4.3.7 Fungi

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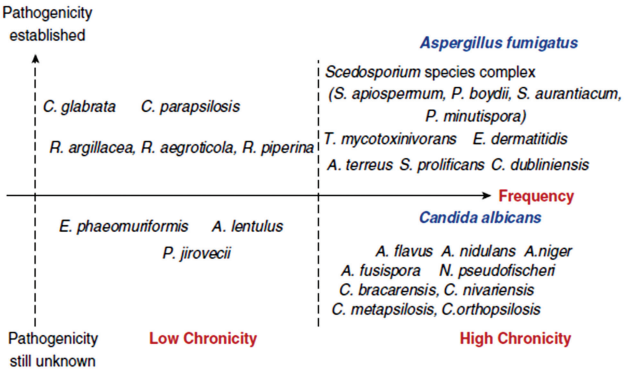
1. INTRODUCTION

- Using new molecular and selective culture techniques, fungi have been detected in up to 75% of CF patients, with some studies reporting a predominance of yeasts. Interestingly though, some microbiome analyses have challenged that fungal colonization is a common event in CF and suggested that the mycobiome may be dominated by transient species, present in the inhaled air.
  - Diversity of identified fungi has increased beyond *Aspergillus fumigatus* and *Candida albicans* to include other yeasts and filamentous fungi, particularly *Scedosporium* spp.
  - Interspecies co-infection studies have revealed interdependence between bacteria and fungi and suggested, for example, inhibition of *A. fumigatus* and *Scedosporium spp.* growth by *P. aeruginosa* under specific conditions.
- In CF patients, the **spectrum of host-fungi interactions** in the respiratory tract includes
  - Colonization (common), hypersensitivity responses (less common) and fungal infection (uncommon).
  - The sites involved include the lungs but also the nasal passages and the paranasal sinuses.
- **Colonization** denotes the presence of fungi without clinical symptoms and radiological or laboratory signs of active disease.
  - Colonization poses two challenging questions in CF patients: 1) should any sign/evolution of the lung disease be attributed to the presence of fungi and 2) does the fungal presence influence growth of other potential pathogens.
  - As a result, the overall effect of fungal colonization on the progression of CF-disease remains unclear.
- **Hypersensitivity responses** range from IgE-mediated sensitization (asthma) to immune complex and delayed hypersensitivity (allergic bronchopulmonary mycosis).
- The term **fungal infection** includes:
  - Fungal bronchitis: currently the only form described is "*Aspergillus* bronchitis" (rare).
  - Aspergilloma (very rare).
  - Invasive fungal disease (very rare).

2. THE SPECTRUM OF FUNGI

- A wide range of fungi have been identified in CF, with variable frequency/chronicity and pathogenicity **(Figure 1).** The most frequently isolated filamentous fungi are *A. fumigatus and Scedosporium* ssp, and yeast, *C. albicans*.

Figure 1: Cystic fibrosis fungal biodiversity. The frequency of isolation is depicted in the *x axis* and the established pathogenicity on the *y axis*. The fungi are further divided according to their chronicity. The most frequently isolated filamentous fungi (*A. fumigatus* and *Scedosporium* spp.) and yeast (*Candida albicans*) are highlighted. **Reprinted with permission of the American Thoracic Society. Copyright® 2017 American Thoracic Society. Chmiel et al. Ann Am Thorac Soc 2014; 11 (8): 1298–1306[1]. *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society.**



2.1 Aspergillus fumigatus

- *A. fumigatus* is the most commonly isolated filamentous fungus in CF (prevalence approx. 30%). This ubiquitous saprophytic fungus reaches the distal airways by inhalation of airborne *Aspergillus* conidia. The abnormal mucus and the defective airway clearance observed in CF facilitate the establishment of *Aspergillus* in the lungs.
- Baxter et al. described 4 distinct classes of aspergillosis in CF based on the assessment of sputum galactomannan, real-time PCR (RT-PCR) and serologic markers **(Table 1)**.
  - This is the only CF-specific classification currently available in the literature, however it remains controversial and requires validation before it can be used in the clinical setting.
  - This classification illustrates the different clinical phenotypes associated with *Aspergillus* in CF, but its predictive value for patient outcomes has not been evaluated yet. Furthermore, it relies on sputum galactomannan testing, which is not readily available and for which the role in the diagnosis of ABPA or aspergillus infection remains debated.

2.1.1 Colonization

- The role of *Aspergillus* colonization in the progression of CF-lung disease is unclear. Inconsistent and conflicting results have been published about its effect on the frequency of exacerbations and the rate of FEV_1 decline.

Table 1: Classes of aspergillosis proposed by Baxter et al.[2a]

	Sputum RT-PCR[b]	Blood immunologic markers	Sputum galactomannan[c]
Class I (non-diseased)	Positive or negative	Negative	Negative
Class II (serologic ABPA)	Positive	Increased total and specific *A. fumigatus* IgE/IgG	Positive
Class III (*A. fumigatus* sensitized)	Positive or negative	Increased *A. fumigatus* IgE (but not IgG)	Negative
Class IV (*A. fumigatus* bronchitis)	Positive	Increased *A. fumigatus* IgG (but not IgE)	Positive

Abbreviations: ABPA=allergic bronchopulmonary aspergillosis, RT-PCR=real time PCR
[a] This classification needs validation before it can be used in clinical practice.
[b] This analysis is not part of routine investigations and is not readily available.
[c] In the study of Baxter et al., a sputum galactomannan index >0.5 had a sensitivity of 98% and a specificity of 96% to differentiate classes II+IV from classes I+III. However, this analysis is not standardized and not readily available in clinical practice.

- Interventional studies, regarding antifungal treatment in this setting, are difficult to design and yielded conflicting results.
- Currently, no definite evidence exists that would favor targeted antifungal treatment or that would allow general recommendations in this setting. The decision to treat with an antifungal agent should be made:
  - on an individual basis (evidence of lung function decline that cannot be attributed to another cause) and
  - after consideration of the individual risks (interactions, side-effects, development of resistance).

2.1.2 Hypersensitivity responses

- CF patients can develop IgE-mediated sensitization to *Aspergillus* (**Table 1**, Class III according to Baxter et al).
- Allergic bronchopulmonary aspergillosis (ABPA), the most common form of allergic bronchopulmonary mycosis (prevalence in CF 2-15%), is an immune response against *A. fumigatus* resulting in inflammation and decreased lung function in CF patients. For more details see **Chapter *"ABPA"***.

2.1.3 Aspergillus *bronchitis*

- This recently described clinical entity has not been clearly defined in the literature and is a diagnosis of exclusion.
- It is based on the observation that some CF patients with repeatedly positive cultures for *Aspergillus* and concomitant symptoms of exacerbation do not respond to antibiotics but improve with antifungal therapy.

- It refers to a non-invasive ("superficial", "mucosal") *Aspergillus* infection of the lower airways characterized by the findings described in **Table 2**. The reported prevalence is 1.6-9%.
- Although it can be assumed that other fungi may also cause similar manifestations, currently, in adult CF patients, this type of bronchitis has been recognized only for *Aspergillus*.

Table 2: Findings indicating the presence of *Aspergillus* bronchitis (adapted from [2,3])

Persistently increased (>4 weeks) respiratory symptoms or recurrent respiratory exacerbations
Repeated identification of *Aspergillus* in sputum (by culture or RT-PCR*)
Increased *A. fumigatus* IgG (but not IgE)
Positive sputum galactomannan*
No evidence of invasive fungal disease
Lack of response to appropriate antimicrobial therapy
Good response to antifungal therapy

RT-PCR: reverse transcription-polymerase chain reaction
* These analyses are not part of routine investigations and they are not readily available.
Note: Bronchoscopic findings are non-specific and are commonly observed in CF patients even without fungal bronchitis. These include tenacious sputum, mucoid impaction/plugging, erythema, fragile mucosa that bleeds easily, ulceration, superficial invasion of the mucosa by fungal hyphae.

2.1.4 Aspergilloma (mycetoma, fungal ball)

- A rare presentation that occurs in previously damaged areas of the lungs (e.g. cavities, bronchiectasis).
- Complications include: progressive destruction of the pulmonary parenchyma with necrosis and cavitation, vascular erosion leading to massive hemoptysis, and rarely, progression to invasive fungal infection.

2.2 Scedosporium spp.

- The taxonomy of *Scedosporium* spp. (teleomorph/sexual state called *Pseudallescheria*) has evolved over the last years. Currently the term *Scedosporium apiospermium* complex is used for five closely related species, four of which have been described in CF: a) *S. apiospermum, b) S. boydii,* c) *S. aurantiacum*, and d) *S. minutispora*. *S. prolificans* has been renamed as *Lomentospora prolificans*.
- Their prevalence in CF is 3-10%, but a recent study reported a high rate of false negative cultures on non-selective medium, mainly with concomitant growth of *A. fumigatus*.
- *Scedosporium* spp. can result in colonization, hypersensitivity responses or invasive infection. Especially after lung transplantation, this fungus can cause invasive, disseminated infection associated with high mortality.

2.2.1 Colonization

- Little is known about the factors associated with *Scedosporium* spp. colonization: one study has shown that patients colonized with mucoid *P. aeruginosa* were less likely to be colonized with *Scedosporium* spp., whereas previous treatment with anti-staphylococcal penicillins was a risk factor for *Scedosporium* colonization. Another study showed that potted plants were a reservoir increasing the risk for *Scedosporium* colonization.
- Eradication is difficult and potentially not achievable. However, given the risk of invasive disease especially after transplantation, an eradication attempt should be considered for transplant candidates (**see paragraph 5.1 "treatment").**

2.2.2 Hypersensitivity responses

- Hypersensitivity responses: *S. apiospermium* has been associated with allergic broncho-pulmonary disease.

2.3 Candida albicans

- *C. albicans* is very frequently isolated from the respiratory tract of CF patients (up to 75% of respiratory samples).
- Its role in the progression of CF-lung disease is not clearly established. A few observational studies suggested that *C. albicans* colonization was associated with a higher exacerbation rate and an accelerated decline of FEV_1 and BMI.

2.3.1 Colonization

- Predisposing factors for colonization of the respiratory tract with *C. albicans* include exposure to antibiotics, inhaled corticosteroids and CFRD.
- As its isolation is very common in CF, and its role in the progression of CF-lung disease not clearly established, preemptive antifungal treatment is not recommended.

2.3.2 Hypersensitivity responses

- Sensitization to *C. albicans* has not been associated with pulmonary exacerbations or a decline in FEV_1. Allergic bronchopulmonary candidiasis has been rarely reported (non-CF case reports, some with concomitant *Aspergillus* hypersensitivity).

3. FUNGAL RHINOSINUSITIS

- Rhino-sinus isolation of fungi, especially *A. fumigatus*, is common in CF (up to 40% of patients) and suggests colonization in the vast majority of cases.
- Fungal rhinosinusitis refers to a group of entities including mycetoma (fungal ball), allergic fungal rhinosinusitis (AFS) and invasive fungal rhinosinusitis.
- AFS is considered a distinct form of chronic rhinosinusitis. Its prevalence is unknown in CF (in the non-immunocompromized CF population, there is only case report

evidence), but in the general population it accounts for about 5-10% of chronic rhinosinusitis cases.
  - It has been described as the upper airway equivalent of allergic bronchopulmonary mycosis (such as ABPA), but the two entities have some differences (e.g. in AFS total IgE is moderately elevated, precipitins may not be positive) and it is extremely uncommon for the two conditions to coexist.
  - AFS is difficult to diagnose because it develops slowly and, unless complications develop, it presents with symptoms similar to the other forms of chronic rhinosinusitis.
  - It is associated with the presence of eosinophilic mucin (macroscopically thick, brown or black coloured mucous, microscopically presence of fungal hyphae and degranulating eosinophils).

4. INVASIVE FUNGAL INFECTIONS

- Invasive fungal infections (IFI) are rare in CF patients before transplantation and their diagnosis is challenging.
  - *Aspergillus spp* and *Scedosporium* spp can cause invasive infections, especially after transplantation in the setting of immunosuppression.
  - In CF, there are case reports of catheter-related, *Candida* ssp blood stream infections.
- Imaging (CT scan) and histopathological proof of tissue invasion are crucial.
- No CF-specific guidelines for the diagnosis of IFI have been established.
  - As in solid organ transplantation, the *European Organization for Research and Treatment of Cancer (EORTC)* consensus definitions, originally designed for neutropenic patients, can be applied for diagnosis, but this should be done with caution as they have never been formally validated in the non-neutropenic CF-population. In these guidelines, 3 diagnostic categories are used: possible, probable, proven IFI.
  - A recent review (Schwarz C et al. 2017) focusing on CF-patients described a group of findings that together suggested IFI and was tentatively categorized as "highly probable" IFI. This new category is based on expert-opinion without epidemiological confirmation, and should be used with caution, since it has not been validated yet.

5. TREATMENT

- **Table 3** gives examples of available antifungal agents, their dosage in CF and some special considerations.
- **Role of antifungal susceptibility testing:** The incidence of azole resistance is rising in *Aspergillus* spp. in the setting of extended use of azoles in agriculture. Therefore, susceptibility testing should be obtained whenever feasible. Susceptibility testing is recommended at treatment initiation for:
  - patients at risk for resistant fungi (e.g. previous treatment with an antifungal agent, all cases of *Scedosporium* spp.)
  - before modification of antifungal therapy (e.g. in cases of poor response to the initial treatment). Given the fact that treatment failures occur despite *in vitro* activity, guidance by an infectious disease expert should be obtained.

5.1 Treatment of colonization

- **For fungi other than *Scedosporium* spp.:** the scarcity and contradictory nature of available data does not allow a general recommendation on preemptive antifungal therapy in this setting. Given the caveats such as development of resistance, side effects and potential drug interactions (both frequent with azoles), the decision to treat with antifungals should be made on an individual basis with great caution.
- **For *Scedosporium* spp.: due to the increased risk of invasive disease especially after transplantation, an eradication attempt should be considered for transplant candidates balancing the risks and benefits of treatment.**
  - Treatment choice should be based on antifungal susceptibility testing. *Scedosporium* is resistant to amphotericin B and occasionally resistant to azoles. Therefore, surgical debridement of infectious foci should be considered on a case-by-case basis and performed whenever feasible. Voriconazole has the lowest minimum inhibitory concentration (MIC) against *Scedosporium* spp. Posaconazole, isavuconazole and echinocandins have a moderate activity against some *Scedosporium* strains. Azoles and echinocandins may have a synergistic effect against *Scedosporium*. *Lomentospora proliferans* is potentially resistant to all antifungal agents.
  - For eradication, voriconazole is given orally (loading dose 400 mg every 12h for two doses, and then 200 mg 2x/day) as monotherapy. An initial phase of IV voriconazole treatment may be considered **(see Table 3)**. Treatment duration should be for a minimum of 4 weeks and adapted individually according to the persistence of *Scedosporium* in respiratory samples. Treatment adherence should be assessed regularly. In the absence of eradication, prolonged exposure (>3 months) to voriconazole during preemptive therapy should be avoided due to the increased risk of squamous cell carcinoma. Therapeutic drug monitoring (TDM) is recommended routinely for voriconazole use. For general recommendations regarding patient monitoring during voriconazole treatment see **Table 3.** For TDM recommendations **see Chapter "*Therapeutic drug monitoring*"**.
  - Bronchoalveolar lavage (BAL) cultures may provide guidance regarding treatment duration, with negative cultures on two different occasions suggesting successful eradication.
  - No data are available for an optimal surveillance strategy following an eradication attempt, however increasing the frequency of sputum cultures (once per month) for the first months after eradication is recommended. Surveillance bronchoscopy with BAL may also be considered for selected cases.

5.2 Treatment of ABPA

- Treatment of ABPA is detailed in **Chapter *"ABPA"***.

5.3 Treatment of Aspergillus bronchitis

- Limited evidence has been published to allow general recommendations concerning choice of antifungal agents and treatment duration:
  - Azoles (itraconazole or voriconazole) are considered the first line treatment.
    Note: to date, there are only limited data on the use of isavuconazole in the CF-population but it might be an alternative in case of side effects or drug interactions.
  - Susceptibility testing is recommended before treatment initiation and in case of insufficient response to treatment to assess antifungal resistance.

Table 3: Examples of systemic and inhaled antifungal agents and their dosage in non-transplanted CF patients

	Agent	Usual dosage	Comments
Oral	Itraconazole	5mg/kg/day (max 600 mg/day) When daily dose exceeds 200 mg/day administer 2x/day	– Only for non-invasive fungal infection – Monitor liver function tests, QT-interval, drug interactions – Limited and individualized bioavailability: a) Preferential use of the liquid formulation b) For the liquid formulation: administration on an empty stomach, concomitant administration with a low pH drink (e.g. orange juice, coca cola) and avoidance/spaced use of acid-blocking agents and proton pump inhibitors. c) For capsules: administration with food – TDM is recommended
	Voriconazole	Loading dose 400 mg every 12h for two doses, and then 200 mg 2x/day	– Alternative to itraconazole (improved gastrointestinal tolerance, bioavailability) – First choice for invasive aspergillosis – Monitor liver function tests, visual disturbances, photosensitivity, QT-interval, drug interactions. Prolonged voriconazole exposure has been associated with increased risk for skin cancer. – Take on empty stomach (1 hour before or 1 hour after meal) – TDM is recommended
	Posaconazole	Delayed-release tablets: Loading dose 300 mg every 12h for two doses, and then 300 mg 1x/day Solution: 200 mg 3-4 x/day	– Very poor bioavailability of solution, always favor delayed-release tablets. As this affects dosing, always specify on prescription whether the dose refers to tablets or solution. – For the solution, improve bioavailability by: adding high fat meal and acid liquid drinks, fractionating dosing 3-4 x/day – Monitor liver function tests, QT interval, drug interactions – TDM is recommended – **Off-label use**

	Isavuconazole	Loading dose 200 mg every 8h for two days (6 doses), and then 200 mg 1x/day	– Compared to other azoles: good bioavailability, less drug interactions, reduced liver toxicity – No data on the necessity of TDM so far; if available could be performed but not required
IV	L-AMB (AmBisome®)	3 mg/kg/day	– Only for invasive diseases – Given kidney toxicity always request infectious disease specialist advice – Monitor renal function, electrolytes, liver enzymes – Dosing of L-AMB differs from the one used for AMB-d (attention during prescription)
	Voriconazole	Loading dose 6mg/kg every 12h for two doses, and then 4 mg/kg every 12h	– Contains cyclodextrin which accumulates in those with renal insufficiency, therefore the IV formulation should not be used with renal clearance below 50 ml/min Monitor liver function tests, renal function, visual disturbances, photosensitivity, drug interactions and QT prolongation – TDM is recommended
	Posaconazole	Loading dose 300 mg every 12h for two doses, and then 300 mg 1x/day	– Contains cyclodextrin which accumulates in case of renal insufficiency, therefore the IV formulation should not be used with renal clearance below 50 ml/min – Monitor liver function tests – TDM is recommended **Off-label use**
	Isavuconazole	Loading dose 200 mg every 8h for two days (6 doses), and then 200 mg 1x/day	– Compared to other azoles: good bioavailability, less drug interactions, reduced liver toxicity – Does not contain cyclodextrin and can be used in case of renal insufficiency – No data on the necessity of TDM so far; if available could be performed but not required

(continued)

	Agent	Usual dosage	Comments
	Caspofungin	Loading dose 70 mg 1x/day for day 1 and then 50 mg 1x/day	– Second line antifungal agent for *Aspergillus* – Very low liver toxicity **May be off-label (depends on the indication)**
	Anidulafungin	Loading dose 200 mg 1x/day for day 1 and then 100 mg 1x/day	– Second line antifungal for *Aspergillus* – Very low liver toxicity **May be off-label (depends on the indication)**
Nebulized	L-AMB (AmBisome®)	25 mg twice a day 3 days/week in the first month and then 2 days/week [50 mg in 12 ml of WFI (4mg/ml) → nebulisation using a dedicated jet nebulizer such as PARI-Turboboy® over 15 min]	– Bronchospasm may occur. It is recommended to perform spirometry before and after administration of the first dose, and to administer bronchodilators before each dose. – Dosing of L-AMB differs from the one used for AMB-d (attention during prescription) – Incompatible with NaCl: reconstitution with WFI only! – Reconstituted L-AMB can be stored for a maximum of 24h at 2-8°C.
	Conventional AMB-d (Fungizone®)	10 mg twice a day 3 days/week [50 mg of AMB-d dissolved in 10 ml of WFI (5mg/ml) → nebulisation of 10mg (2ml) using a dedicated such as PARI-Turboboy® over 15 min]	– Bronchospasm may occur. It is recommended to perform spirometry before and after administration of the first dose, and to administer bronchodilators before each dose. – Dosing of AMB-d differs from the one used for L-AMB (attention during prescription) – Incompatible with NaCl: reconstitution with WFI only! – Reconstituted AMB-d can be stored for a maximum of 7 days at 2-8°C. **Off-label use**

AMB-d=amphotericin B deoxycholate, L-AMB= liposomal amphotericin B, TDM=therapeutic drug monitoring, WFI=water for injection

Details on TDM can be found in the **Chapter *"Therapeutic drug monitoring***

- A clinical response after 2-8 weeks of antifungals may support the diagnosis of *Aspergillus* bronchitis. A high rate of relapse has been described in some patients requiring long-term therapy (to be balanced with the risk of skin cancer with prolonged voriconazole exposure).

5.4 Treatment of Aspergilloma

- Treatment should be discussed on an individual basis taking into account the risks and benefits of medical, surgical or intra-lesional management.
- The indication for bronchial-artery embolization, to prevent or to treat hemoptysis, should be assessed in collaboration with an experienced interventional radiologist.
- Factors to be considered include: severity of the underlying pulmonary disease, location and progression of aspergilloma (increases in size), presence of local invasion (e.g. "halo sign" on chest-CT scan, referring to a ground glass area surrounding a nodular opacity, and positive galactomannan assay in the blood), and the risk for complications such as hemoptysis.

5.5 Treatment of invasive fungal infections

- IFI should be treated in collaboration with an infectious disease expert according to the current available guidelines (Patterson et al. 2016).

6. REFERENCES[1-22]

1. Chmiel JF, Aksamit TR, Chotirmall SH, et al. Antibiotic management of lung infections in cystic fibrosis. II. Nontuberculous mycobacteria, anaerobic bacteria, and fungi. Ann Am Thorac Soc 2014;11:1298-306.
2. Baxter CG, Dunn G, Jones AM, et al. Novel immunologic classification of aspergillosis in adult cystic fibrosis. J Allergy Clin Immunol 2013;132:560-6 e10.
3. Chrdle A, Mustakim S, Bright-Thomas RJ, Baxter CG, Felton T, Denning DW. Aspergillus bronchitis without significant immunocompromise. Ann N Y Acad Sci 2012;1272:73-85.
4. Fayemiwo S, Moore CB, Foden P, Denning DW, Richardson MD. Comparative performance of Aspergillus galactomannan ELISA and PCR in sputum from patients with ABPA and CPA. J Microbiol Methods 2017;140:32-9.
5. Schwarz C, Hartl D, Eickmeier O, et al. Progress in Definition, Prevention and Treatment of Fungal Infections in Cystic Fibrosis. Mycopathologia 2017; https://doi.org/10.1007/s11046-017-0182-0.
6. Kramer R, Sauer-Heilborn A, Welte T, Guzman CA, Abraham WR, Hofle MG. Cohort Study of Airway Mycobiome in Adult Cystic Fibrosis Patients: Differences in Community Structure between Fungi and Bacteria Reveal Predominance of Transient Fungal Elements. J Clin Microbiol 2015;53:2900-7.
7. Willger SD, Grim SL, Dolben EL, et al. Characterization and quantification of the fungal microbiome in serial samples from individuals with cystic fibrosis. Microbiome 2014;2:40.
8. Delhaes L, Monchy S, Frealle E, et al. The airway microbiota in cystic fibrosis: a complex fungal and bacterial community--implications for therapeutic management. PLoS One 2012;7:e36313.
9. Ferreira JA, Penner JC, Moss RB, et al. Inhibition of Aspergillus fumigatus and Its Biofilm by Pseudomonas aeruginosa Is Dependent on the Source, Phenotype and Growth Conditions of the Bacterium. PLoS One 2015;10:e0134692.

10. Maturu VN, Agarwal R. Prevalence of Aspergillus sensitization and allergic bronchopulmonary aspergillosis in cystic fibrosis: systematic review and meta-analysis. Clin Exp Allergy 2015;45:1765-78.
11. Amin R, Dupuis A, Aaron SD, Ratjen F. The effect of chronic infection with Aspergillus fumigatus on lung function and hospitalization in patients with cystic fibrosis. Chest 2010;137:171-6.
12. Williams C, Ranjendran R, Ramage G. Pathogenesis of Fungal Infections in Cystic Fibrosis. Curr Fungal Infect Rep 2016;10:163-9.
13. Aaron SD, Vandemheen KL, Freitag A, et al. Treatment of Aspergillus fumigatus in patients with cystic fibrosis: a randomized, placebo-controlled pilot study. PLoS One 2012;7:e36077.
14. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813-21.
15. Patterson TF, Thompson GR, 3rd, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63:e1-e60.
16. Burgel PR, Baixench MT, Amsellem M, et al. High prevalence of azole-resistant Aspergillus fumigatus in adults with cystic fibrosis exposed to itraconazole. Antimicrob Agents Chemother 2012;56:869-74.
17. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008;46:327-60.
18. Blyth CC, Middleton PG, Harun A, Sorrell TC, Meyer W, Chen SC. Clinical associations and prevalence of Scedosporium spp. in Australian cystic fibrosis patients: identification of novel risk factors? Med Mycol 2010;48 Suppl 1:S37-44.
19. Sedlacek L, Graf B, Schwarz C, et al. Prevalence of Scedosporium species and Lomentospora prolificans in patients with cystic fibrosis in a multicenter trial by use of a selective medium. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2015;14:237-41.
20. Lackner M, de Hoog GS, Verweij PE, et al. Species-specific antifungal susceptibility patterns of Scedosporium and Pseudallescheria species. Antimicrob Agents Chemother 2012;56:2635-42.
21. Callejas CA, Douglas RG. Fungal rhinosinusitis: what every allergist should know. Clin Exp Allergy 2013;43:835-49.
22. Abela IA, Murer C, Schuurmans MM, et al. A cluster of scedosporiosis in lung transplant candidates and recipients: The Zurich experience and review of the literature. Transpl Infect Dis 2018;20.