusions

- **At present** fungal infections do not seem to represent a major challenge in patients with CF
- **ABPA** and **CVC-related candidemias** are the most frequent clinical features, but invasive infections due to *Aspergillus* and *Scedosporium* are described with increasing frequency, especially **after lung transplant**
- This scenario may change in the (next) future because of the overall increase in patients survival and therefore it is possible that fungal pathogens become (soon) a challenge also in CF
- Considering the **peculiarity of pharmacokinetics** of drugs in CF and the **great number of drugs administered** to these patients, **specific studies** are needed in order to identify the correct schedules and the possible risk of adverse events due to drugs interactions